1.0 Title Page

Statistical Analysis Plan

Study M13-813

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

Date: 23 Apr 2019

Version 2.0

Prepared in collaboration by

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Document history

Statistical Analysis Plan	Date
Original (version 1.0)	**03-Dec-2018**
Amendment 1 (version 2.0)	**23-Apr-2019**

Summary of changes in Amendment 1 (version 2.0)

- The definition of deterioration in HVLT-R Total recall score has been updated to use 5-point change in raw score.

Rationale: To match the deterioration definition used in prior RTOG studies (Wefel et al).

- The censoring rule for the PFS analysis was updated to exclude any PD or death that occurs > 20 weeks after the previous scan date.

Rationale: To avoid prolonging PFS estimates when there are missing RANO assessments. The 20-week window was chosen to reflect 2 consecutive missed RANO assessments (8-week intervals) plus the 4-week assessment window specified in the study protocol.

- Additional sensitivity analyses for PFS including investigator assessed PFS and PFS with varying censoring rule and are included.

Rationale: These additional sensitivity analyses for centrally assessed PFS are included to evaluate the robustness of the primary PFS analysis. In addition, investigator assessed PFS analysis is also included.

- Visit windows for different endpoints were clarified with greater details.

Rationale: The details were added to provide appropriate information in the SAP for clarification purpose, including providing windows suitable for the procedure schedule for different endpoints.

- Other changes: Following changes are also implemented:
  - Editorial changes to improve consistency and clarity.
  - Analysis related to targeted ophthalmologic evaluation (TOE) endpoints are updated
  - Definition of prior medication is updated to include medications that started before first study treatment and continue to be taken after first study treatment.
  - Questionnaire of COWA-FAS added in the Appendix VI.
  - Definition of baseline value for all the parameters except steroids use is updated to include all the records with study Rx day ≤ 1 to minimize the number of patients with missing baseline values. The definition of baseline value for steroids use is updated to include all the records within 14 days prior to the first dose of study drug.
  - Figure 2 was updated as some of the text was not legible.
  - Time to deterioration (TTD) is renamed as Deterioration Free Survival (DFS) throughout the document.
  - Sensitivity analysis for HVLT-R Total score is added.

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3.0 Abbreviation

AE(SI)	Adverse Event (of Special Interest)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
CI	Confidence Interval
COWA-FAS	Controlled Oral Word Association – FAS version
CTC(AE)	Common Terminology Criteria (for Adverse Events)
Depatux-M	Depatuxizumab mafodotin
DFS	Deterioration Free Survival
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 Dimensions 5 Level
EQ VAS	EuroQol Visual Analog Scale
FAS	Full Analysis Set
FH	Fleming Harrington
FLAIR	Fluid Attenuated Inversion Recovery
GBM	Glioblastoma
GGT	Gamma-glutamyl transferase
Gy	Gray
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HVLT-R	Hopkins Verbal Learning Test-Revised
IDMC	Independent Data Monitoring Committee
IRT	Interactive Response Technology
KM	Kaplan Meier
KPS	Karnofsky Performance Status
LLN	Lower Limit of Normal
MDASI-BT	M.D. Anderson Symptom Inventory Brain Tumor Module

MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguaninemethlytransferese
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire – 25
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PPS	Per-protocol Set
PRO	Patient-Reported Outcomes
PT	Preferred Term
QLQ-BN20	Quality of Life Questionnaire Brain Cancer Module
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of Life
RANO	Response Assessment in Neuro Oncology
RCI	Reliable Change Index
ROW	Rest of the World
RT	Radiation Therapy
RPA	Recursive Partitioning Analysis
RS	Raw Score
RTOG	RTOG Foundation
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
SS	Scale Score
TE(AE)	Treatment Emergent Adverse Event
TMZ	Temozolomide
TOE	Targeted ophthalmology exam
TTE	Time to Event
ULN	Upper Limit of Normal
WHO	World Health Organization

4.0 Introduction

This statistical analysis plan (SAP) will provide details statistical methods for the analysis of efficacy and safety data collected in Study M13-813 (INTELLANCE 1) as outlined in Protocol Amendment 8 (dated 29 November 2018)[21] and will describe analysis conventions to guide the statistical programming work.

Efficacy and safety analyses will be performed using SAS Version 9.3 or higher (SAS Institute, Inc., Cary, NC 27513) under the UNIX operating system. The SAP will be signed off before any unblinded analysis is performed.

5.0 Study Objectives, Design and Procedures

5.1 Objectives

Primary objective

To determine whether the addition of Depatuxizumab mafodotin or Depatux-M (ABT-414) to concomitant radiotherapy (RT) and Temozolomide (TMZ) as well as to adjuvant TMZ prolongs Overall Survival (OS) among subjects with newly diagnosed glioblastoma (GBM) harboring epidermal growth factor receptor (EGFR) amplification.

Secondary objectives

To determine whether the addition of Depatux-M to concomitant RT and TMZ as well as to adjuvant TMZ improves outcomes among subjects with newly diagnosed GBM harboring *EGFR* amplification in terms of the following endpoints:

- Progression Free Survival (PFS), assessed centrally
- OS for the MGMT unmethylated group
- OS for the MGMT methylated group
- Deterioration Free Survival in M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) symptom severity score
- Deterioration Free Survival in MDASI-BT symptom interference score

- Deterioration Free Survival in Hopkins Verbal Learning Test Revised (HVLT-R) Total Recall score
- OS for the *EGFRvIII*-mutated tumor subgroup
- PFS for *EGFRvIII*-mutated tumor subgroup

Safety:

- Assessment of comparative safety

Exploratory objectives

To determine whether the addition of Depatux-M to concomitant RT and TMZ as well as to adjuvant TMZ improves outcomes among subjects with newly diagnosed GBM harboring *EGFR* amplification in terms of the following endpoints:

- OS at 0.5, 1, 2, 2.5, 3, 4, and 5 years
- Centrally-assessed PFS at 0.5, 1, 2, 2.5, 3, 4, and 5 years
- Centrally-assessed PFS for the MGMT unmethylated and methylated sub-groups
- OS and centrally-assessed PFS for non-*EGFRvIII* mutated subgroup
- OS and centrally-assessed PFS for Total EGFR expression levels
- Progression Free Survival (PFS), assessed by investigator
- *EGFRvIII* status as a prognostic factor independent of treatment assignment overall and among molecular subgroups
- Change from baseline in HRQoL and health status measures
  - QLQ-C30: Global health status, Physical Functioning, Cognitive Functioning, and Role Functioning scale
  - QLQ-BN20: Visual Disorder, Motor Dysfunction, and Communication Disorder scale
  - MDASI-BT: neurologic, cognitive, treatment, symptom interference (activity-related, mood-related), and vision item scores
  - COWA-FAS: verbal fluency score

  - HVLT-R: Total Recall score, Delayed Recall Score, Recognition Discrimination Index
  - EQ-5D-5L and EQ VAS scale scores
  - Karnofsky Performance Status (KPS)
- Median time for which KPS score was maintained at 70 or higher
- Deterioration Free Survival in neurocognitive functioning on Controlled Oral Word Association (COWA-FAS)
- Changes in EGFR molecular profile during therapy among subjects who undergo additional surgery as part of routine care
- Pharmacokinetics of Depatux-M, total ABT-806, and free cys-mcMMAF
- Change from baseline in corticosteroid dosing

5.2 Study Design

5.2.1 Study Design and Design Diagram

This is a Phase 3 randomized double-blind, placebo-controlled trial comparing the efficacy and safety of Depatux-M versus placebo, each as concurrent treatment with standard-of-care therapy (comprised of concomitant RT/TMZ and adjuvant TMZ) and followed by monotherapy, in subjects with newly diagnosed GBM. For this study, subjects will be stratified by MGMT methylation status (methylated and unmethylated), RPA class (III, IV, and V), region of the world (North America (includes USA and Canada) and rest of the world (ROW)) and EGFRvIII mutation status (mutated and wild type/indeterminate). A total of 640 evaluable subjects will be randomized on a 1:1 ratio to receive:

- Arm A: Depatux-M plus TMZ during the Chemoradiation and Adjuvant Phases.
- Arm B: Placebo plus TMZ during the Chemoradiation and Adjuvant Phases.

The study comprises the following 4 phases/periods: a Screening Period, followed in sequence by a Chemoradiation Phase, an Adjuvant Phase and a Follow-up Phase.

Screening Period

Screening procedures must be completed prior to Day 1 of the Chemoradiation Phase. The baseline brain magnetic resonance imaging (MRI) will be obtained no more than 28 (but preferably fewer) days prior to Day 1 of the Chemoradiation Phase. Safety related evaluations will be conducted 14 or fewer days prior to Day 1 of the Chemoradiation Phase. If a subject has a repeat surgery prior to randomization, the extent of surgical resection after the repeat surgery (biopsy-only vs. partial/total resection) will be used for determining RPA class.

Chemoradiation Phase

Treatment in the Chemoradiation Phase should begin ≤ 7 weeks after surgery/biopsy. During this Phase, all subjects will undergo fractionated focal radiotherapy (RT), with one treatment of approximately 2 gray (Gy) given daily 5 days per week for a total of approximately 60 Gy over approximately 6 weeks (and no more than 7 weeks). TMZ will be administered continuously from Day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. Subjects will receive blinded Depatux-M or Placebo 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).

Adjuvant Phase

The Adjuvant Phase is comprised of 28-day cycles. The first cycle starts approximately 28 days after the last day of radiotherapy. Subsequent cycles will start approximately 28 days from the start of the previous cycle. Subjects receives concomitant TMZ (on Day 1 - 5) and Depatux-M/Placebo (on Day 1 and Day 15) for the first 6 cycles, and study drug (Depatux-M/Placebo) monotherapy for the following 6 cycles. TMZ treatment for an additional 6 cycles (up to 12 cycles total) is allowed at investigator discretion. If after completing 12 cycles of adjuvant treatment, the subject is tolerating study drug (Depatux-M or placebo) and the investigator believes the subject is continuing to benefit from ongoing study drug treatment, the investigator may extend the Adjuvant Phase after consultation with the Neuro-Medical Oncology Chair or AbbVie Medical Monitor, as

long as subject's disease has not progressed. Adjuvant treatment will be discontinued once disease progression occurs. A final study drug visit will be performed upon discontinuation of study drug (Depatux-M/placebo) for any reason, followed by a 49-Day Follow-Up Visit (± 3 days).

