STATISTICAL ANALYSIS PLAN

FOR THE PHASE 2 COMPONENT
OF THE PROTOCOL ENTITLED
"A Phase 1 / 2 Trial for Patients with Newly Diagnosed High Grade Glioma Treated with Concurrent Radiation Therapy, Temozolomide, and BMX-001"
Protocol #: BMX-HGG-001

Adapted from the Statistical Section included in the Research Protocol

Version Date: June 1, 2023

1 List of Abbreviations

AE	Adverse Events
ANCOVA	Analysis of covariance
COWA	Controlled Oral Word Association
CSR	Clinical Study Report
FDA	Food and Drug Administration
Gy	Gray
HGG	High Grade Glioma
HRQoL	Health related Quality of Life
HVLT-R	Hopkins Verbal Learning Test - Revised
ICH	International Conference on Harmonization
ITT	Intent to Treat
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetic
PRO	Patient Reported Outcome
RANO	Response Assessment in Neuro-Oncology
RT	Radiation Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
TMT	Trails Making Test
TMZ	Temozolomide
WHO	World Health Organization

2 SIGNATURES

The following persons have read and agreed the content of this Statistical Analysis Plan.

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3 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the current trial protocol (version 9.0 dated 25 May 2019). If statistical methods differ substantially between the SAP and the protocol, refer to the SAP.

The SAP describes the datasets and the statistical methods to be used for reporting and analysis of all data collected during the trial.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, the SAP will be amended. If, after the database is locked, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the final Clinical Study Report (CSR).

We have considered the following guidelines when writing this SAP:

- International Conference on Harmonization (ICH) E9, Guidance for Industry: Statistical Principles for Clinical Trials
- ICH E3, Guidance for Industry: Structure and Content of Clinical Study Reports.

Statistical analysis will primarily be conducted using SAS version 9.4, with additional analyses and data visualization performed using the R software (version 4.2.1 or later).

4 OVERVIEW OF STUDY DESIGN

TREATMENT ARMS

Arm A: Concurrent daily TMZ and RT with BMX-001

Arm B: Concurrent daily TMZ and RT alone

The Phase 2 portion of this protocol is a multi-center randomized open-label study comparing the impact of concurrent daily Temozolomide (TMZ) and Radiation Therapy (RT) with BMX-001 (Arm A) versus concurrent daily TMZ and RT alone (Arm B) on survival in patients among patients with newly diagnosed high grade glioma (HGG - WHO grade III and IV). Subjects were randomized with a treatment arm allocation ratio of 1:1, with a goal of enrolling 160 patients in this phase of the study (80 subjects per arm). A permuted block randomization stratified by histologic grade (grade III / IV) and institution will be used to assign patients to treatment with or without BMX-001.

Subjects in Arm A were administered BMX-001 subcutaneously first as a loading dose (28 mg) given 0 to 4 days before the start of chemoradiation and then at subsequent dose (14 mg) twice a week for eight weeks. Subjects in Arm A and Arm B received TMZ dosed at 75 mg/m^2 orally daily for 42 days and RT delivered in daily fractions of 1.8-2 Gy given 5 days a week for 6 weeks for a total of 59.4-60 Gy.

In all subjects, cognitive performance was measured at the time of enrollment and 2 weeks after the completion of RT, and standard of care (SOC) clinic visits (approximately 8 weeks apart +/- 2 weeks) until death, or patient's choice to discontinue study measures. Cognitive testing was to continue after noted progression until the 12 month follow up timepoint is reached.

In order to characterize the repeated dose pharmacokinetic (PK) profiles of BMX-001 in combination with RT and TMZ in newly diagnosed HGG patients, PK blood samples were drawn on Days 8 and 36 only from the first 6 patients enrolled and assigned to Arm A at a single center (Duke). Measures were obtained at approximately the following times: Pre-

dose, then 0.5 hour, 1 hour, 2 hours, 6 hours and 24 hours post-dose. Samples will be analyzed for BMX-001 using validated analytical methods at the Duke PK lab.

The study's primary phase 2 endpoint is overall survival (OS), defined as the time between randomization and death. A logrank test will be used to compare the survival experience of the two treatment arms. An intent-to-treat philosophy will be used in the analysis of survival by including all patients who are randomized in the analysis. Other analysis sets are defined in this document.

