SAP BBI608-201GBM

A Phase Ib/II Clinical Study of BBI608 in Combination with Temozolomide for Adult Patients with Recurrent or Progressed Glioblastoma

Statistical Analysis Plan (SAP)

Version: 3

Author: [redacted]

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	September 5, 2018	[redacted]	Statistical Analysis Plan
Version 2.0	November 19, 2018	[redacted]	• Safety endpoints have been edited (Laboratory, ECG, ECOG, Physical Exam, Vital Signs) • AECR section has been added • Adding some additional TEAE summaries • By dose analyses have been deleted • Full Analysis Set has been added, and ITT, Safety, Per Protocol, Response and PD/Biomarker Analysis Sets have been deleted • Methods for handling additional missing data have been added, such as age • PK section has been edited • Deleting Dose Changes Section • Deleting PD/Biomarker Analysis Section • Editing dosing intensity and compliance section • Editing prior therapies (surgery, radiotherapy, hormone/biologics/chemotherapy /other)
Version 3.0	March 6, 2019	[redacted]	• Editing dosing intensity and compliance section • Adding abbreviations • Adding back PD/Biomarker Analysis Section • Rearranging secondary objectives by Phase

			• Adding language regarding sponsor terminated follow-up • Adding information about last dose of study treatment • Elaborating on the statistical analyses of PFS, DCR and ORR

STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AECR	Adverse event of clinical relevance
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate transaminase (SGOT)
AUCinf	The area under the plasma concentration-ime curve from zero to infinity
AUCext	The percentage of the AUC extrapolated beyond the last measurable concentration
AUClast	The AUC from time zero to time of the last measured concentration above the limit of quantification
AUCtau	The AUC during a dosing interval at steady state
BBI608, BBI-608	Napabucasin
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CDER	Center for Drug Evaluation and Research
Cmax	Maximum plasma drug concentration
Cmin, ss	Minimum plasma drug concentration at steady state
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent systemic clearance
CLss/F	Total body clearance at steady state
CR	Complete response
CRF	Case report form
CT	Computed tomography
CV	Coefficient of variation
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity

ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit
HED	Human equivalent dose
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIPAA	Health Information Portability and Accountability Act
IC50	Inhibitory concentration, 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
LDH	Lactic dehydrogenase
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observable adverse effect level
NOEL	No observable effect level
ORR	Overall response rate
PD	Progressive disease
PK	Pharmacokinetic

PR	Partial response
QD	Once daily
Racc Cmax	The acumulation ratio for Cmax
Racc AUCtau	The acumulation ratio for AUCtau
RANO	Response Assessment in Neuro-oncology
RP2D	Recommended Phase 2 dose
RBC	Red blood cell (count)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
Tmax	Time to maximum plasma concentration
Tlast	Time of last measurable (positive) observed concentration
t½	Terminal phase half-life
TMZ	Temozolomide
TNM Scale	Tumor node metastases scale
ULN	Upper limits of normal
Vz/F	Apparent total volume of distribution in the terminal phase
WBC	White blood cell (count)
λz	The elimination rate constant
λz_upper	Upper limit on time for values to be included in the calculation of λz
λz_lower	Lower limit on time for values to be included in the calculation of λz
λz_No	Number of points used in computing λz

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the third version of the statistical analysis plan, based on the BBI608-201GBM protocol dated March 9th, 2017 [1]. The major changes in this amendment are editing dosing intensity and compliance section, adding some abbreviations, adding back the PD/Biomarker analysis section,rearranging the secondary objectives by phase, adding language regarding sponsor terminated follow-up, adding information about last dose of study treatment, and elaborating on the statisticial methodology for PFS, DCR and ORR used in the statistical analyses section.

2. INTRODUCTION

2.1. Study Design

Phase Ib

This is an open-label, multi-center, phase Ib/II study of BBI608 administered in combination with temozolomide (TMZ) to patients with recurrent or progressive GBM who have not received prior bevacizumab therapy. The study is designed to explore the safety, tolerability and pharmacokinetics of BBI608, and to define a recommended phase 2 dose (RP2D) of BBI608 when administered in combination with TMZ.

ARM A: Patients who are candidates for surgical resection will receive BBI608 as monotherapy prior to resection, followed by post-operative BBI608 administered in combination with TMZ.

BBI608 will be administered at a dose-level of 480 mg twice daily for 7 (±2) days prior to a planned surgical resection or biopsy of recurrent GBM. BBI608 will be discontinued immediately prior to the surgical procedure and will remain discontinued pending clinical post-operative recovery of the patient.