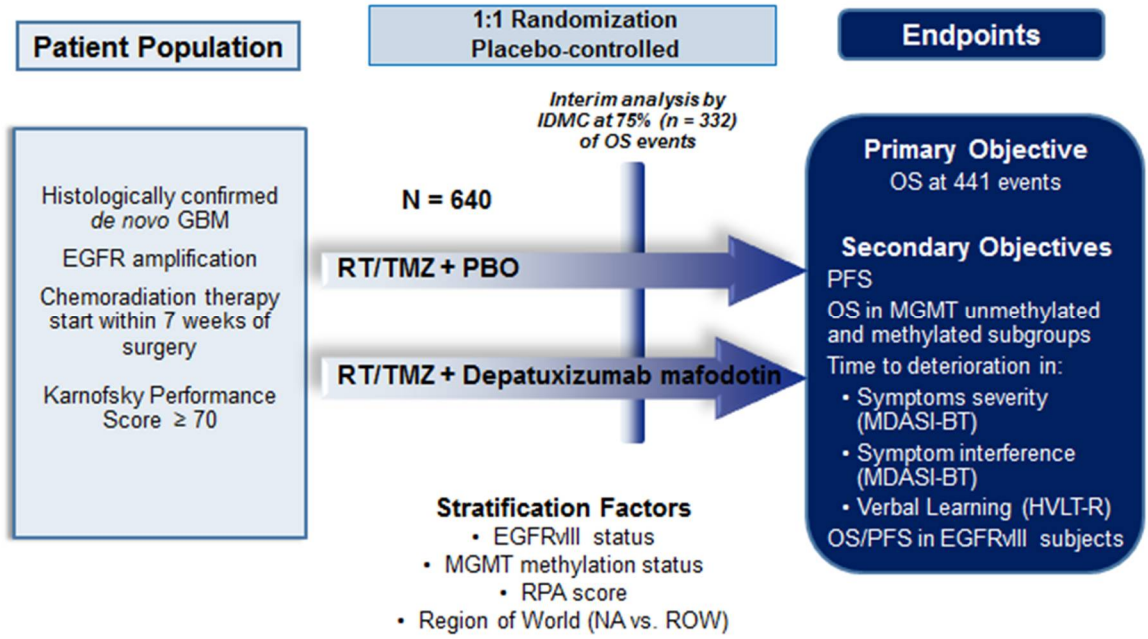
Follow-Up Phase

Subjects who complete adjuvant treatment or discontinue study drug prior to disease progression will continue to undergo MRI assessment, assessment of neurocognitive functioning, and assessment of PROs approximately every 8 weeks up to and including the time of disease progression. After disease progression, overall survival will continue to be assessed quarterly.

Doses of study drug (i.e., Depatux-M/Placebo and TMZ) in chemoradiation and adjuvant phases can be modified or interrupted (see Protocol Section 8.1, Section 8.2 and Section 8.3). Post-baseline scans will be obtained ≤ 14 days before Day 1 of each odd-numbered cycle (Cycles 1, 3, 5, etc.) of the Adjuvant Phase and ≤ 14 days before each visit (approximately every 8 weeks) of the Follow-Up Phase. OS will be assessed quarterly after study discontinuation.

A schematic of the study design is shown in Figure 1. The study activities for each visit in Chemoradiation and Adjuvant phases are outlined in Table 1 and Table 2 of study protocol, respectively.

Figure 1. Schema of study design



5.2.2 Variables used for Stratification at Randomization

All screening activities must be completed and reviewed prior to randomization. Subjects who meet the eligibility criteria will be stratified according to the following 4 factors:

- *MGMT* methylation status: Methylated and Unmethylated
- RPA classes: III, IV, and V
- Region of the World: North America (includes USA and Canada) and Rest of the World (ROW)
- *EGFRvIII* status: Mutated and Other.

EGFRvIII Other includes wild type, indeterminate due to test failure, invalid, or insufficient tissue. Within each stratum, subjects will be randomized to either Arm A (i.e.,

Depatux-M + TMZ) or Arm B (i.e., Placebo + TMZ) in a 1:1 ratio via the interactive response technology (IRT) system.

Screening numbers will be unique 5-digit numbers with the first 3 digits representing the investigative site, and the last 2 digits representing the subjects at that site. Randomized subjects will keep their screening number as their subject identification number. During randomization each patient will receive a separate unique 6 digit randomization number. This randomization number will be recorded automatically in the electronic case report forms (eCRFs) through the IRT system.

5.3 Endpoints

5.3.1 Primary Efficacy Endpoint

Primary efficacy endpoint is overall survival (OS). OS is defined as time from the randomization to death due to any cause. For subjects who are alive at the end of this study, OS will be right-censored on the last date the subject is known to be alive.

5.3.2 Secondary Efficacy Endpoints

Overall Survival (OS) related secondary endpoint

The following OS related endpoints are considered as secondary endpoints:

- OS for the MGMT unmethylated group
- OS for the MGMT methylated group
- OS for the *EGFRvIII*-mutated tumor subgroup

Progression Free Survival (PFS) related endpoints

PFS is defined as time from randomization to the date of progression of disease (PD) assessed centrally per Response Assessment in Neuro-Oncology (RANO) criteria or death, whichever occurs first. Any PD or death that occurs > 20 weeks after the previous scan date will be excluded along with the following scans. Subjects without an event will be right-censored at the date of last follow up for disease progression. Patients with no

post baseline follow up for progression and who doesn't experience a death event within 20 weeks after the randomization date will be censored at the day of randomization.

The PFS related secondary endpoints are:

- PFS, assessed by independent central review
- PFS, assessed by independent central review for *EGFRvIII*-mutated tumor subgroup

MDASI-BT symptom severity and interference score

This is a validated PRO instrument used to assess the severity of brain tumor related symptoms and its impact on daily function in last 24 hours. It consists of 22 symptom items and 6 interference items. Each item is rated from 0 to 10, with higher score indicating worse symptoms/interference.

MDASI-BT symptom severity score is defined as average over 13 core symptom items and 9 brain tumor symptom items. The MDASI-BT symptom severity score will be obtained if more than 50% of the items (at least 12 out of 22 items) are completed on a given assessment using the formula: (sum of items answered) × 22/number of items answered.

MDASI-BT symptom interference score is defined as an average of 6 interference items. The MDASI-BT symptom interference score will be obtained if more than 50% of the items (at least four out of six items) are completed on a given assessment using the formula: (sum of items answered) × 6/number of items answered.[18,28]

A change of ≥ 1 point on a 10-point scale at follow-up assessment with respect to baseline will be considered as clinically relevant. Changes in symptom severity score and symptom interference score at each time point will be classified into 3 categories: improved (≤ –1), stable (> –1 and < 1), and deteriorated (≥ 1).

The secondary endpoints based on this measure are as follows:

- Deterioration Free Survival (i.e., decrease by 1 unit or death, whichever comes first) in MDASI-BT symptom severity score
- Deterioration Free Survival (i.e., decrease by 1 unit or death, whichever comes first) in MDASI-BT symptom interference score

HVLT-R

This standardized neurocognitive function test is used to assess change in verbal memory over time. This test has been validated within brain-disordered population. The HVLT-R Total Recall Score will be computed by summing the total number of words across 3 trials (Trial 1, Trial 2 and Trial 3). Then, the Total Recall Score will be standardized using the published age specific normative data from a healthy population.

A change of ≥ 5 points in raw HVLT-R total recall score with respect to baseline will be considered as clinically relevant. Changes in HVLT-R total recall score at each post-baseline time point will be classified into 3 categories: deteriorated (≤ -5), stable (> -5 and < 5) and improved (≥ 5) (Wefel et al., 2011).

The secondary endpoint based on this measure is:

- Deterioration Free Survival in HVLT-R total recall score.

5.3.3 Exploratory Efficacy Endpoints

Overall Survival (OS)

- Survival rates at the end of 0.5, 1, 2, 2.5, 3, 4, and 5 years
- OS in non-EGFRvIII subjects

Progression Free Survival (PFS)

- Centrally-assessed PFS rates at the end of 0.5, 1, 2, 2.5, 3, 4, and 5 years

- Centrally-assessed PFS for the MGMT unmethylated and methylated sub-groups
- Centrally-assessed PFS in non-EGFRvIII subjects
- Progression free survival (PFS), assessed by investigator

HRQoL assessments per QLQ-C30 questionnaire developed by EORTC:

The Quality of Life Questionnaire Core 30 (QLQ-C30) is a 30-item patient self-report questionnaire validated for use in a cancer patient population. Subjects rate items 1 - 28 on a four-point scale (1 = "not at all" to 4 a = "very much") with higher score indicating worse functioning/symptoms and the items 29 - 30 on 1 - 7 points scale. It is composed of global health status/QoL scale; five functional scales (physical, role, emotional, cognitive, and social); three symptom scales (fatigue, nausea and vomiting, and pain); and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The following endpoints based on this measure will be analyzed:

- Change from baseline in Global Health Status, Physical Functioning, Cognitive Functioning, Role Functioning

HRQoL assessments per QLQ-BN20 questionnaire developed by EORTC:

Quality of Life Questionnaire Brain Cancer module (QLQ-BN20) is a 20-item patient self-report questionnaire is specifically developed for brain cancer patients. Subjects rate items on a four-point scale (1 = "not at all" to 4 a = "very much") with higher score indicating worse symptoms. It is composed of 11 symptom scales (7 single item scales and 4 multi-item scales).

The following endpoints based on this measure will be analyzed:

- Change from baseline in symptom scales of Visual Disorder, Motor Dysfunction and Communication Disorder

MDASI-BT symptom severity score

Details of MDASI-BT symptom severity score are provided in Section 5.3.2. The following exploratory endpoints will be analyzed:

- Change from baseline in neurologic domain score (mean over seizures, numbness, pain, and weakness)
- Change from baseline in cognitive domain score (mean over difficulty understanding, difficulty remembering, difficulty speaking, and difficulty concentrating)
- Change from baseline in treatment domain score (mean over dry mouth, drowsiness, and appetite)
- Change from baseline in Vision item score (one of the 9 brain tumor-specific items)

MDASI-BT symptom interference score

Details of MDASI-BT symptom interference score is provided in Section 5.3.2. The following exploratory endpoints will be analyzed:

- Change from baseline in activity-related interference domain score (mean over general activity, work, and walking)
- Change from baseline in mood-related interference domain score (mean over mood, relations with other people, and enjoyment of life)

Karnofsky Performance Status (KPS):

- Change from baseline in KPS score
- Median time for which KPS score was maintained at 70 or higher

COWA-FAS verbal fluency

This standardized neurocognitive function test is used to assess change in executive function over time. In this test, patients are asked to name words beginning with F, A and

S in English (and frequency matched letters in other languages). The COWA-FAS verbal fluency score will be computed by summing the total number of unique words.

At each post-baseline assessment, change in raw and standardized COWA-FAS verbal fluency score relative to baseline will be calculated and categorized as deteriorated or not using the reliable change index (RCI) criterion based on the standardized scores. The details are provided in Appendix VII.