Among the secondary endpoints are two that are of particular interest: cognitive function and thrombocytopenia. The mean change in cognitive functioning between baseline (enrollment) and week 24 within each treatment arm will be computed, and analysis of covariance will be conducted to compare groups with respect to that change. Treatment group assignment will be included in the model as a predictor, and the baseline measure of cognitive function will be included as a covariate.

The proportion of patients who experience grade 3 or 4 thrombocytopenia during concurrent temozolomide and radiation, a period that terminates 2 weeks after completion of radiation treatment, will be summarized. A chi-square test will be conducted to compare the prevalence of such thrombocytopenia observed in patients with and without BMX-001.

5 PATIENT CHARACTERISTICS

The clinical and socio-demographic characteristics of all randomized patients will be summarized using descriptive statistics (e.g., means/standard deviations, percentiles, frequencies). Patient characteristics will be summarized by treatment group assignment. Characteristics that will be summarized include:

- Institution
- Race
- Ethnicity
- Gender
- Tumor Grade, according to WHO grade at time of enrollment and WHO 2021[1]*
- Performance Status (KPS)
- Histology
- Disease Description (Unifocal / Multifocal)
- MGMT Status (Methylated / Unmethylated)
- IDH: mutated or wildtype
- Extent of Resection (Gross total Resection / Subtotal Resection / Biopsy Only)
- Age

6 ANALYSIS POPULATIONS

The following populations will be identified:

- Intent to Treat Population (ITT): All patients randomized into the clinical trial, regardless of compliance.

[1] During study accrual, a new WHO classification system for CNS tumors was published [1]. Though the classification system in use at the time of study activation was used throughout the conduct of the study, the classification of all patients under the new WHO 2021 system will also be described.

- Safety Population: All patients who received at least one dose of BMX-001 or temozolomide
- Treated Population: All patients who completed chemoradiation with or without BMX-001. BMX-001 must be given for at least 6 weeks (or 13 doses).
- PK Population: Subjects who participated in the PK portion of the study (n=6).

7 TREATMENT AND SUBJECT DISPOSITION

A CONSORT diagram will be generated that displays the number of patients randomized within each treatment arm, the number of patients within each arm who are treated with chemoradiation, as well as the number of cycles of adjuvant treatment received. For treatment during chemoradiation, the total dose of BMX-001 administered will be summarized, as well as the total dose of TMZ and RT administered.

All subjects who withdrew or were withdrawn from the study will be listed by treatment arm with the reason for withdrawal.

8 PRIMARY OBJECTIVE: SURVIVAL

The primary goal of this randomized, open-label Phase 2 study is to examine the impact of BMX-001 on overall survival among patients newly diagnosed with HGG who are receiving SOC treatment consisting of daily TMZ and RT. After the primary endpoint analysis at 84 deaths, we will continue following patients for survival and disease progression even after the primary endpoint analysis. Per protocol, patients will be followed indefinitely.

8.1 ENDPOINT

The study's primary endpoint is overall survival (OS) which is defined by the time between randomization and death, or the last follow-up if the patient remains alive.

8.2 METHOD OF PRIMARY ENDPOINT ANALYSIS

This study will assess the hypothesis that BMX-001, when added to standard RT and TMZ, will sensitize the malignancy and result in enhanced patient survival as well as protect normal tissues from RT, resulting in better quality of life.

The primary analysis of survival will be done with the ITT population.

Kaplan-Meier methods will be used to graphically describe the distribution of overall survival (OS) among patients within the BMX-001 treatment group (Arm A) and within the control group (Arm B). Median OS, as well as 6-, 12-, 24-, and 36-month estimates of OS will be estimated from the Kaplan-Meier curve. A logrank test will compare arms with respect to the survival outcome.

As an additional descriptive statistic, the mean overall survival over a time interval chosen to maintain reasonable coverage of observed survival will be calculated.

If the underlying assumptions for the planned analyses are not satisfied, alternative methods of analysis depending on the observed distribution of the data will be explored.

8.3 INTERIM ANALYSES

Interim analyses using an O'Brien-Fleming boundary will be conducted with the goal of terminating accrual early to accept or reject the null hypothesis of no difference in survival. Given the inflated type I error rate for this Phase 2 study, early termination will only be considered if it appears that the addition of BMX-001 treatment to radiation and temozolomide is decreasing survival. The interim analysis will be conducted to determine whether the addition of BMX-001 is possibly detrimental to the survival of patients.