Upon the clinical recovery of the patient and at a time between 15-28 days following surgery, BBI608 will be administered orally, daily, in combination with temozolomide that is administered at 150 mg/m^2 for days 1 through 5 of each 28-day cycle. The dose of temozolomide can be increased to 200 mg/m^2 as per standard TMZ dosing guidelines for patients who complete at least one cycle at 150 mg/m^2. The initial dose of BBI608 will be 480 mg twice daily. Dose adjustment is allowed.

Pre-Operative Period *BBI608 monotherapy*	SURGERY/BIOPSY	Post-Operative Period *BBI608 with TMZ*
BBI608 will be administered orally, daily, at a dose-level of 480 mg twice daily for 7 (±2) days prior to a scheduled resection for recurrent GBM.		BBI608 will be administered orally, daily, at a dose-level of 480 mg twice daily in combination with TMZ 150 mg/m^2 that is administered on days 1 through 5 of each 28-day cycle. Cycles will repeat until disease progression or another discontinuation criterion is met.
Approximately 7 (±2) days		*Begins between 15-28-days after surgery*

ARM B: Patients who are not candidates for surgical resection will receive BBI608 administered orally, daily, in combination with temozolomide 150 mg/m^2 that is administered on days 1 through 5 of each 28-day cycle. The dose of temozolomide can be increased to 200 mg/m^2 as per standard TMZ dosing guidelines for patients who complete at least one cycle at 150 mg/m^2. The initial dose of BBI608 will be 480 mg twice daily. Dose adjustment is allowed.

For patients in Arm A during the run- in period with BBI608 monotherapy, the same DLT rules as for the combination therapy will apply. Enrollment will be held if $\geq$2 of 6 patients are unable to undergo resection due to DLTs. Enrollment will also be held if $\geq$ 2 of 6 patients have an unexpected surgical complication.

Initial enrollment will be to a 6-patient safety cohort in each arm. These patients will be evaluated for the occurrence of DLT during the first 28 days of combination treatment with BBI608 and TMZ. If DLT is observed in $\geq$ 2 of 6 patients evaluable for DLT, the initial dose of BBI608 for all patients in that arm will be reduced to the next lower dose level of 240mg twice daily, and an additional 6-patient safety cohort will be enrolled at that dose-level and evaluated for DLT as above. Enrollment will continue at a dose-level at which $\leq$ 1 of 6 patients experiences DLT. Dose modification is allowed according to the standard schedule for BBI608.

Cycles of therapy will consist of the patient taking BBI608 daily in combination therapy for 28 days. Tumor assessments will be performed every two cycles (eight weeks), or as otherwise clinically indicated.

The RP2D is defined as the dose level at which no more than one patient with DLT is observed among six patients. Once the RP2D has been reached for a given arm based on

DLT assessment rules outlined above, up to 24 additional evaluable patients may be enrolled at RP2D.

It is expected that up to 30 patients (including those enrolled to the DLT evaluation cohorts) will be enrolled in each arm.

Phase II

In both Phase Ib and Phase II, a study cycle will consist of 28 days of daily administration of BBI608 and TMZ administration on days 1-5 of each cycle. Pharmacokinetic (PK) and pharmacodynamic assessments will be performed in the first cycle only. Safety and tolerability of BBI608 in combination with TMZ will be assessed for the duration of the study treatment and for 30 days after the last dose of BBI608. Evaluation of anti-tumor activity of BBI608 in combination with TMZ will be performed at 8-week intervals while patients remain on study according to RANO.

Patients will continue treatment with BBI608 and TMZ until the investigator has determined that they are no longer clinically benefiting due to progression of disease, or unacceptable toxicity, or until another discontinuation criterion is met. Treatment with BBI608 as monotherapy can continue if TMZ is discontinued for any reason. Also, the investigator may continue BBI608 in combination with TMZ or BBI608 monotherapy after the initial demonstration of radiological progression and in the absence of intolerable toxicities, performance status decline, worsening of disease related symptoms, radiographical findings that would warrant acute intervention and no ongoing severe toxicities that may be related to BBI608. The patient will also get repeat tumor assessments after 4-6 weeks.

2.2. Study Objectives

2.2.1. Primary Objectives

Phase Ib:

To determine the safety, tolerability, and RP2D of BBI608 when administered in combination with temozolomide in adult patients with recurrent or progressed glioblastoma (GBM).

Phase II:

To assess the progression free survival (PFS) of BBI608 administered with TMZ at 6 months.