The endpoints based on this measure are as follows:

- Deterioration free survival in verbal fluency score
- Change from baseline in verbal fluency score

Neurocognitive functioning based on HVLT-R

Details of HVLT-R score is provided in Section 5.3.2. In addition to Total Recall Score (over Trials 1 - 3), the following two scores will also be evaluated:

- Delayed Recall Score (Trial 4) and
- Recognition Discrimination Index (= total number of true positives – total number of false positives)

The following exploratory endpoints will be analyzed:

- Change from baseline in Total Recall score
- Change from baseline in Delayed Recall Score
- Change from baseline in Recognition Discriminant Index

EQ-5D-5L Health Index and EQ-VAS

EuroQol 5 Dimensions 5 levels (EQ-5D-5L) is a validated instrument to measure generic health status. It is a 5-item patient self-report questionnaire. Subjects rate items on a five-point scale (1 = "no problems" to 5 a = "extreme problem") with higher score indicating worse health. The EQ-5D-5L health states, defined by the EQ-5D-5L

descriptive system, will be converted into a single preference-weighted health utility index score by applying country-specific weights. If country is not available in the look-up table, then weights based on the United States will be applied. Scores will be computed according to procedures outlined in EQ-5D-5L scoring manual, available at https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf.

In the assessment of EuroQol Visual Analog Scale (EQ VAS), subjects are asked to indicate their overall health status on a 0 to 100 visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine.' This information is used as a quantitative measure of health as judged by the individual respondents.

The endpoints based on this measure are as follows:

- Change from baseline in EQ-5D-5L index value
- Change from baseline in EQ VAS score.

Change from baseline in corticosteroid dosing

Average daily corticosteroid dose (dexamethasone equivalent) at baseline is defined as any use of systemic steroid within 14 days prior to randomization. Post-baseline steroid use is defined as any use of systemic steroid on or after randomization. Steroid doses will be converted to a dexamethasone equivalent dose.[3]

Corticosteroids (mg)	Conversion Factor*
Cortisone	0.75/25
Hydrocortisone	0.75/20
Methylprednisolone	0.75/4
Prednisolone	0.75/5
Prednisone	0.75/5
Triamcinolone	0.75/4
Betamethasone	0.75/0.6

* Dexamethasone equivalent dose (mg) = Conversion factor × Corticosteroid dose (mg).

Baseline steroid dose is defined as the average dose within 14 days prior to randomization. Post-baseline steroid dose is defined as average dose from randomization to last dosing of study drug + 49 days.

The endpoint based on this measure is as follows:

- Change from baseline in average daily (dexamethasone equivalent) corticosteroid dosing during treatment period.

5.3.4 Safety Endpoints

Safety endpoints in this study are as follows:

- Incidence of adverse events
- Incidence of lab abnormalities (Chemistry, hematology, urinalysis and hepatic)
- Change from baseline in vital signs parameters
- Change from baseline in ECG parameters

5.4 Sample Size Justification

The primary endpoint for the study is overall survival (OS). A total of 640 evaluable subjects are expected to be randomized to observe 441 deaths. A planned interim analysis will be carried out at 75% OS event (i.e., 332 OS events).

It is assumed that the median OS for the placebo arm will be approximately 16 months. Treatment with Depatux-M is hypothesized to increase median OS to 21.3 months (i.e., a hazard ratio (HR) of 0.75). With 441 deaths, there will be 85% overall power to detect a 25% reduction in the hazard of death (i.e., HR = 0.75) using a log-rank test at a one-sided 2.5% level of significance.

Subjects will be accrued for a total of 640 evaluable subjects randomized in the study. Once the target accrual is met, subjects will then be followed to observe 441 deaths overall for comparison of OS between arms.

5.5 Interim Analysis

5.5.1 Interim analysis for early efficacy and futility

An interim efficacy analyses on OS will be performed after observing 332 deaths (i.e., 75% of the 441 deaths required at final analysis) for declaring early efficacy or futility stop. Based on the Fleming-Harrington's version of weighted a log-rank test with parameters $\rho = 0$ and $\gamma = 0.2$, approximately 66% information will be accumulated at the interim analysis (see Section 5.6.1). Interim analysis will be carried out at one-sided type I error of 0.0058. Interim analysis will be carried out according to the methods describe in Section 10.0 and justification of type I error is given at Section 5.6.1. The trial may also be stopped for futility if the estimated Cox HR of Depatux-M to Placebo at interim analysis exceeds 0.9.

The trial will be considered for early stopping if the Independent Data Monitoring Committee (IDMC) makes such a recommendation after consideration of the unblinded interim results. This interim review will include results for the primary and secondary efficacy endpoints, safety and other supportive evidence.

5.5.2 Interim reporting for the DMC

The IDMC, as coordinated by RTOG Foundation, will review the study at least twice a year with respect to subject accrual, pretreatment characteristics of accrued subjects, the frequency and severity of toxicities and morbidity. The IDMC is also available to review the study on an "as needed" basis. Details are described in the DMC charter.

5.6 Multiplicity Testing Procedures for Type-I Error Control

5.6.1 Type I error control for interim analysis

O'Brien-Fleming method will be used to adjust for multiple testing to maintain overall one-sided type I error level at 2.5%. As described in Section 10.2, Fleming-Harrington version of weighted log-rank test[10,12] would be used for primary efficacy analyses with weights for the events occurring at time t as

$$w(t) = \left[1 - \hat{S}_{KM}(t)\right]^{0.2}$$

where, $\hat{S}_{KM}(\cdot)$ is the KM estimate of the survival function in the pooled data.

The weight for d^{th} event occurring at time t_d can be calculated as

$$w_d \equiv w(t_d) = \left[1 - \hat{S}_{KM}(t_d)\right]^{0.2} \quad ,$$

and the information fraction (IF) can be estimated as (Hasegawa, 2016)

$$\text{IF} = \left(\sum_{d=1}^{D_{IA}} w_d^2\right) \Big/ \left(\sum_{d=1}^{D_{FA}} w_d^2\right)$$

where D_{IA} and D_{FA} denote the planned number of events at the interim and final analysis, respectively. With interim analysis planned at 332 events and final analysis planned at 441 events, the simulation results suggest that the IF at the interim analysis is estimated to be approximately 66%. With this IF at interim analyses, a one-sided type I error of 0.0058 will be used for interim analysis with 332 events for early efficacy, and final analysis will be carried out at one-sided type I error of 0.0232 to preserve overall type I error at one sided 2.5%.

5.6.2 Type I error control for testing multiple endpoints

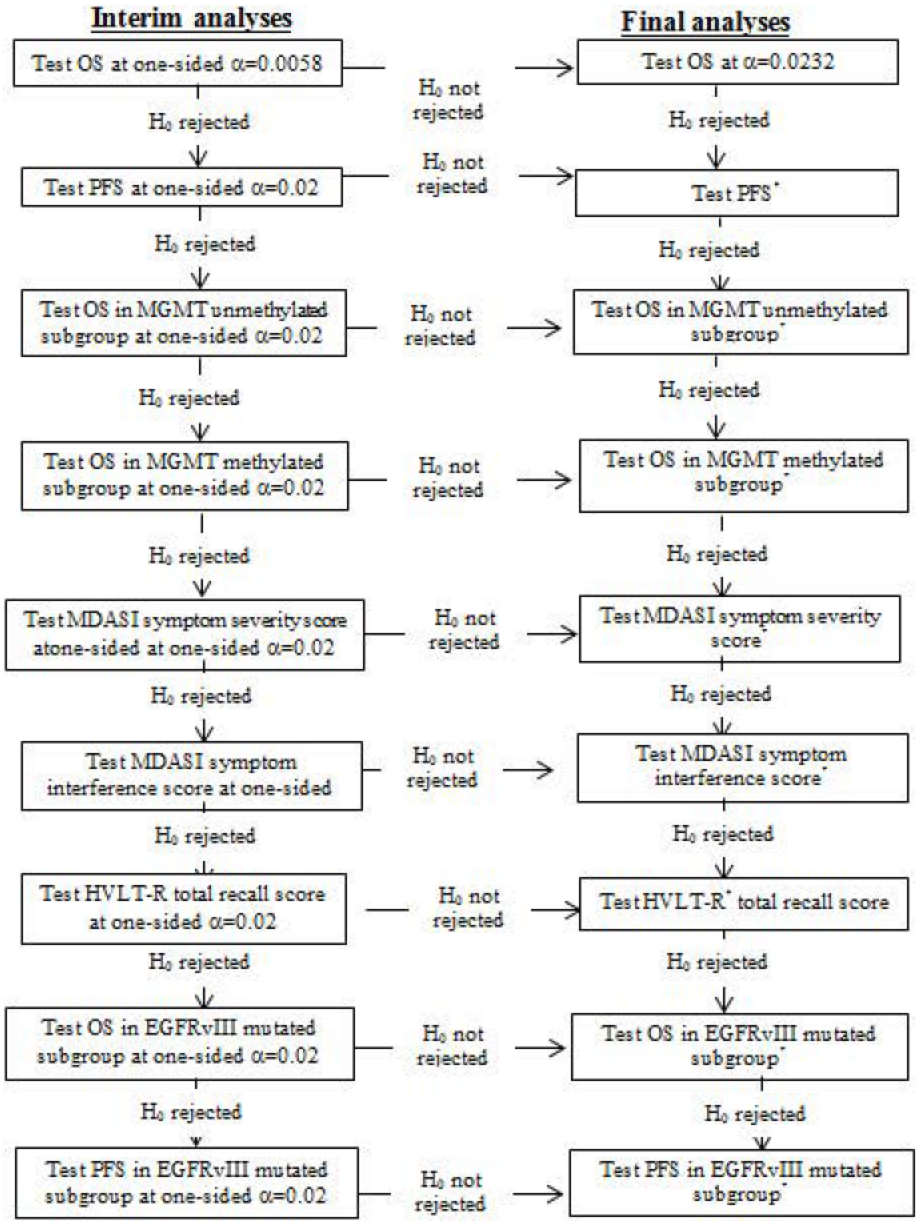
As mentioned above, the overall one-sided type I error for testing the primary and all secondary endpoints will be preserved at 2.5%. The primary and secondary endpoints will be tested using a fixed-sequence hierarchical testing strategy. At each analysis timepoint (i.e., interim and final analyses), the treatment effects on primary and secondary endpoints will be tested in the following order.

Testing Order	Endpoint
1	OS
2	PFS, centrally assessed
3	OS for the MGMT unmethylated tumor subgroup
4	OS for the MGMT methylated tumor subgroup
5	Deterioration free survival in MDASI-BT symptom severity score
6	Deterioration free survival in MDASI-BT symptom interference score
7	Deterioration free survival in HVLT-R Total recall score
8	OS for the EGFRvIII-mutated subgroup
9	PFS for the EGFRvIII-mutated subgroup

To protect overall Type I error across primary and all the secondary endpoints, we will follow "overall hierarchical" testing strategy.[11] The O'Brien Fleming alpha spending function will be used for the OS endpoint. For all the secondary endpoints one-sided alpha of 0.02 will be allocated for the interim analysis; the alpha spend in the final analysis will be calculated using the group sequential design methodology and estimated information fraction at interim analysis. For example, the one-sided alpha for the PFS endpoint in the final analysis would be 0.014 and 0.018 if the information fraction at the interim analysis is 0.8 and 0.9, respectively. The interim analysis will be driven by the timing of observed 332 OS events.