8.3.1 INTERIM ANALYSIS #1

The study was originally designed with one interim survival analysis after approximately 42 deaths. The decision rule for accrual suspension was defined by the O'Brien-Fleming spending function and is dependent upon the number of deaths that will have been reported by the time of the interim analysis. If the boundary was crossed, accrual was to be suspended while all other data (e.g., cognitive function data) is reviewed to determine whether accrual should be permanently terminated.

The first interim analysis was conducted in December 2021 when 46 deaths had been observed in the ITT population (20 in Arm A and 26 in Arm B). The study was not terminated early as a result of the first interim analysis.

8.3.2 INTERIM ANALYSIS #2

An unplanned interim analysis was conducted in March 2022 to support an FDA application for breakthrough therapy designation. That analysis was conducted when 54 deaths had been observed among treated subjects (22 in Arm A and 30 in Arm B). The study was not terminated early as a result of the first interim analysis.

8.3.3 PRIMARY ENDPOINT ANALYSIS

After these 2 interim analyses, no further interim analysis will be conducted until the primary endpoint analysis. The primary endpoint analysis is scheduled to occur after 84 deaths have been observed.

8.4 POWER OF SURVIVAL COMPARISONS & FINAL ANALYSIS

The primary goal of the Phase 2 portion of this study is to assess the effect of BMX-001 treatment in conjunction with standard of care treatment consisting of temozolomide and radiation on the survival of patients newly diagnosed with grade III or IV glioma.

8.4.1 ORIGINAL POWER ANALYSIS

With standard treatment, the median survival of Grade IV patients is 14.6 months, and the median survival of Grade III is approximately 36 months. Before study activation, we anticipated that approximately 10% of patients to be Grade III. With 10% of patients as grade III, we estimated that the overall median survival with standard treatment to be roughly 16.7 months

Though this Phase 2 study is comparative, the goal is to determine whether BMX-001 is worthy of further investigation in combination with standard RT and TMZ treatment. Many aspects of the new treatment will be considered in the decision-making concerning further investigation, including relative toxicity and ease of treatment administration. As a Phase 2 study, there is a need to constrain the sample size requirements at the expense of either an increased false negative or false positive rate. A false-positive rate of 0.2 will be used to test the primary statistical hypothesis while maintaining reasonably high power [3-5].

The power of a statistical comparison of survival is a function of the number of deaths observed. In order that a 1-tailed logrank test conducted at the 0.2 level to have 90% power to detect a hazard ratio of 0.63, 84 deaths need to be observed among the 160 randomized patients. Under the assumption that survival is exponentially distributed, this hazard ratio represents an increase in median survival from 16.7 to 26.5 months.

8.4.2 REVISED POWER ANALYSIS

In actuality, approximately 20% of patients enrolled were Grade III. With 20% of patients to be grade III, we estimate that the median overall survival with standard of care treatment to be roughly 18.9 months.

With these modifications the power analysis has been revised:

The power of a statistical comparison of survival is a function of the number of deaths observed. In order that a 1-tailed logrank test conducted at the 0.2 level to have 90% power to detect a hazard ratio of 0.63, 84 deaths need to be observed among the 160 randomized patients. Under the assumption that survival is exponentially distributed, this hazard ratio represents an increase in median survival from 18.9 to 30.0 months.

8.5 ADDITIONAL ANALYSES, INCLUDING SUBGROUP ANALYSES

The analyses described in Section 8.2 will be repeated within the treated population.

Within the ITT and treated patient populations, various subgroups analyses will be conducted. Subgroups will be defined by the following factors:

- Original histologic WHO grade (III or IV)
- New histologic WHO grade (III or IV)
- MGMT (present or absent)
- IDH status
- 19q FISH
- Age: subjects > 65 at time of consent
- Others as needed

The Kaplan-Meier estimator will describe the survival within each combination of histologic grade and treatment arm. Several analyses may be conducted:

1. Within each subgroup defined by the variables above, Cox proportional hazards model will assess the effect of treatment on survival.