2.2.2. Secondary Objectives

Phase Ib:

- To determine the pharmacokinetic profile of BBI608 administered in combination with TMZ

- To assess the preliminary anti-tumor activity of BBI608 when administered in combination with TMZ

- To determine the pharmacodynamics (i.e., identify biomarkers) of BBI608 administered in combination with TMZ

Phase II:

To assess the disease control rate (DCR), median progression free survival (PFS), objective response rate (ORR), and overall survival (OS) of BBI608 administered in combination with TMZ in patients with recurrent or progressed GBM

3. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Phase Ib

Dose Limiting Toxicities (DLTs): For definition of DLT, see section 4.5 of Protocol [1].

3.1.2. Phase II

Progression free survival (PFS) at 6 months of BBI608 administered in combination with TMZ: is defined as the proportion of patients who have survived without objective disease progression per RANO criteria for at least 6 months after enrollment.

3.2. Secondary Endpoints

3.2.1. Phase Ib

- PK parameters of BBI608 administered in combination with TMZ
- Objective tumor response, as assessed using the Response Assessment in Neuro-Oncology (RANO) (4)
- Pharmacodynamic parameters (or biomarkers in archival tumor tissues), if identified appropriately, of BBI608 administered in combination with TMZ

3.2.2. Phase II

- Disease control rate (DCR), objective response rate (ORR), progression free survival (PFS), and overall survival (OS) of BBI608 administered in combination with TMZ (see 10.1 for Response Criteria and PFS/OS definitions).

3.3. Safety Endpoints

3.3.1. Adverse Events and Laboratory Abnormalities in Phase 1b and Phase 2

- Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI

CTCAE] version 4.0), seriousness, and relationship to study therapy

- Other safety endpoints include physical examination, electrocardiogram (ECG) and vital sign data

3.4. Covariates

Demographic and baseline disease characteristics may be considered as covariates in population PK, PK/PD (biomarker) and anti-tumor efficacy exploratory analyses.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There is no hypothesis testing in this study.

4.2. Statistical decision rules

4.2.1. Phase Ib

4.2.1.1. Dose escalation and de-escalation

Dosing of BBI608 in each arm of this trial will be initiated at 480 mg twice daily; this dose is the monotherapy RP2D for BBI608 and is also the RP2D of BBI608 in combination with weekly paclitaxel or capecitabine. The BBI608 dose can be modified according to the following schedule:

Dosing Level	Description
Initial Dose	480 mg twice daily (960 mg total daily)
Modification Level –1	240 mg twice daily (480 mg total daily)
Modification Level—2	80 mg twice daily (160 mg total daily)
Modification Level—3	80 mg once daily (80 mg total daily)

The dose of TMZ can be escalated from 150 mg/m^2 daily to 200 mg/m^2 daily as per standard TMZ dosing guidelines for patients who complete at least one cycle at 150 mg/m^2.

Number of Subjects with DLT at a Given Dose Level for a Given Study Arm	Dose De-escalation Decision Rule
≤1 out of 6	This dose level will be considered RP2D for the combination regimen (BBI608+TMZ)
≥2 out of 6	Initial dose level will be reduced to a dose chosen by the Investigator and BBI medical monitor. Six (6) additional subjects will be entered at this lower dose level and evaluated for DLT over the first 28 days of combination therapy.

4.2.1.2. MTD and RP2D

MTD is defined as maximum tolerated dose, which is the highest dose-level at which <1 out of 6 patients experiences DLT.

The RP2D for a given combination arm is defined as the dose level at which no more than one patient with dose-limiting toxicity (DLT) is observed among six patients for each combination.

4.2.1.3. Sample size justification

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of three to six patients, if the true underlying rates of DLT are 0.1, 0.2, 0.3, 0.4, and 0.5, there will be a 91%, 71%, 49%, 31%, and 17% chance, respectively, of escalating to the next full dose.

4.2.2. Phase 2

The Phase 2 portion of this study will use an estimation approach for PFS-6. For each of the study arms, with a sample size of 30, the lower bound of the two-sided 80% confidence interval, using the exact binomial method using a projected PFS-6 of 20%, will be greater than 10%. This provides meaningful information for further clinical evaluation.

5. INTERIM ANALYSES

No formal interim analyses are planned for this study.

6. ANALYSIS SETS

6.1. Full Analysis Set

The full analysis set (FAS) includes all patients who received at least one dose of any study drug

6.2. PK Analysis Set

The PK analysis set will include all patients from Phase 1b/DLT assessment cohorts who received at least one dose of BBI608 and have at least one quantifiable concentration.