All endpoints will be tested for between arm differences at the interim and final analyses. The testing procedure displayed in Figure 2 will be used to determine statistical significance and thus will guide the interpretation of the results.

Figure 2. Testing procedure (all the tests are one-sided)



* The alpha for the final analysis will be calculated using the group sequential design methodology and estimated information fraction at interim analysis.

6.0 Analysis Populations

The database for Study M13-813 includes subjects for the main part of the study as well as patients in the China sub-study (which enrolls Chinese patients) and hepatic impairment sub-study. The main part of the study targeted enrollment of 640 randomized subjects (i.e., not including open-label hepatic sub-study subjects). The enrollment of the main part of the study was closed on 31-Mar-2018, and all subjects randomized by that date were to be included in the main study analysis population. Enrollment for the Chinese sub-study cohort remains ongoing, and Chinese subjects enrolled after 31-Mar-2018 will not be included in the main study analysis population. Patients enrolled in the open-label hepatic impairment sub-study will not be included in the main study analysis population.

A total of 639 subjects, including 2 subjects in the Chinese cohort, were enrolled by 19-Mar-2018 and will be included in the main study analysis population.

6.1 Definition of Analysis Populations

6.1.1 Efficacy Populations

Full Analysis Set (FAS) will comprise all randomized subjects regardless of whether they received study treatment satisfying the following criteria:

- Enrollment date was on or prior to 31-Mar-2018
- Enrolled in the main study (not in the open-label hepatic sub-study)

Subjects will be classified in the treatment groups, "Depatux-M + RT/TMZ" or "PBO + RT/TMZ," according to the treatment they were assigned at the time of randomization. Unless otherwise specified (and except for subgroup and sensitivity analyses), the FAS will be the default dataset for analysis of efficacy data.

Per-protocol Set (PPS) will be comprised of a subset of patients in FAS. Subjects meeting any of the following criteria will be excluded from PPS:

- Those entered into the study even though did not satisfy the entry criteria
- Those who developed withdrawal criteria during the study but were not withdrawn
- Those who received the wrong treatment
- Those who received an excluded concomitant treatment

Subjects will be classified according to treatment assigned.

6.1.2 Safety Populations

Safety Analysis Set will be comprised of a subset of subjects who receive at least one dose of study treatment (either RT, TMZ or Depatux-M) satisfying the following criteria:

- Enrollment date was on or prior to 31-Mar-2018
- Enrolled in the main study (not in the open-label hepatic sub-study)

Subjects will be classified according to the treatment they had received (as-treated).

7.0 Analysis Conventions

7.1 Definition of Baseline

The baseline for all the parameters except the steroids use is defined as the last non-missing measurement collected prior or on the first dose date of study drug (i.e., Study Rx Day $\leq$ 1). For steroid use, the baseline is defined as the average dose taken during Study Day –14 to Study Day –1.

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, either the arithmetic average (for continuous summary) or the worst value (e.g., for shift tables) will be used for further analyses.

7.3 Definition of Treatment Emergent Observation for Safety Analysis

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/Placebo.

If an incomplete onset date is collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that is it not.

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 pre-dating 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 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/Placebo) 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

Adjuvant Rx Day is defined only for observations made during the Adjuvant phase and is defined as the number of days from the day of the first dose of any study drug (TMZ or Depatux-M/Placebo) in the Adjuvant Phase to the date of observation. It is calculated for each observation in adjuvant and follow-up phases as follows:

Adjuvant Rx Day = Date of observation – Date of first dose of any study drug in adjuvant phase + 1

7.5 Definition of Visit Windows

Visit windows for individual endpoints will be defined according to their planned collection schedule. All time points and corresponding time windows will be based on Study Rx Days (i.e., days since first dosing in chemo-radiation phase) for the assessments that are scheduled to be collected after first dosing in chemo-radiation phase but before adjuvant phase. For the assessments that are scheduled to be collected after first dosing in adjuvant phase but before adjuvant phase time windows will be based on Adjuvant Rx Days (i.e., days since first dosing in adjuvant phase). If more than one observation is included in a time window, the observation closest to the planned day should be used. If there are two observations equidistant from the nominal day, the later one will be used in analyses.

Per protocol, subjects receive Chemoradiation for 6 weeks (up to 7 weeks), followed by an approximately 4-week treatment-free period before starting Adjuvant treatment.

7.5.1 Definition of Visit Windows for HRQoL and Neurocognitive Function assessments

Visit windows for the HRQoL and Neurocognitive function assessments are displayed Table 1.

Table 1. Visit window for HRQoL and Neurocognitive Function assessments

Scheduled Visit	Nominal Adjuvant Rx Day	Time Window
Baseline	Rx Day ≤ 1	Rx Day –21 to Rx Day 1
Adjuvant Phase Week 1	Adjuvant Rx Day 1	Rx Day 2 to Adjuvant Rx Day 29
Adjuvant Phase Week 9	Adjuvant Rx Day 57	Adjuvant Rx Day 30 to Adjuvant Rx Day 85 (i.e., Week 9 Day 1 ± 4 weeks)
Adjuvant Phase Week 17	Adjuvant Rx Day 113	Day 86 to Day 141 (i.e., Week 17 Day 1 ± 4 weeks)
	…	
Adjuvant Phase Week (8*X + 1)	Adjuvant Rx Day (56*X + 1)	Adjuvant Rx Day 56*X + 1 - 27 to Adjuvant Rx Day 56*X + 1 + 28 (i.e., Week (8*X + 1) Day 1 ± 4 weeks)

7.5.2 Definition of Visit Windows for Laboratory assessments

Visit windows for the biochemistry and hematology assessments are displayed Table 2 and Table 3.

Table 2. Visit window for biochemistry and hematology lab parameter assessments in chemo-radiation phase

Scheduled Visit	Nominal study Rx Day	Time Window (Study Rx Day Range)
Baseline	≤ 1	–21 to 1 days
Week 2	8	2 to 11 days
Week 3	15	12 to 18 days
Week 4	22	19 to 25 days
Week 5	29	26 to 32 days
Week 6	36	33 to 39 days
Week 7	43	40 to Adjuvant Rx Day –8*

* replace Adjuvant Rx Day – 8 by end of chemo-radiation phase, if no adjuvant dosing was done.

Table 3. Visit window for hematology and biochemistry lab parameter assessments in adjuvant phase

Scheduled Visit	Nominal Adjuvant Rx Day	Time Window (Adjuvant Rx Day Range)
Adjuvant phase Week 1	Day 1	Day –7 to Day 1
Adjuvant phase Week 5	Day 29	Day 2 to Day 43
Adjuvant phase Week 9	Day 57	Day 44 to Day 71
…	…	…
Adjuvant phase Week (4*X +1)	Day (28*X + 1)	Day 28*X + 1 - 13 to Day 28*X + 1 + 14 (i.e., Week (4*X + 1) Day 1 ± 2 weeks)
Final study drug visit	NA	As indicated in study visit
35-day follow-up	NA	As indicated in study visit

7.5.3 Definition of Visit Windows for Vital signs and KPS assessments

Visit windows for vital sign and KPS assessments are displayed Table 4 and Table 5.

Table 4. Visit window for vital signs and KPS assessments in chemo-radiation phase

Scheduled Visit	Nominal study Rx Day	Time Window (Study Rx Day Range)
Baseline	≤ 1	–21 to 1 days
Week 3	15	2 to 22 days
Week 5	29	23 to Adjuvant Rx Day –8*

* replace Adjuvant Rx Day –8 by end of chemo-radiation phase, if no adjuvant dosing was done.

Table 5. Visit window for vital signs and KPS assessments in adjuvant phase

Scheduled Visit	Nominal Adjuvant Rx Day	Time Window (Adjuvant Rx Day Range)
Adjuvant phase Week 1	Day 1	Day –7 to Day 1
Adjuvant phase Week 3	Day 15	Day 2 to Day 22
Adjuvant phase Week 5	Day 29	Day 23 to Day 36
Adjuvant phase Week 7	Day 43	Day 37 to Day 50
…	…	…
Adjuvant phase Week (2*X + 1)	14*X +1	14*X + 1 – 6 to 14*X + 1 + 7 days
Final study drug visit	NA	As indicated in study visit
35 day follow-up	NA	As indicated in study visit

7.5.4 Definition of Visit Windows for Targeted ophthalmology exams (TOE) assessments

Visit windows for the TOE assessments are displayed Table 6 and Table 7.

Table 6. Visit window for TOE assessments in chemo-radiation phase

Scheduled Visit	Nominal study Rx Day	Time Window (Study Rx Day Range)
Baseline	≤ –1	–21 to 1 days
Week 4	22	2 to 29 days
Week 6	36	30 to Adjuvant Rx Day –8*

* replace Adjuvant Rx Day –8 by End of chemo-radiation phase, if no adjuvant dosing was done.

Table 7. Visit window for TOE assessments in adjuvant phase

Scheduled Visit	Nominal Adjuvant Rx Day	Time Window (Adjuvant Rx Day Range)
Adjuvant phase Week 1	Day 1	Day –7 to Day 1
Adjuvant phase Week 9	Day 57	Day 2 to Day 85
Adjuvant phase Week 17	Day 113	Day 86 to Day 141 (i.e., Week 17 Day 1 ± 4 weeks)
	…	
Adjuvant Phase Week (8*X + 1)	Day (56*X + 1)	Day 56*X + 1 - 27 to Day 56*X + 1 + 28

7.5.5 Definition of Visit Windows for steroids dosing

For steroid use, the baseline window is defined as Study Rx Day –14 to Study Rx Day –1.

The post-baseline window is defined as Study Rx Day 1 (i.e., day of first dosing) to last dosing date of Depatux-M/Placebo in the study + 49 days.

7.6 Data Handling Convention at Database Level

There is no applicable data handling convention at database level.

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

Data for demographic, baseline characteristics, medical history, prior/concomitant medications, and cancer history will be summarized by treatment groups using the FAS population.

8.1 Demographic and Baseline Characteristics

The following demographic, current disease history and baseline disease characteristics (including stratification variables) will be summarized by treatment groups.

Demographic variable	Baseline disease characteristics

• 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, Han Chinese, Other)
• Age
  ○ < 18, 18 - < 65, 65 - < 75, ≥ 75 yr
• History of tobacco product use and alcohol use (current, former, never, unknown)
• Region of the world (North America vs Rest of the world)
	• Histology (Glioblastoma, Gliosarcoma, Other)
	• Level of neurological function (worse than minor neurofunction impairment, no worse)
	• RPA classes (III, IV, V)
	• MGMT methylation status (methylated, unmethylated, indeterminate)
	• EGFRvIII status (mutated or other).
	• Karnofsky performance status (KPS)
	  ○ < 70, 70 - < 90, ≥ 90

	Baseline disease status
	• Time since diagnostic GBM surgery to start of study treatment • Systemic corticosteroid use (yes/no) • Type of surgery (Gross total resection, partial resection, biopsy)

Continuous variables will be summarized with N, mean, standard deviation (SD) median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical variables.