2. The Cox model will explore the joint effect of the clinical predictor and treatment assignment, and possibly their interaction. Such an analysis will explore whether the effect of BMX-001 treatment is consistent across levels of the clinical predictors.

3. The Cox model may also explore the joint effects of age, gender, histologic grade, MGMT, and other prognostic factors on survival.

9 SECONDARY OBJECTIVE: COGNITION

The first secondary objective involves an assessment of whether the addition of BMX-001 to standard RT and TMZ treatment for patients newly diagnosed with HGG has an impact upon cognition. The BAC App (provided by VeraSci) and paper forms (HVLT-R, COWA, TMT) were used to assess patient cognition.

BAC App (i-Pad based testing)

The BAC battery of tests was implemented through an iPad-based app called the BAC App (the vendor that provides this is called VeraSci, previously called NeuroCog). Subtests included:

- Verbal Memory
- Digit Sequencing
- Token Motor
- Semantic Fluency
- Letter Fluency
- Symbol Coding
- Tower of London

Beginning at baseline, the BAC will be obtained longitudinally:

- Screening (for the baseline assessment),
- After standard RT and TMZ (within 2 to 4 weeks), and
- Approximately every 8 weeks when a subject returns for a Standard of Care visit during adjuvant TMZ.

Paper cognitive testing

Paper forms were used to assess patient cognition using the following instruments:

- Hopkins Verbal Learning Test-Revised (HVLT-R)
- Trails Making Test Parts A and B (TMT), and
- Controlled Oral Word Association Test (COWA)

Timepoints completed:

- Baseline (prior to the start of RT)
- Standard of care visit before the start of the first cycle of adjuvant temozolomide,
- Standard of care visits that are 6 and 12 months from the completion of radiotherapy/ chemotherapy.

When a subject came off study for disease progression before the approximate 6 and 12 months post completion of treatment timepoint, cognitive testing was supposed to continue and be collected at those timepoints and if present will be included.

The analysis of Cognition data will focus on the cohort of patients who were treated. Typically, patients who were not treated did not provide any cognitive data follow-up.

9.1 DROP-OUT PATTERNS

The ultimate goal of this objective is to compare groups with respect to longitudinal changes in cognition over time. Unfortunately, due to the patient population that are eligible to participate in this study, a significant amount of the follow-up cognitive assessments may be missing due to health decline, disease progression, and death. Some of the missing data may be intermittently missing (i.e., missing observations between observed assessments); however, much of the missing data will be "drop-out" (i.e., subject permanently drops out of longitudinal assessment). The pattern of "drop-out" in the two treatment arms will be assessed.

The proportion of patients within each treatment arm who lack assessments after the baseline assessment will be determined and compared using a chi-square test. We will also explore whether there are subgroups defined by clinical, cognitive, or HRQoL data that are predictive of a subject lacking a post-baseline assessment.

Drop-out may also occur after one or more follow-up assessments are completed. The relationship between the time of the last completed assessment and treatment group will be assessed via a contingency table and chi-square test.

9.2 ENDPOINT

Though the study is a longitudinal analysis, the initial focus of the analyses of this objective is an examination of the mean change in cognitive functioning between baseline and week 24 (occurs after completion of RT) within each treatment arm. The baseline measure is the last assessment obtained before initiation of standard chemoradiation.

There is variability in the timing of follow-up measurements. For the purpose of this analysis a +/- 4 week window will define the 24 week assessment.

Clearly a patient without an assessment post-baseline will not be included in these analyses. Analyses described in Section 9.1 explore how the patients excluded from analyses differ from those who are included in analyses.

9.3 METHOD OF ANALYSIS

For the analysis of change in cognition between baseline and week 24, an analysis of covariance (ANCOVA) will be conducted to compare treatment groups within the treated patient cohort. The outcome of this model is change in cognitive function. Treatment group assignment will be included in the model as a predictor, and the baseline measure of cognitive function will be included as a covariate.

As noted earlier, a significant amount of the follow-up cognitive assessments may be missing due to health decline, disease progression, and death. Much of the missing data is due to a subject permanently dropping out of the longitudinal assessment. A linear random coefficient model stratified by drop-out pattern will assess whether cognitive changes over time are consistent across treatment groups and drop-out patterns. This pattern-mixture model accounts for within subject correlation of longitudinal assessments.