6.3. PD/Biomarker Analysis Set

The PD/Biomarker analysis population is defined as all patients treated and have at least one of the PD/Biomarkers evaluated (including both the patients with only pre-treatment data and those with both pre- and/or post-treatment data).

7. DATA HANDLING

7.1. Methods for Handling Missing Dates

All analyses and descriptive summaries will be based on the observed data. Except for the data otherwise specified in the language below, missing data will not be imputed or "carried forward". For the subject data listings, no imputation of incomplete dates will be applied. The listings will present the incomplete dates without any change.

Missing or Partial Death Dates

- If the entire date is missing, the death date will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, the death date will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
    - If day is missing, day will be 1st of the month
    - If both day and month are missing, death month and day will be January 1st.

Date of Last Dose of All Study Drugs

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and the End of Treatment eCRF page has not been completed and no death date has been entered, the patient should be considered ongoing and the cutoff date for the analysis should be used as the last dosing date.

- If the last date of study drug is completely or partially missing and there is EITHER a completed End of Treatment eCRF page OR a death date available (within the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < Month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

Missing Dates in Adverse Events/Concomitant Therapies

Dates missing the day or both the day and month of the year will adhere to the following conventions:

- The missing day of onset of an AE or start date of a therapy will be set to:
  - first day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment
  - the day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment
  - the date of informed consent, if the onset yyyy-mm is before the yyyy-mm of the first treatment

- The missing day of resolution of an AE or end date of a therapy will be set to:
  - the last day of the month of the occurrence. If the subject died in the same month, then set the imputed date as the death date

- If the onset date of an AE or start date of a therapy is missing both the day and month, the onset date will be set to:
  - January 1 of the year of onset, if the onset year is after the year of the first study treatment
  - the date of the first treatment, if the onset year is the same as the year of the first study treatment
  - the date of informed consent, if the onset year is before the year of the first treatment

- If the resolution date of an AE or end date of a therapy is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence. If the subject died in the same year, then set the imputed date as the death date

- If date is completely missing, then no imputation will be done and the event will be considered as treatment emergent (for AEs) or concomitant (for medications) unless the end date rules out the possibility.

Missing Efficacy Endpoints

For primary and secondary efficacy analyses no values will be imputed for missing data. For time to event endpoints, non-event observations will be censored and for ORR/DCR, patients with no post-baseline tumor evaluations or missing baseline tumor evaluation will be counted as non-responders.

Missing Age

If age is missing, age will be computed from birth date to the date of Informed Consent, as (Date of Informed Consent – Date of Birth +1)/365.25 round down to the nearest integer.

- If birth date is missing day, day will be set to 15th to minimize bias
- If missing both month and day, birth date will be set to July 1 of the birth year

7.2. Definition of Baseline Values

The baseline value is defined as the value collected at the time closest to, but prior to the start of study drug administration (BBI608 or TMZ, whichever was administered first). Values will be considered baseline if they are up to 10 days prior to first dose. An MRI scan performed within 28 days of the first schedule dose of BBI608 can be used for baseline assessment if it was performed while the patient was off steroids or on a stable or decreasing steroid dosage for at least 5 days; otherwise, MRI should be performed within 14 days of dosing. This will be the baseline scan for patients in Arm B; repeat MRI obtained within 48-72 hours following surgery will be the baseline scan for the patients in Arm A for purposes of response assessment.

7.3. Visit Windows

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.4. Dropouts

Time to event parameters will be censored if patients drop out (withdraw from consent or lost to follow-up) before documentation of the events (progressive disease / death). Rules for censoring for PFS are detailed in 10.2

7.5. Pharmacokinetics

For individual concentration-time plots and the calculation of PK parameters using noncompartmental analysis, individual BLQ values will be converted using the following rules:

- If a BLQ value occurs in a profile before the first quantifiable concentration, it will be assigned a value of zero.
- If a BLQ value occurs after a quantifiable concentration in a profile and is immediately followed by a value above the LLQ, then the BLQ value should be treated as missing.
- If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration) it will be treated as missing.
- If two BLQ values occur in succession after Cmax, the profile will be deemed to have terminated at the first BLQ value and any subsequent quantifiable concentrations will be omitted from PK calculations by treating them as missing.

When imputing BLQ concentrations for the generation of summary statistics at a given time point, all BLQ values will be set to zero except when an individual BLQ falls between two quantifiable values, in which case it will be treated as missing. These same imputations apply to imputation of BLQ concentrations used for generation of concentration-time profiles based on summary statistics.