8.2 Medical and Surgical History

Medical and surgical history data will be summarized and presented using body systems and conditions/diagnoses 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 with a particular condition/diagnosis will be summarized for each arm. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

There will be no statistical comparison between the treatment and placebo arms. Listing of medical and surgical history will be provided along with start date, CTCAE grade and symptomatic or requiring treatment status at study entry (Yes/No).

8.3 Prior/Concomitant Medications (excluding protocol-required prophylactic eye drops)

Prior medications are any medications excluding the protocol-required prophylactic eye drops with start date 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. For reporting purpose, the following conservative approach will be followed for determination of prior and concomitant medication:

Start date	**End date**	
Prior to Study Day 1	Prior to Study Day 1	Prior medication
Missing	Prior to Study Day 1	Prior medication
Prior to Study Day 1	Study Day 1 to Last dose + 49 day	Both prior medication and concomitant medication
Study Day 1 to Last dose + 49 day	Study Day 1 to Last dose + 49 day	Concomitant medication
Missing	Study Day 1 to Last dose + 49 day	Concomitant medication
Study Day 1 to Last dose + 49 day	Missing	Concomitant medication
Missing	Missing	Concomitant medication

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. In addition, the number of prior and concomitant medications will also be presented for each treatment arm. There will be no statistical comparison for the prior and concomitant medications between treatment arms.

8.4 Prior/Concomitant Medications (protocol-required prophylactic eye drops)

Concomitant use of eye drops from screening will be summarized by generic name. 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 entered adjuvant phase, subjects who completed 6 or more TMZ cycles in adjuvant phase, subjects who completed 12 or more Placebo/Depatux-M cycles in adjuvant phase, and subjects discontinued from the study.

In addition, a subject disposition summary will be presented on the FAS by treatment group and overall, including the following information

- Subjects randomized
    i. Subjects did not receive any study drug
    ii. Subjects received randomized study drug
    iii. Subjects received other than randomized study drug
- Subjects entered in Adjuvant Phase
- Subjects entered in survival follow-up phase
- Reason for discontinuation from study

In addition, median follow up time, number of patients alive on treatment period, number of patients alive in the follow-up period, and reason for study drug discontinuations will be summarized by treatment arms.

9.2 Study drug exposure

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

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

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

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

- Overall treatment duration for Depatux-M/Placebo and TMZ, separately
- Percentage of patients received cumulative dose of RT < 57 Gy, 57 - 63 Gy, > 63 Gy
- Number of doses of Depatux-M/Placebo and TMZ in chemo-radiation phase, separately
- Cumulative doses (mg/kg) of Depatux-M/Placebo and TMZ in chemo-radiation phase, separately
- Weekly dosing of Depatux-M/Placebo in chemo-radiation phase
- Number of cycles of Depatux-M/Placebo and TMZ in adjuvant phase, separately
- Number of doses of Depatux-M/Placebo in adjuvant phase

10.0 Efficacy Analysis

10.1 General Considerations

For the analysis of efficacy endpoints, the Full Analysis Set (FAS) will be the primary analysis set whereas the Per Protocol Set (PPS) will be used for supportive analysis only. Analysis for the sub-groups will be carried out in the subset of FAS meeting the sub-group selection criteria at the enrollment.

For Deterioration free survival of HRQoL and neurocognitive measures and change from baseline analysis, patients with missing baseline value will be excluded. Descriptive summaries for the efficacy endpoints will be reported by treatment groups. These summaries will also be reported at the individual levels of each stratification factors. There will be additional exploratory analyses for the HRQoL and neurocognitive data and the detailed analysis plan is documented in "Analysis of PRO/COA Instruments in the Phase 3 Intellance-1 Study" [AbbVie Project ID – HEOR - 00000880].

The statistical comparisons for the primary and secondary endpoints will be done according to the multiplicity adjustment plan described in Section 5.6.2 to preserve the familywise one-sided type 1 error rate to 0.025. The statistical comparisons for all the other exploratory efficacy endpoints will be performed at a nominal one-sided 2.5% significance level. Confidence intervals for parameters (e.g., median survival times, HR) will be constructed with 2-sided 95% confidence level, whenever applicable. No type I error adjustment for multiple comparisons will be carried out for these exploratory endpoints.

10.1.1 Analysis of Efficacy Endpoints by Variable Type

Time to events (TTE) variables

All TTE endpoints defined in this study are concerned with only the first incidence of an event of interest, and recurrence of the same event is not considered for endpoint derivation. An event however may be defined in a composite manner, i.e., as the occurrence of one among several different outcomes. The composite event is observed when at least one of the component events occurs, and the time to the earliest among the occurring component events is considered to be the TTE for the composite event.

Follow-up time for TTE endpoints will be derived as follows:

Date of first occurrence of an event or censoring – date of randomization + 1.

TTE endpoints will be computed in days and converted into months (1 month = 30.4375 days) for analysis. Thus, for subjects who experience the event of interest, time to event will be defined as the time from randomization to the first occurrence of the event. When multiple assessments are needed to ascertain the occurrence of an event, the earliest date among all of these assessments is taken to be date of the event or censoring. For a subject who does not experience an event on the study, time will be right censored at the time of his last available adequate post-baseline assessment that rules out the occurrence of the event. If a subject had no post-baseline assessment and did not experience the event of interest, then TTE will be censored at the date of randomization and we will set TTE = 1 day, by convention.

TTE endpoints will be summarized by number of events observed, number of subjects censored, and times corresponding to 25% (1st quartile), 50% (median) and 75% (3rd quartile) event probabilities. Kaplan-Meier (KM) estimates[15] will be calculated and plotted. Comparison between treatment arms will be based on stratified weighted log-rank tests (only for OS) or stratified log-rank tests (for other TTE endpoints) as specified. Measure of treatment effects will be provided in term of HR (Depatux-M + RT/TMZ to Placebo + RT/TMZ) from Cox proportional hazards regression model adjusting for the main effects of the stratification factors with HR value less than 1 representing treatment benefit.

Deterioration Free Survival (DFS) variables for PRO assessments

All the DFS endpoints defined in this study are concerned with only the first incidence of a deterioration, and recurrence of the same event is not considered for endpoint derivation. The deterioration is defined as satisfying the deterioration criteria without further improvement (i.e., failing to satisfy deterioration criteria) within 8 weeks or occurrence of death. Follow up time for all DFS endpoints will be derived as follows:

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

In case there is no subsequent assessment within 8 weeks of first documented deterioration, the date of first documented deterioration will be considered as date of deterioration. For time-to-deterioration endpoints, death will be considered as event. If a subject had no post-baseline assessment and did not experience the event of interest, then DFS will be censored at the date of randomization and we will set DFS = 1 day, by convention. Also for the subjects with missing baseline, DFS will be censored at the date of randomization.

Continuous variables

Summary of continuous endpoints (e.g., change from baseline) will include the mean, standard deviation, median and range. In the context of change from baseline analyses, summary of baseline and post-baseline data will also be provided. Change from baseline analyses will be analyzed by an analysis of covariance (ANCOVA) model including stratification factors and baseline as covariates and 95% CI for treatment group difference will be provided.

10.1.2 Missing Data Imputation for Efficacy Endpoints

No imputation of missing data is planned for the primary and secondary endpoints of this study. For TTE, if the event of interest is not observed for a subject in the study, such as when the subject is lost to follow-up, the endpoint will be right censored at the last adequate observation time when occurrence of an event can be ruled out. For patient reported outcomes (PRO) including MDASI-BT symptom score, QLQ-C30, and QLQ BN20, the imputation strategies will be based on the scoring manuals and no additional imputation will be done.

10.2 Primary Efficacy Analysis

The primary endpoint OS will be compared between treatment arms Depatux-M + RT/TMZ and Placebo + RT/TMZ. Superiority of Depatux-M + RT/TMZ to Placebo + RT/TMZ in terms of OS will be evaluated using stratified weighted log-rank test, adjusting for the study stratification factors. Recently available data from the

INTELLANCE-2 trial[27] as well as published studies on GBM patients[22,25] suggest increasing separation over time. To account for the possibility of late separation in OS (and consequently, non-proportional hazards), use of a weighted log-rank test in a pre-specified manner is considered to be a more appropriate and statistically efficient test to detect statistical differences in OS compared to the standard log-rank test. Under the weighted log-rank test, each event is weighted differently based on timing of the events from randomization. The Fleming-Harrington (FH) version of weighted log rank test[10] will be used with following weight function:

$$w(t|\rho,\gamma) = \left[\hat{S}_{KM}(t)\right]^{\rho}\left[1-\hat{S}_{KM}(t)\right]^{\gamma}, \qquad \rho,\gamma \geq 0$$

where, $\hat{S}_{KM}(\cdot)$ is the KM estimate of the survival function in the pooled data. The events that occur later in the study should get more weights to account for late separation. This can be achieved with parameters, $\rho = 0$ and $\gamma > 0$. In this study, we pre-specify $\rho = 0$ and $\gamma = 0.2$ for the FH weights in the weighted log-rank test.

The Fleming-Harrington (FH) version of weighted log-rank tests are well recognized statistical methods that do not inflate the type 1 error if pre-specified.[9,24] The hazard-ratio of OS for Depatux-M + RT/TMZ compared to Placebo + RT/TMZ will be estimated by fitting Cox-proportional hazards regression models adjusting for the main-effects of the stratification factors.

This FH test will be implemented in SAS using LIFETEST procedure as follows:

```
proc lifetest method=km;
   time <follow-up time>*<Censoring status>(<censoring codes>);
   strata <stratification factors> / group=<treatment>
                          test=FLEMING(0, 0.2) trend;
run;
```

The hazard-ratio of OS for Depatux-M + RT/TMZ compared to Placebo + RT/TMZ will be estimated by fitting Cox-proportional hazards regression models adjusting for the main effects of the stratification factors. Treatment difference in restricted mean survival time (RMST) up to 24 and 30 months will also be estimated.