If assumption for conducting either the ANCOVA model or the pattern mixture model are not satisfied, alternative approaches to analyses may be conducted. Options include transformation of the outcome data, as well as use of nonparametric methods.

Given that numerous endpoints will be examined that relate to cognition, adjustments for multiple comparisons (e.g., false discovery rate methods or Bonferroni) may be considered.

9.4 POWER FOR COGNITIVE COMPARISONS

9.4.1 ORIGINAL POWER ANALYSIS

We focus on the week 24 assessment of cognitive function in this power calculation given that the study is a randomized study, even though we are interested in comparing groups with respect to change in cognitive function between baseline and week 24. Studies recently conducted at Duke suggest that the standard deviation associated with a one-time assessment of executive function, a component of cognitive function, is approximately 30 units.

We anticipate that 120 of the 160 patients will have pre- and post-measurements of cognitive function. A two-tailed t-test conducted at the 0.05 level of significance (two-tailed) will have 80% power to detect a difference of 15.5.

9.4.2 REVISED POWER ANALYSIS

Collection of measures of health-related quality of life and cognition is plagued with mistiming and drop-outs due to factors described in Section 9.1.

For the purpose of the analyses that focus on the change in cognition between baseline and week 24, the follow-up assessment should have occurred within +/- 4 week window of the scheduled week 24 assessment.

With this adjustment, there are 94 patients (52 in Arm A and 42 in Arm B) that has pre- and post-measurements of cognitive function. Assuming a standard deviation of 30 units, a two-tailed t-test conducted at the 0.05 level of significance (two-tailed) will have 80% power to detect a difference of 17.6.

9.5 ADDITIONAL ANALYSES

The analyses described in Section 9.3 will also be conducted within subgroups defined by WHO grade (original or revised), and tumor markers which have been captured in the study database. Additionally, the joint effect of these clinical predictors, treatment assignment, and their interaction will be explored in the context of these models.

10 SECONDARY OBJECTIVE: THROMBOCYTOPENIA

The second secondary objective is to assess protection of bone marrow against chemotherapy-induced thrombocytopenia of standard RT and TMZ in combination with BMX-001 compared to standard RT and TMZ alone in newly diagnosed HGG patients.

10.1 ENDPOINT

The proportion of patients who experience grade 3 or 4 thrombocytopenia during concurrent temozolomide and radiation will be estimated within each treatment group. The proportion of patients who experience a platelet count less than 100K during concurrent temozolomide and radiation will also be estimated within each treatment group. The period of observation for these events will extend until 2 weeks after completion of radiation treatment.

10.2 METHOD OF ANALYSIS

For both endpoints described in Section 10.1, a chi-square or Fisher's exact test will be conducted to compare the prevalence of such thrombocytopenia observed in patients with and without BMX-001.

10.3 POWER FOR THROMBOCYTOPENIA ENDPOINT

10.3.1 ORIGINAL POWER ANALYSIS

Platelet counts will be obtained during radiation and temozolomide treatment and ending 2 weeks after termination of radiation. The percentage of patients within each treatment group that experience grade 3 or 4 thrombocytopenia will be estimated. Gerber [2] reports that 15% of patients who receive standard radiation and temozolomide experience grade 3 or 4 thrombocytopenia. With 80 patients per arm, there is 80% power with a one-tailed chi-square test (α=0.05) to detect a reduction in grade 3 or 4 thrombocytopenia from 15% in Arm B (without BMX-001) to 4% in Arm A (with BMX-001).

10.3.2 REVISED POWER ANALYSIS

For this endpoint to have relevance, a patients must have received some treatment with temozolomide and radiation in either Arm A or B. At this point, analyses suggest that 78 patients in Arm A and 71 patients in Arm B received protocol treatment. With 78 and 71 patients in Arms A and B, respectively, there is 80% power with a one-tailed chi-square test (α=0.05) to detect a reduction in grade 3 or 4 thrombocytopenia from 15% in Arm B (without BMX-001) to 3.7% in Arm A (with BMX-001).

11 SECONDARY OBJECTIVE: ADVERSE EVENTS (AE)

The third secondary objective is to assess the safety and tolerability of standard RT and TMZ in combination with BMX-001 compared to standard RT and TMZ alone in newly diagnosed HGG patients. The collection of adverse events was stopped 30 days after completion of chemoradiation treatment +/- BMX-001. Adverse events were coded by clinical center staff.