7.6. Pharmacodynamic parameters

Missing data for the pharmacodynamic parameters will be treated as such and no imputed values will be derived.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Whilst every effort has been made to pre-specify all analyses in this statistical analysis plan, if any additional exploratory analyses be found to be necessary, the analyses and the reasons for them will be detailed in the clinical study report (CSR).

8.1.1. Analysis for Time to Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (2) will be provided. There will be no subjects that remain in follow-up because sponsor has terminated all follow-up after 29JUN2018.

8.1.2. Analysis for Binary Data

Point estimates of binary endpoints for each treatment arm will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method (3).

8.1.3. Analysis for Continuous Data

Descriptive statistics, such as the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. Linear or non-linear models may be employed to analyze the continuous data.

8.2. Statistical Analyses

8.2.1. Standard Analysis

Standard analaysis below will be conducted by arm. Overall summary for each arm will also be provided. Adverse Events, Concomitant Medications, and Medical History will be coded.

Study Conduct and Patient Disposition

Patient disposition includes the number and percentage of patients for the following categories: patients in each of the study populations, patients discontinued from the treatment, primary reason to discontinue from the treatment, and patients discontinued from the study. All percentages will be based on the number of patients in the full analysis dataset (FAS).

Demographic and Baseline Characteristics

Baseline characteristics such as demographics, baseline disease characteristics, prior therapies, and ECOG performance status score will be tabulated and listed.

Prior and concomitant medications

Prior and concomitant medications will be coded to ATC (Anatomical Therapeutic Chemical) classification and Drug Name using WHO Drug Dictionary (WHO-DD) version 19.0 March 2016.
Summaries of concomitant medications will be provided by level 3 ATC classification and preferred term using frequencies and percentages for the full analysis set.

Prior Treatment

Prior treatment will be summarized by arm and listed for each patient in the full analysis set.

Prior cancer surgery will be summarized by type and procedure. The number and percentage of subjects in each type of prior cancer surgery will also be reported by overall.

The total dose and type of prior cancer radiotherapy will be summarized. The number and percentage of subjects with the various anatomical locations will be reported.

The type, treatment setting, and number of prior cancer Hormone/Biologics/Chemotherapy/Other will be summarized. The number and percentage of patients reporting each category will be reported.

Medical History

Medical history will be coded by SOC and PT using MedDRA. Medical history will be summarized by SOC and PT using the number and percentage of patients for the full analysis set.

Duration of Follow-up

The duration of follow-up is defined as time from the date of first dose of study treatment to the death or last known visit. If a subject dies, the duration is equal to date of death minus study start + 1 with censor variable =1 (censored for follow up). If a subject is alive, the duration is equal to the date subject last known to be alive minus study start + 1 with censor variable=0 (event for follow up).

Extent of Exposure

Exposure may be summarized (overall and by period for Arm A subjects) as dose received (cumulative dose or actual dose intensity) or as dose received relative to intended dose (relative dose [RD], or relative dose intensity [RDI]), or both.

The information that will be summarized depends on how the study drug is dosed (e.g., infusion cyclical, oral daily, oral cyclical).

In what follows "time unit" can be e.g., weeks or days.

Drug accountability will be summarized in a listing.

Intended treatment duration = intended end of treatment date – date of first dose of study drug +1, where the intended end of treatment date is (start date of last cycle + intended cycle duration – 1 day) for each treatment arm

- For BBI608, intended cycle duration= max{28, date of last dose of the cycle – date of first dose of the cycle+1}
- For BBI608 in pre-surgical period for Arm A patients, intended cycle duration= surgical procedure date – first dose date + 0.5. Subjects in Arm A took BBI608 in the morning of the surgical procedure and thus took a half day's dose of BBI608.
- For cyclic combination drug TMZ, intended cycle duration=5 days

Actual treatment duration = actual end of treatment date – date of first dose of study drug +1,

- For BBI608 and TMZ, actual end of treatment date is last dosing date

Cumulative dose in a period (for Arm A subjects), cycle, or overall for BBI608 is the sum of the actual doses received in a period or cycle or overall, respectively. Cumulative dose overall for TMZ is the sum of the actual doses received overall.

Actual Dose Intensity [DI]

- For Arm A subjects: By period actual DI (*dose unit/week*) = [cumulative dose in the period]/[intended period duration in weeks]
- By cycle actual DI (*dose unit/week*) = [cumulative dose in cycle] / [intended cycle duration in *weeks*].
- Overall actual DI (*dose unit/week*) = [overall cumulative dose] / [intended treatment duration in *weeks*].