Estimation of HR

A Cox proportional-hazards regression model[6] with the treatment and stratification factors as covariates will be used to estimate the HR of Depatux-M + RT/TMZ to Placebo + RT/TMZ and its two-sided 95% CI:

$$\lambda(t|\text{treatment, stratum } s) = \lambda_0(t) \cdot \exp(\theta \cdot \text{treatment} + \phi_1 \cdot x_1 + \phi_2 \cdot x_2 + \phi_3 \cdot x_3 + \phi_4 \cdot x_4)$$

where, treatment takes value 1, if treated with Depatux-M + RT/TMZ, otherwise 0, for Placebo + RT/TMZ. x_1, x_2, x_3 and x_4 represent the coefficient for the 4 stratification factors, namely, region of the world, RPA class, MGMT methylation status, and EGFRvIII status. The estimated value of exp(θ) represents the hazard ratio on Depatux-M + RT/TMZ (adjusting for the effect of stratification factors) compared to Placebo + RT/TMZ. Effron's approximate method (1977) will be used for handling ties. In SAS, the estimate of HR will be estimated using PHREG procedure and Effron's method[7] will be employed by using TIES = EFFRON option in MODEL statement.[20] The following SAS code will be used

```
PROC PHREG;
  CLASS <treatment> <strata variables>;
  MODEL <follow-up time>*<Censoring status>(<censoring codes>)=
<treatment> <strata variables>/TIES=EFFRON RL;
RUN;
```

Supportive analysis: Difference in restricted mean survival time (RMST)

RMST up to 24 months and 30 months will be reported in each treatment arm separately. Difference between treatment arms will also be reported. RMST is expressed as

$$E[\min(\text{OS time}, t^*)] = \int_0^{t^*} S(t)dt$$

where t^* (24 or 30) represents the restriction. In SAS, RMST will be calculated using TIMELIM option in LIFETEST procedure as follows after censoring the largest observation:

```
PROC LIFETEST TIMELIM=<24 or 30>;
  TIME <follow-up time>*<Censoring status>(<censoring codes>);
  STRATA <treatment>;
RUN;
```

10.3 Secondary efficacy analysis

Secondary efficacy endpoints are defined in Section 5.3.2. Each of the following secondary efficacy endpoints will be analyzed in the order it is mentioned:

1. PFS per central assessment
2. OS for the MGMT unmethylated subgroup
3. OS for the MGMT methylated subgroup
4. Deterioration free survival in MDASI-BT symptom severity score
5. Deterioration free survival in MDASI-BT symptom interference score
6. Deterioration free survival in HVLT-R total recall score
7. OS for the EGFRvIII-mutated tumor subgroup
8. PFS (assessed centrally) for the EGFRvIII-mutated tumor subgroups

OS for the EGFRvIII-mutated tumor subgroup will be analyzed in the subset of FAS using stratified weighted log-rank test (FH ($\rho = 0$, $\gamma = 0.2$)) with stratification factors as region of the world, RPA classes and MGMT methylation status. OS for the MGMT methylated subgroups will be analyzed in the subset of FAS using stratified weighted log-rank test (FH ($\rho = 0$, $\gamma = 0.2$)) with stratification factors as region of the world, RPA classes and EGFRvIII status.

Remaining secondary endpoints (#1, #4, #5, #6, and #8 in the above list) will be analyzed in the FAS using the standard stratified log-rank test. Standard log-rank test will be carried out in SAS using PHREG procedure specifying TEST = LOGRANK and TREND option in the STRATA statement as follows:

```
proc lifetest method=km;
   time <follow-up time>*<Censoring status>(<censoring codes>);
   strata <stratification factors> / group=<treatment>
                          test=LOGRANK trend;
run;
```

10.4 Other efficacy analyses

10.4.1 Additional analyses based on OS, centrally assessed PFS and local investigator assessed PFS

Kaplan-Meier (KM) estimate of OS rates and centrally assessed PFS rates at 0.5, 1, 2, 2.5, 3, 4, and 5 years will be determined for each treatment group along with 95% confidence intervals (CIs) based on Greenwood's method. Estimates will be provided both in overall population and for the subgroups based on stratification factors.

PFS per local investigator assessment will be analyzed using the same statistical methodology as that for the centrally assessed PFS described in Section 10.3.

10.4.2 Analyses of QLQ-C30 and QLQ-BN20 response

Change from baseline in Global Health Status score, Physical Functioning, Cognitive Functioning, Role Functioning in QLQ-C30 questionnaire

Change from baseline in Visual Disorder, Motor Dysfunction, and Communication Disorder scale in QLQ-BN20 questionnaire

Baseline data along with post-baseline and change from baseline at each visit will be descriptively summarized. The treatment group differences will be evaluated by analyzing the change from baseline to each of the post-baseline time-point and to the final measurement (last QoL assessment per subject) using an analysis of covariance

(ANCOVA) model adjusting for baseline and stratification factors. Treatment difference along with 95% confidence interval will be provided.

10.4.3 Analysis of EQ-5D-5L index value and EQ VAS score

Change from baseline in EQ-5D-5L index value and EQ VAS score will be analyzed in a similar way to that described in "Change from baseline" in Section 10.4.2.

10.4.4 Analysis of COWA-FAS verbal fluency score

Verbal fluency score obtained from COWA-FAS verbal fluency test will be analyzed for change from baseline by using methods described in Section 10.4.2.

Deterioration Free Survival in verbal fluency score will be analyzed in the FAS using the standard stratified log-rank test with stratification factors as region of the world, RPA classes, MGMT methylation status, and EGFRvIII status.

10.4.5 Additional analysis of HVLT-R scores

Total Recall score, Delayed Recall score and Recognition Discrimination Index obtained from HVLT-R will be analyzed separately for change from baseline, by using methods described in Section 10.4.2.

10.4.6 Analysis of KPS score

KPS score will be analyzed for change from baseline by using methods described in Section 10.4.2. Time-to- KPS < 70 will be analyzed by the standard stratified log-rank test with stratification factors as region of the world, RPA classes and EGFRvIII status. In addition, median time to KPS score was maintained at 70 or higher will be obtained for each treatment arm through Kaplan-Meier analysis considering death, progression, or KPS < 70 as event.

10.4.7 Additional analyses for MDASI-BT symptom severity score

Following endpoint will be analyzed in a similar way to that described in "Change from baseline" in Section 10.4.2:

- Change from baseline in MDASI-BT symptom severity score
- Change from baseline in MDASI-BT symptom interference score
- Change from baseline in neurologic domain score
- Change from baseline in cognitive domain score
- Change from baseline in treatment domain score
- Change from baseline in Vision item score (one of the 9 brain tumor-specific items)
- Change from baseline in MDASI-BT activity-related score
- Change from baseline in MDASI-BT mood-related score

10.4.8 Analysis of corticosteroid use data

Change from baseline in average daily (dexamethasone equivalent) corticosteroid dosing during the treatment period will be analyzed in a similar way to that described in "Change from baseline" in Section 10.4.2.

10.5 Sensitivity Analyses

Sensitivity analyses will be conducted to evaluate the robustness of efficacy results. PFS and OS will be analyzed in the PPS using the same statistical methodology.

The primary endpoint of OS will be analyzed based on a stratified log-rank test, adjusting for the study for the study stratification factors.

Two sensitivity analyses will be carried out for PFS endpoint by implementing different censoring rules in the definition of PFS (i.e., modified PFS endpoint). These sensitivity analyses will be conducted in the FAS population using the same statistical methodology as that for the PFS endpoint described in Section 10.3.

Sensitivity analysis 1: PFS as time from randomization to the date of progression of disease (PD) assessed centrally per RANO criteria or death, whichever occurs first. Subjects without an event will be right-censored at the date of last follow up for disease progression.

Sensitivity analysis 2: PFS as time from randomization to the date of progression of disease (PD) assessed centrally per RANO criteria or death, whichever occurs first. Subjects with 2 or more consecutive missed assessments (i.e., > 20 weeks since last RANO assessment) without any subsequent assessment prior to the PFS event (i.e., progression or death) will be considered progressed at the planned date of the earliest missed RANO assessment (i.e., last scan date prior to event + 8 weeks). Subjects without an event will be right-censored at the date of last follow up for disease progression.

As a sensitivity analysis, at each post-baseline assessment, change in standardized HVLT-R total recall score relative to baseline will be calculated and categorized as deteriorated or not using the reliable change index (RCI) criterion based on the raw scores. The details are provided in Appendix I. Deterioration free survival in HVLT-R total recall score (using the RCI criterion) will be analyzed using the stratified log-rank test.

10.6 Subgroup Analyses

Efficacy endpoints (OS and PFS) will be assessed for the following subgroups on an as-stratified basis at randomization using the similar methodologies described in Section 10.2 and Section 10.3.

- Region of the world (North America (includes USA and Canada) and rest of the world (ROW))
- RPA classes (III, IV, and V)
- *MGMT* methylation (methylated and unmethylated)
- *EGFRvIII* status (mutated and other)

In addition, Forest plot for OS and PFS will be generated to display the HR with 95% CI for the subgroups defined by stratification factors, age categories (< 65, 65 - < 75,

≥ 75 years), gender (male and female), KPS categories (< 80, 80 - 90, 100), time from diagnostic GBM surgery to start of study treatment (< 4, 4 - 6, > 6 weeks), and type of surgery (gross total resection, partial resection, biopsy).

10.7 Pharmacokinetic Analyses

Analysis of pharmacokinetics of Depatux–M, total ABT-806, and free cys-mcMMAF are not covered in this SAP and will be described in a separate document.

11.0 Safety Analyses

11.1 General Considerations

Safety analysis will be carried out in the safety population. For most the safety endpoints (e.g., AEs, lab values, vital sign values and ECG values) except for TOE assessments, only the treatment emergent (TE) assessments (as defined in Section 7.3) will be included in the analyses. Incidence of TEAEs and treatment emergent lab abnormalities will be summarized in chemo-radiation phase and adjuvant phase separately and also in the overall study. A summary of continuous safety endpoints (e.g., change from baseline values in laboratory values, vital signs parameters) will include the mean, standard deviation, median and range. In the context of change from baseline analyses, summary of baseline and post-baseline data will also be provided. Categorical safety endpoints (e.g., incidence of AEs, incidence of potentially clinically significant values) will be summarized using frequencies and percentages. All the analyses will be carried out by treatment groups.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events (TEAEs)

TEAEs are defined as any AE with onset or increased severity after the first dose of study drug (RT/TMZ/Depatux–M or matching placebo) and no more than 49 days after the last dose of Depatux-M/placebo. Incidence of TEAEs will be summarized in chemo-radiation phase and adjuvant phase separately and also in the overall study.

Chemo-radiation phase is defined as from the Study Rx Day 1 to the day before the first adjuvant dosing. If adjuvant dosing is missing then, last Depatux-M/Placebo dosing + 49 days would be the end date of chemo-radiation phase. Adjuvant phase is defined as day of first adjuvant dosing to the last Depatux-M/Placebo dosing + 49 days.

Adverse Event Overview

The number and percentage of subjects experiencing TEAEs between the treatment groups will be summarized for the following adverse event categories.