11.1 ENDPOINTS

The phase 2 portion of this study has two adverse event endpoints:

(1) The proportion of patients who experience any grade 3 or 4 adverse event during radiation and temozolomide treatment, and

(2) The proportion of patients who experience a grade 3 or 4 adverse event that is definitely, possibly, or probably related to BMX-001 treatment during this same period.

Adverse events occurring between baseline through 2 weeks after discontinuation of radiation will be the focus of these analyses and will be summarized.

11.2 METHOD OF SUMMARIZATION AND ANALYSIS

11.2.1 ADVERSE EVENTS DURING CHEMORADIATION

Each participating institution coded adverse events with their preferred term and organ class using MedDRA system organ class. Whether or not the adverse event was related to BMX-001 was determined for each event.

The initial summary of adverse events will consider all Treatment Emergent AE (TEAE) occurring during chemoradiation regardless of attribution to BMX-001. A TEAE is an event emerging during treatment having been absent pre-treatment or having worsened relative to pre-treatment. The period of observation that will be the focus of this tabulation will extend 2 weeks after termination of radiation treatment.

The population for these summaries will be the safety population as defined in Section 6.

For each study arm, the number of subjects with at minimum one Treatment Emergent AE (TEAE) will be tabulated by preferred term and MedDRA system organ class. Subjects with more than one TEAE will be counted only once, at casualty, for each system organ class /preferred term. Multiple TEAEs in a subject will be counted once per system organ class and preferred term. Summaries will be sorted by system organ class and decreasing total incidence of preferred term.

11.2.2 SERIOUS ADVERSE EVENTS DURING CHEMORADIATION

Serious Adverse Events (SAEs) will be summarized by system organ class and preferred term. A listing of the reasons for considering a SAE will be provided. Narratives of SAEs will be included.

11.2.3 ADVERSE EVENTS DURING CHEMORADIATION ATTRIBUTABLE TO BMX-001

Given that this is an open-label treatment study, adverse events attributable to BMX-001 will only occur in patients within Arm A who receive BMX-001.

For Arm A, the number of subjects with at least one BMX-001 related Treatment Emergent AE (TEAE) will be tabulated by preferred term and MedDRA system organ class. Subjects with more than one BMX-001 related TEAE will be counted only once, at casualty, for each system organ class /preferred term. Multiple TEAEs in a subject will be counted once per system organ class and preferred term. This summary will be sorted by system organ class and decreasing total incidence of preferred term.

11.2.4 OTHER SAFETY MEASURES AND TABULATIONS

All AEs will be listed. A listing of the relationship between system organ class and verbatim text will also be presented.

Listings of the following data will be generated:

- Clinical Laboratory Evaluations: all laboratory values of clinical significance (as defined by site principal investigator) will be listed.
- Vital signs: Vital signs pre and post BMX-001 injection will be summarized. Only vital signs of clinical significance as defined by the site principal investigator will be summarized and listed.
- Physical Examinations: Abnormal physical examination findings of clinical significance will be summarized and listed.

12 SECONDARY OBJECTIVE: PROGRESSION-FREE SURVIVAL

The fourth secondary objective is to assess the effect on progression-free survival (PFS) of standard RT and TMZ in combination with BMX-001 compared to standard RT and TMZ alone in newly diagnosed HGG patients.

12.1 ENDPOINT

Progression-Free Survival (PFS) is defined as the time between initiation of protocol treatment and disease progression or death. If the patient remains alive without disease progression, then PFS will be censored at last follow-up. Analyses similar to those described for OS will be generated for PFS.

12.2 METHOD OF ANALYSIS

The primary analysis of PFS will consider all patients, and consider them in their assigned treatment arm regardless of compliance. This approach to analysis is consistent with an intent-to-treat analysis approach.

As with survival, Kaplan-Meier methods will be used to graphically describe the distribution of PFS among patients within the BMX-001 treated group (Arm A) and within the control group (Arm B). Median PFS, as well as 6- and 12-month estimates of PFS will be estimated from the Kaplan-Meier curve. A logrank test will compare arms with respect to the PFS outcome.