- Any TEAE
- Any TEAE possibly related to any study drug
- Any TEAE possibly related to Depatux-M, TMZ and RT, separately
- Any TEAE with CTCAE grade 3 or higher
- Any TEAE with CTCAE grade 4 or higher
- Any Grade 3 or higher TEAE possibly related to any study drug
- Any Grade 3 or higher TEAE possibly related to Depatux-M, TMZ and RT, separately
- Any Grade 4 or higher TEAE possibly related to any study drug
- Any Grade 4 or higher TEAE possibly related to Depatux-M, TMZ and RT, separately
- Any TE serious AE (SAE)
- Any TE SAE possibly related to any study drug
- Any TE SAE possibly related to Depatux-M, TMZ and RT, separately
- Any TEAE leading to discontinuation of Depatux-M or Placebo, TMZ and RT, separately
- Any TEAE leading to discontinuation of Depatux-M possibly related to any study drug
- Any TEAE leading to discontinuation of Depatux-M/Placebo, possibly related to Depatux-M
- Any TEAE leading to discontinuation of TMZ, possibly related to TMZ
- Any TEAE leading to discontinuation of RT, possibly related to RT

- Any TEAE leading to dose-reduction of any study drug
- Any TEAE leading to dose-interruption of any study drug
- Any TEAE leading to death
- Deaths

This overview output will also be generated for each AESI, separately.

Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing TEAEs will be tabulated according to the primary MedDRA system organ class (SOC) and MedDRA preferred term (PT) for each treatment group. Subjects reporting more than one adverse event for a given MedDRA PT will be counted only once for that term. Subjects reporting more than one type of adverse event within a MedDRA SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

AEs by Preferred Term

The number and percentage of subjects experiencing adverse events will be tabulated according to the MedDRA PT for each treatment group. Subjects reporting more than one AE for a given MedDRA PT will be counted only once for that term.

AEs by Maximum Severity

Adverse events will be summarized by SOC, PT and maximum severity per NCI CTCAE v.4 grading in each treatment arm. If a subject has an AE with unknown severity, then the subject will be counted in the severity category of "unknown," unless the subject does not have another occurrence of the same AE with a severity present. In addition, Grade 3 or higher AE and Grade 4 or higher events will also be summarized by SOC and PT.

AEs by Relationship

Adverse events possibly related to Depatux–M, TMZ, and radiotherapy as assessed by the investigator, will be summarized separately in each treatment arm. Following summaries

will be presented for the AEs possibly related to Depatux–M, TMZ, and radiotherapy, separately:

- Summary of AE by PT (possibly related to Depatux-M and TMZ only)
- Summary of AE by SOC and PT (possibly related to Depatux-M and TMZ only)
- Summary of Grade 3 or higher AE by SOC and PT
- Summary of Grade 4 or higher AE by SOC and PT
- Summary of SAE by SOC and PT
- Summary of Depatux-M/Placebo discontinuation by SOC and PT (possibly related to Depatux-M only)
- Summary of TMZ discontinuation by SOC and PT (possibly related to TMZ only)

If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," unless the subject does not have another occurrence of the same AE with a relationship present.

AE of special interest (AESI)

AESIs will be assessed and summarized using standardised MedDRA query (SMQ) or AbbVie-defined company MedDRA query (CMQ). The AESIs below include events related to identified or potential risks of Depatux-M (corneal epitheliopathy, hepatotoxicity), events that are anticipated to occur in the study population due to underlying GBM or RT/TMZ treatment and independent of depatuxizumab mafodotin exposure (seizures, venous thromboembolic events, thrombocytopenia, neutropenia, infection), and events commonly associated with biologic therapies (hypersensitivity reactions). Specific AESI will be identified by the following search criteria:

AESI	Search Criteria[a]
Corneal Epitheliopathy (corneal AE)	CMQ "80000184"; Preferred Terms: Topography corneal abnormal, Corneal abrasion, Injury corneal, Persistent corneal epithelial defect, Abnormal sensation in eye, Acquired corneal dystrophy, Conjunctival irritation, Corneal cyst, Corneal decompensation, Corneal defect, Corneal degeneration, Corneal deposits, Corneal disorder, Corneal epithelial microcysts, Corneal epithelium defect, Corneal erosion, Corneal exfoliation, Corneal hypertrophy, Corneal infiltrates, Corneal irritation, Corneal lesion, Corneal neovascularisation, Corneal oedema, Corneal opacity, Corneal perforation, Corneal striae, Corneal thinning, Dry eye, Excessive eye blinking, Eye irritation, Eye opacity, Eye pain, Eye paraesthesia, Eye pruritus, Eye ulcer, Foreign body sensation in eyes, Glare, Keratic precipitates, Keratitis, Keratitis interstitial, Keratitis sclerosing, Keratopathy, Lacrimation decreased, Lacrimation disorder, Lacrimation increased, Limbal stem cell deficiency, Noninfective conjunctivitis, Ocular discomfort, Ocular hyperaemia, Ocular surface disease, Ocular toxicity, Photophobia, Punctate keratitis, Scleral oedema, Scleral thinning, Superior corneal epithelial arcuate lesion, Superior limbic keratoconjunctivitis, Ulcerative keratitis, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Xerophthalmia, Cornea verticillata,
Hepatotoxicity	Drug related hepatic disorders - comprehensive search (Broad SMQ) – 20000006
Hepatotoxicity – severe events	Drug related hepatic disorders – severe events only (Broad SMQ) – 20000007
Thrombocytopenia	Haematopoietic thrombocytopenia Broad SMQ (SMQ, 20000031)
Neutropenia	Haematopoietic leukopenia Broad SMQ (SMQ 20000030)
Venous thromboembolic events	Embolic and thrombotic events, venous - Narrow SMQ (SMQ 20000084)
Infection events with 14 days after neutropenia events*	Infections - CMQ (CMQ 80000018) Hematological toxicity - neutropenia – Narrow CMQ (CMQ 80000154)
Hypersensitivity reactions	Hypersensitivity - Broad SMQ (SMQ 20000214)
Seizures	Convulsions - Narrow SMQ (SMQ – 20000079)

* Includes only infections that start anytime from start of neutropenia to end of neutropenia + 14 days.

a. Preferred terms are included in each CMQ are documented in ABT-414 Integrated Summary Safety (ISS) Statistical Analysis Plan.

Time to the first occurrence (onset) of any corneal AEs 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 2 or higher corneal AEs, Grade 3 or higher corneal AEs, and Grade 4 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 corneal AE. If a subject has not experienced an corneal AE, 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 or placebo), whichever is earliest. If the subject has not experienced a corneal AE and had no post-baseline assessment, the data will be censored on the day of first dosing date.

11.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs and AEs leading to Depatux–M/Placebo and TMZ discontinuation, dose reduction and dose interruption, and death will be summarized separately by SOC and PT in each treatment arm. Separate listings for SAEs, AEs leading to death and AEs leading to treatment discontinuation will also be provided.

11.2.3 Listing of Adverse Events

The following additional summaries of adverse events will be prepared.

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

11.3 Analysis of Depatux-M targeted ophthalmologic exam (TOE) results

The following assessments from the TOE will be analyzed using shift table for each treatment arm, separately.

- Visual acuity (20/10 - 20/20, 20/25 - 20/40, 20/50 - 20/100, 20/125 - 20/160, 20/200 OR worse) – Best eye and worst eye separately
- Microcysts/Edema (None/Trace/Mild/Moderate/Severe) – Worst eye
- Superficial Punctate Keratopathy (None/Trace/Mild/Moderate/Severe) – Worst eye
- Photophobia (None/Mild/Moderate/Severe) – Worst eye
- Eye Pain (Yes /No) – Worst eye

For each of the endpoints above, summary tables and shift tables will be created for the timepoints:

For all subjects in the safety population:

- baseline value
- worst value in chemo-radiation phase
- worst value in whole study
- final value on treatment (up to 49 days after last dose)
- last value in follow-up

For subjects who received at least one adjuvant dose of any study treatment:

- baseline value
- worst value in chemo-radiation phase
- last value in chemo-radiation phase
- worst value in adjuvant phase
- final value in adjuvant phase (up to 49 days after last dose)
- last value in follow-up

Data will be summarized by n (%) by severity level at each of the above timepoints. Shift tables will be produced for baseline to post-baseline timepoint for each of the endpoints above.

Chemo-radiation phase is defined as from the Study Rx Day 1 to the day before the first adjuvant dosing. If adjuvant dosing is missing then, last Depatux-M/Placebo dosing + 49 days would be the end date of chemo-radiation phase. Adjuvant phase is defined as day of first adjuvant dosing to the last Depatux-M/Placebo dosing + 49 days. Follow-up phase starts after last Depatux-M/Placebo dosing + 49 days to the study completion.

In addition, selected continuous TOE endpoints will be summarized for change from baseline.

11.4 Analysis of Laboratory Data

The hematology and clinical chemistry lab parameters listed in Table 8 are planned to be collected for each subjects at baseline and scheduled post-baseline visits. The urinalysis lab parameters are planned to be collected at baseline only.

Table 8. Clinical laboratory test

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

11.4.1 Variables and Criteria Defining Abnormality

NCI CTCAE v. 4 grading criteria for laboratory abnormalities are shown in Table 9 and Table 10.

Table 9. Criteria for NCI CTCAE Grades for Laboratory Values Hematology Variables

	Units	NCI CTCAE Grade ≥ 3		NCI CTCAE Grade ≥ 4	
		Low	High	Low	High
Hematology Variables					
Hemoglobin	g/L	< 80	> ULN + 40		
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*		

* Or baseline if on antigoagulation.

Table 10. Criteria for NCI CTCAE Grades for Laboratory Values - Chemistry Variables

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
Alanine aminotransferase (ALT/SGPT)	U/L		> 5 × ULN		> 20 × ULN
Aspartate aminotransferase (AST/SGOT)	U/L		> 5 × ULN		> 20 × ULN
Alkaline phosphatase (ALP)	U/L		> 5 × ULN		> 20 × ULN
Gamma glutamyl transferase (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
Glucose	mmol/L	< 2.2	> 13.9	< 1.7	> 27.8
Cholesterol	mmol/L		> 10.34		> 12.92
Triglycerides	mmol/L		> 5.7		> 11.4
Albumin	g/L	< 20			
Magnesium	mmol/L	< 0.4	> 1.23	< 0.3	> 3.3

Definition of Potentially Clinically Significant Laboratory Values

Laboratory values will be considered as potentially clinically significant if they are Grade 3 or higher as shown in Table 4 and Table 5, with the following exceptions:

- GGT: Grade 4
- Total bilirubin: > 2 × ULN
- Concurrent ALT or AST > 3 × ULN and total bilirubin ≥ 2 × ULN

- Concurrent ALT or AST > 3 × ULN, ALP < 2 × ULN and total bilirubin ≥ 2 × ULN

The maximum ratio relative to the ULN will be used to determine if subjects met the criteria listed above. The ALT, AST, and total bilirubin values need to be concurrent (i.e., collected on same date) and should be collected within 49 days following the last dose date of any study drug in order to meet the defined criteria.

11.4.2 Statistical Methods

Treatment emergent lab abnormalities will be summarized in chemo-radiation phase and adjuvant phase separately and also in the overall study. For each of the continuous laboratory parameters, the following outputs will be produced for each treatment group:

- Summary of lab measurements at each scheduled visits
- Summary of changes from baseline at each post-baseline visits along with treatment group difference
- Shifts from baseline grades to worst post-baseline grades (only for the parameters where CTCAE grading is possible)
- The number and percentage of subjects with maximum treatment-emergent laboratory values meeting the potentially clinically significant criteria (excluding hepatic tests)
- For hepatic tests, the number and percentage of subjects with hepatic laboratory values meeting several cut-off values (e.g., > 3 × ULN, > 5 × ULN, > 10 × ULN, etc.) specified for each test
- Listing of laboratory values for subjects with potentially clinically significant values

11.5 Analysis of Vital Signs

11.5.1 Variables and Criteria Defining Abnormality

Pre-defined criteria for potentially clinically significant vital signs values are given in Table 11.

Table 11. 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

11.5.2 Statistical Methods

Vital sign parameters (diastolic/systolic blood pressure, pulse rate, and body temperature) and body weight will be descriptively summarized by treatment groups. For each of the vital signs parameters, the following outputs will be produced:

- Summary of vital signs parameters at each scheduled visit
- Summary of changes from baseline at each post-baseline visit along with treatment group difference
- Summary of subjects with post baseline values meeting criteria for potentially clinically significant Vital Signs values

Change from baseline analyses will be summarized at each post-baseline visit and treatment group difference will be reported.

11.6 Analysis of ECG parameters

ECG will be performed at screening, final visit and when clinically indicated. These ECG values will be summarized by visit and treatment group. Change from baseline at each post-baseline visit will also be summarized using shift table.

12.0 Reference

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13.0 Appendix

Appendix I: Determining deterioration in HVLT-R Total Recall score and COWA FAS score

Raw Score will be standardized using the published age-specific normative data from a healthy population as follows.

$$\text{Z score} = \frac{\text{Raw Score} - \text{Mean norm Score}}{\text{Norm standard deviation}}$$

At each post-baseline assessment, change in raw score relative to baseline will be calculated and categorized as declined or not using the reliable change index (RCI) criterion based on the raw scores. The RCI is derived from the standard error of measurement of each test and represents the 90% confidence interval for the difference in raw score from baseline to the next assessment that would be expected if no real change occurred:[2,14]

RCI = 1.64(SEdiff), where SEdiff = $[2(SEM^2)]^{1/2}$ and SEM = $SD[(1 - r)^{1/2}]$

SEdiff is the standard error of difference, SEM is the standard error of measurement, SD is the standard deviation, and r is the test-retest reliability statistic. All RCI thresholds were rounded to the nearest whole number. For HVLT-R total score and COWA-FAS score, $r = 0.74$ and 0.70 will be used, respectively.[4] Deterioration in raw score should be compared against the RCI threshold to determine the meaningful deterioration.

Appendix II: Summary of RANO response criteria

Tumor progression will be assessed using the RANO criteria as outlined below according to Wen, et al,[30] "Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group." Note: Only PFS data will be analyzed in this study.

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

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

FLAIR = fluid-attenuated inversion recovery

Pseudoprogression and Radiation Effects

The proposed new response criteria suggest that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease. It is recognized that the proposed histologic criteria have important limitations, but they provide guidance on the type of findings that are suggestive of progressive disease. For patients in whom pseudoprogression cannot be differentiated from true tumor progression, enrollment onto trials for recurrent gliomas should not be permitted. Patients who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy.

Enhancement as a Result of Surgery and Other Therapies

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

Definition of Clinical Deterioration

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

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

Definition of Radiographic Response

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline should be used for determination of progression. The criteria for radiographic changes after therapy are listed in Table 2. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4 week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease. All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

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

Table 2. Summary of the Proposed RANO Response Criteria

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

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

* Progression occurs when this criterion is present.

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

Appendix III: Scoring manual for MDASI-BT assessment

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of ap…** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with [illegible] life

Symptoms frequently interfere with [illegible] function. How much have your symptoms interfered with the following items in the last 2[illegible]:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Appendix IV: Scoring manual for EORTC QLQ-C30 questionnaire

QLQ-C30	Item (Question) Numbers	Item Range*
Global health status/QoL		
Global health status/QoL	29, 30	6
Functional scales		
Physical functioning	1, 2, 3, 4, 5	3
Role functioning	6, 7	3
Emotional functioning	21, 22, 23, 24	3
Cognitive functioning	20, 25	3
Social functioning	26, 27	3
Symptom scales/Items		
Fatigue	10, 12, 18	3
Nausea and vomiting	14, 15	3
Pain	9, 19	3
Dyspnea	8	3
Insomnia	11	3
Appetite loss	13	3
Constipation	16	3
Diarrhea	17	3
Financial difficulties	28	

* Item range is the difference between the possible maximum and the minimum responses to individual items; most items take values from 1 to 4, giving range = 3.

Individual questions from EORTC QLQ-C30 questionnaire are as follows:

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix V: Scoring manual for EORTC QLQ-BN20 questionnaire

QLQ-BN20	Item (Question) Numbers	Item Range
Symptom scales		
Future uncertainty (FU)	1, 2, 3, 5	3
Visual disorder (VD)	6, 7, 8	3
Motor dysfunction (MD)	10, 15, 19	3
Communication deficit (CD)	11, 12, 13	3
Headaches (H)	4	3
Seizures (S)	9	3
Drowsiness (Dr)	14	3
Hair loss (HL)	16	3
Itchy skin (IS)	17	3
Weakness of legs (WL)	18	3
Bladder control (BC)	20	3

Individual questions from EORTC QLQ-BN20 questionnaire are as follows:

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

Appendix VI: Scoring manual for EQ-5D-5L and EQ VAS assessment

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

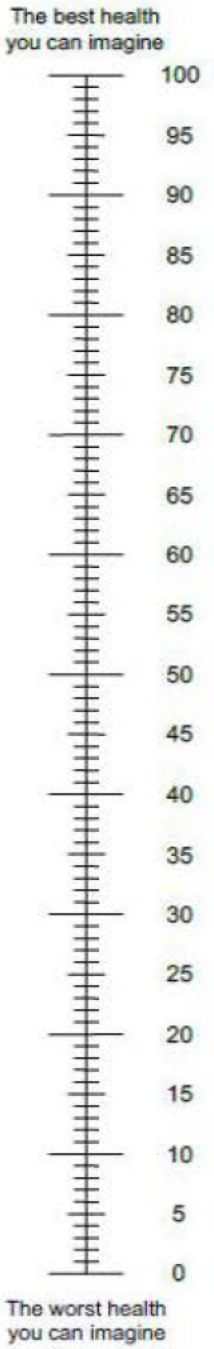
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix VII: Scoring manual for COWA-FAS assessment

	F-WORDS	A-WORDS	S-WORDS
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
16.			
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18.			
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27.			
28.			
29.			
30.			
31.			
32.			
34.			
35.			
36.			
37.			
38.			
39.			
40.			
SCORE			

Appendix VIII: Study activities – Chemoradiation Phase

Chemoradiation Phase	**Screening[a]**		**Chemoradiation Phase[b]**						
Activity	**Screening 1**	**Screening 2**	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 4**	**Day 1 of Wk 5**	**Day 1 of Wk 6**	**Day 1 of Wk 7**
Informed Consent	X								
Medical and Oncologic History		X							
Physical Exam (Including Weight and Karnofsky Performance Status)[c]		X	X		X		X		
Vital Signs		X	X		X		X		
Ophthalmology Exam		X				X[d]		X[d]	
ECG[e]		X							
Serum Pregnancy Test		X	X[f]						
Chemistry		X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X
Urinalysis		X							
Coagulation		X							
MRI With and Without Contrast		X[k]							
Submit Tissue Sample for Confirmation of GBM, testing of *EGFR* amplification, *EGFRvIII* and *MGMT*	X								
Adverse Event Assessment/Concomitant Medications/Supportive Care			X		X		X		

Chemoradiation Phase	**Screening[a]**		**Chemoradiation Phase[b]**						
Activity	**Screening 1**	**Screening 2**	**Day 1 Wk 1 (Fraction 1 of RT)**	**Day 1 of Wk 2**	**Day 1 of Wk 3**	**Day 1 of Wk 4**	**Day 1 of Wk 5**	**Day 1 of Wk 6**	**Day 1 of Wk 7**
Radiation Therapy[g]			X						
Temozolomide Administration			X[h]						
Depatux-M or Placebo Administration			X		X		X		
Prophylactic Eye Drop Administration			X[i]		X[i]		X[i]		
Randomization			X						
EORTC-QLQ-C30/BN20		X[j]							
MDASI-BT		X[j]							
NEI VFQ-25		X[j]							
Neurocognitive Function (HVLT-R, COWA-FAS)		X[j]							
EQ-5D-5L and EQ-5D-VAS		X[j]							

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

Appendix IX: Study Activities – Adjuvant Phase

Adjuvant Phase	Adjuvant Phase – 28-Day Cycles[a]										
Activity	Day 1 of Every Cycle (1, 2, 3 etc.)	Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)	Day 1 of Cycle 2	Day 15 of Every Cycle[b]	Day 22 of Every Cycle[c]	Final Study Drug Visit[d]	35-Day F/U[e]	49 Day Follow Up	Follow-Up Phase (Every 8 Weeks Until Disease Progression)[f]	At Progression	Survival
Physical Exam (Including Weight and Karnofsky Performance Status)[g]	X			X		X[d]	X		X		
Vital Signs	X			X		X	X				
Ophthalmology Exam[h]		X	X				X[i]				
ECG						X					
Chemistry	X					X	X				
Hematology	X				X	X	X				
MRI and Clinical Disease Progression Assessment		X[j]				X[d,k]			X[j]		
Adverse Event Assessment/Concomitant Medications/Supportive Care	X			X		X	X	X			
Temozolomide Administration	X[l]										
Depatux-M or Placebo Administration	X[m]			X[m]							
Prophylactic Eye Drop Administration	X[n]			X[n]							
NEI VFQ-25[o]		X					X				

Adjuvant Phase	Adjuvant Phase – 28-Day Cycles[a]										
Activity	Day 1 of Every Cycle (1, 2, 3 etc.)	Day 1 of Odd-Numbered Cycles (1, 3, 5, etc.)	Day 1 of Cycle 2	Day 15 of Every Cycle[b]	Day 22 of Every Cycle[c]	Final Study Drug Visit[d]	35-Day F/U[e]	49 Day Follow Up	Follow-Up Phase (Every 8 Weeks Until Disease Progression)[f]	At Progression	Survival
EORTC-QLQ-C30/BN20[o]		X							X	X[p]	
MDASI-BT[o]		X							X	X[p]	
Neurocognitive Function (HVLT-R, COWA)[o]		X							X	X[p]	
EQ-5D-5L and EQ-5D-VAS[o]		X							X	X[p]	
Treatment Satisfaction Question		X							X	X[p]	
Survival Assessment[q]											X

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

Document Approval

Study M13813 - Statistical Analysis Plan Version 2 - 23Apr2019 (E3 16.1.9)

Version: 1.0 **Date:** [redacted] 05:08:51 PM **Company ID:** 04242019-00F9F6841A0248-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	[redacted]	Approver
		Approver
		Approver
		Approver