12.3 ADDITIONAL ANALYSES

Analyses similar to those described in Section 8.5 will be conducted for PFS, including analyses within subgroups of patients defined by grade, histological subtype, and tumor markers which have been captured in the study database. Analyses will also explore the interaction between clinical factors and treatment assignment on the PFS outcome.

13 SECONDARY OBJECTIVE: RADIOGRAPHIC RESPONSE

The fifth secondary objective is to assess radiographic response in newly diagnosed HGG patients treated with standard RT and TMZ in combination with BMX-001 compared to standard RT and TMZ alone.

13.1 ENDPOINT

Radiographic response will be determined by brain MRI evaluations for assessment based on the RANO criteria. The radiographic response rate is defined as the proportion of patients of with a complete or partial response.

13.2 METHOD OF ANALYSIS

The response rate within each arm will be calculated and compared using a chi-square test or an exact chi-square test. Exact binomial confidence intervals will be generated for each response rate estimate.

The initial analysis of response rate will focus on the ITT patient population. Those patients who did not receive treatment, or did not have a follow-up radiographic assessment will be included in the denominator for the calculation of response rate. These patients will not be counted a responders.

13.3 ADDITIONAL ANALYSES

Additional analyses will describe the response rate within patient subgroups defined by arm and WHO grade. Response rate will also be summarized within the treated patient population.

14 SECONDARY OBJECTIVE: PHARMACOKINETICS

The sixth secondary objective is to characterize the repeated-dose pharmacokinetic profile of BMX-001 when delivered in combination with RT and TMZ in newly diagnosed HGG patients.

Samples were obtained from the first 6 patients at Duke that are randomized to Arm A. Drug pharmacokinetics were obtained on Day 8 or the next day when drug is administered and Day 36 or the next day when drug was administered during the chemoradiation phase. Measures were obtained at the following time-points will be summarized: Pre-Dose, 0.5 hour, 1 hour, 2 hours, 6 hours and 24 hours.

15 EXPLORATORY OBJECTIVE: HEALTH-RELATED QUALITY OF LIFE (HRQoL)

The first exploratory objective is to describe patient-reported outcomes of HRQoL in newly diagnosed HGG patients treated with standard RT and TMZ in combination with BMX-001 compared to standard RT and TMZ alone.

HRQoL was assessed by the Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale. The FACT-BR (version 4) contains subscales for

- Physical well-being (7-items)
- Functional well-being (7-items)
- Emotional well-being (6-items)
- Social/family well-being (7-items)
- Brain cancer subscale (BCS; 23-items) which assess symptoms commonly reported by brain cancer patients [27].

Cancer-related fatigue was assessed by the 13-item Fatigue Scale using the Functional Assessment of Cancer Therapy-Fatigue (FACIT-Fatigue) subscale, version 4 [67].

Cognitive problems was assessed using version 3 of the Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) subscale [68]. This includes subscales for:

- Perceived cognitive impairments (20 items)
- Comments from others (4 items)
- Perceived cognitive abilities (9 items)
- Impact of quality of life (4 items).

Beck depression inventory (BDI) was used to evaluate for underlying depressive symptoms. We used the revised version (BDI-II) and the scores will range from 0 (no depression) to 63 (severe depression) [69]. The BDI contains 21 questions in regards to mood symptoms and is multiple-choice and self-reported.

Exercise behavior was assessed using the Godin Leisure questionnaire [70].

HRQoL PROs questionnaires were obtained at screening, after standard RT and TMZ (within 2 to 4 weeks), and approximately every 8 weeks when a subject returned for a Standard of Care visit during adjuvant TMZ.

15.1 ENDPOINT

Though the study is a longitudinal analysis, the initial focus of the analyses of this objective is an examination of the mean change in HRQoL between baseline and week 24 (occurs after completion of RT) within each treatment arm of the treated subjects.

There is variability in the timing of follow-up measurements. For the purpose of this analysis a +/- 4 week window will define the 24 week assessment.

15.2 METHOD OF PRIMARY ANALYSIS

The analyses that will be conducted are similar to those described in Section 9.3. For the analysis of change in HRQoL between baseline and week 24, an analysis of covariance will be conducted to compare treatment groups. The outcome of this model is change in cognitive function. Treatment group assignment will be included in the model as a predictor, and the baseline measure of HRQoL function will be included as a covariate.

A linear random coefficient model stratified by drop-out pattern will assess whether HRQoL changes over time are consistent across treatment groups and drop-out patterns. This pattern-mixture model accounts for within subject correlation of longitudinal assessments.

If assumption for conducting these analyses fail, alternative analytic approaches will be considered include, a transformation of the outcome data, or nonparametric methods.

Given the number of HRQoL tests that will be conducted, p-values will be adjusted for multiple comparisons.

15.3 ADDITIONAL ANALYSES

Additional analyses will explore the impact of BMX-001 on HRQoL within patient subgroups defined by WHO grade and histological subtype.

16 EXPLORATORY OBJECTIVE: HAIR LOSS

The second exploratory objectives is to describe changes in hair loss in newly diagnosed HGG patients treated with standard RT and TMZ in combination with BMX-001 compared to standard RT and TMZ alone.

Subjective assessments of hair loss were obtained by the treating provider for subjects at screening (baseline), after standard RT and TMZ finishes (within 2 to 4 weeks), and standard of care (SOC) clinic visit (approximately every 8 weeks) during adjuvant TMZ.

Qualitative assessments of hair loss depicted in longitudinal subject photographs will be conducted and summarized. Changes observed in Arm A will be compared to those observed in Arm B.

The analyses group for this exploratory objective will include all treated patients who have both assessments of their hair at baseline and at one or more follow-up assessments.

17 EXPLORATORY OBJECTIVE: WHITE MATTER INTEGRITY

The third exploratory objective is to describe change in white matter integrity in newly diagnosed HGG patients treated with standard RT and TMZ in combination with BMX-001 in comparison to standard RT and TMZ alone.

17.1 ENDPOINT

The mean change between baseline and each follow-up assessment for white matter integrity, as measured by MRI diffusion tensor/susceptibility imaging will be computed.

These images will be obtained three times during the study: on day -5 to 0, after standard RT and TMZ (within 2 to 4 weeks), and 24 weeks after the start of standard RT and TMZ (within 2 to 4 weeks).

17.2 METHODS OF ANALYSIS

Assuming normality, analysis of variance or a repeated measures analysis may be used to compare change in Arms A and B. Additional analyses will be sub-divided in terms of WHO grade and histological subtype.

18 PROTOCOL DEVIATIONS

Before closing the database, data listings will be reviewed to determine whether data should be excluded from any of the analysis populations.

As a part of this review, there may be a need to conduct sensitivity analyses that assess the impact on inferences when select patients are included or excluded from analyses.

A summary of important protocol deviations such as the following will be generated:

- Patient entered the study even though they did not meet inclusion/exclusion criteria
- Met criteria for withdrawal but were not withdrawn (reason to be documented)
- Patient received the wrong treatment or dose
- Patient received an excluded concomitant medication

19 DESCRIPTION OF TABLES FOR REPORTING

The following tables and figures will be produced, source data listings will be provided

Description	Population
Summary of Subject Disposition	ITT, Safety, Treated
Summary of Important Protocol Deviations*	Safety
DEMOGRAPHICS	
Summary of Demographic Characteristics	ITT, Treated
SAFETY DATA	
Summary of All AEs	Safety
Summary of TEAEs	Safety
Summary of BMX-001 Related TEAEs	Safety
Summary of Baseline AEs	Safety
Summary of all AEs	Safety
Summary of SAEs/Deaths	Safety
Narratives of SAEs	Safety
Summary of Pre and Post dosing Vital Signs	Safety
Listing of Abnormal ECG findings post BMX-001 treatment	Safety
Summary of clinically significant:	Safety
• Clinical Laboratory Evaluations • Physical Examinations: Abnormal physical examination findings	Safety
PK*	PK
OUTCOMES	
OS	ITT, Treated
PFS	ITT, Treated
Thrombocytopenia	ITT, Treated
Cognitive Testing	ITT, Treated
HRQoLs	ITT, Treated
OTHER	
Treatment Disposition: TMZ, RT, BMX-001	Safety

Treatment Exposure: TMZ, RT, BMX-001	Safety
Concomitant Medications	Treated
Analysis Sets, including subjects excluded from analysis	All
List of Withdrawals	All

*= BioMimetix will provide

20 REFERENCES

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