Relative dose [RD]: The basic intent is to evaluate dose per *week* factoring in dose reductions or interruptions.

- Relative dose by period (Arm A subjects), by cycle and overall
  - By period RD (%) = 100 × [cumulative dose in the period] / [intended cumulative dose per period]
  - By cycle RD (%) = 100 x [cumulative dose in the cycle] / [intended cumulative dose per cycle]
  - Overall RD (%) = 100 × [overall cumulative dose] / [total planned or intended dose]
- For a combination regimen
  - if a study drug is discontinued prematurely while other study drug(s) are continued, then the RD is 0 for the discontinued study drug until all other study drug(s) of the regimen are discontinued

Relative Dose Intensity (RDI): The basic intent is to evaluate dose per *week* factoring in dose reductions, interruptions, or delays.

- Relative dose intensity (RDI) by period (Arm A subjects), by cycle and overall
  - Intended DI (*dose unit/week*) = [intended cumulative dose per period/cycle] / [intended number of *weeks* in a period/cycle]
  - By period RDI (%) = 100 × [by period actual DI] / [intended DI]
  - By cycle RDI (%) = 100 x [by cycle actual DI] / [intended DI]
  - Overall RDI (%) = 100 × [overall actual DI] / [intended DI]

Note:

- The intended dose level is fixed at the start of treatment rather than the start of a cycle.

- The intended cumulative dose of BBI608 per period (for Arm A subjects) is calculated by (intended dose level per day) x (intended period duration in days).
- The intended cumulative dose of BBI608 per cycle is calculated by (intended dose level per day) x (intended cycle duration in days).
- Dose unit of BBI608 is mg; dose unit of TMZ is mg/m^2.

Treatment compliance

BBI-608 compliance will be summarized by period (for Arm A), for cycle 1 (Arm A post-operative and Arm B patients) and overall

1. By Period (Arm A): Treatment compliance for BBI-608 is defined as below, (Cumulative actual total dose per period/ total planned or intended dose per period) x 100=% compliance

2. By Cycle (Arm A post-operative and Arm B): Treatment compliance for BBI608 is defined as below, (Cumulative actual total dose per cycle /total planned or intended dose per cycle) x 100= % compliance

3. Overall: Treatment compliance for BBI-608 is defined as below, (Cumulative actual total dose /total planned or intended dose) x 100= % compliance

4. Daily treatment compliance will be reported for each patient for the following dose-levels and intervals

   - The % of days the patient received a total dose of at least 960 mg BBI608 out of intended treatment duration in days.
   - The % of days the patient received a total dose of at least 480 mg BBI608 out of intended treatment duration in days.
   - The % of days the patient received a non-zero dose of BBI608 out of intended treatment duration in days.

Daily treatment compliance will be grouped according to the following categories: < 60%,≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90%, and will be summarized for the treatment group of BBI608 Plus TMZ and BBI608 (for pre-surgery period for Arm A).

Combination drug compliance overall

5. Overall: For TMZ, compliance will be calculated using the following equation: (Number of treatments administered /number of treatments that should have been administered) x 100= % compliance

8.2.2. Analysis for Primary Endpoint

8.2.2.1. DLT (Phase 1b)

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. Listings of the DLTs will be provided for Arm A (BBI608 plus TMZ) and Arm B (BBI608 plus TMZ).

8.2.2.2. Progression Free Survival at 6 months (PFS-6, Phase1 and Phase 2)

PFS data will be analyzed by arm. PFS summary in Arm B will be provided only when the number of patients in that arm is at least 10. The same rule applies to Arm A data.

Progression free survival at 6 months (PFS-6) is defined as the proportion of patients who have survived without objective disease progression per RANO criteria for at least 6 months after enrollment. The censoring rules for PFS will be detailed in 10.2. If a patient has not progressed or died at the time of analysis, PFS will be censored on the date of the last tumor assessment. This includes patients who are lost to follow-up or have withdrawn consent.

PFS in months is calculated as (first event date/censored date – date of first dose of any study drug + 1)/30.4375. Estimates of the PFS curves at 6 months will be obtained using the Kaplan-Meier method and will be presented along with the 80% CI using the normal approximation to the log transformed cumulative hazard rate.

8.2.3. Analyses for Secondary Endpoints

8.2.3.1. Other Efficacy Endpoints Analysis

Response data (including Disease Control Rate (DCR) and Objective Response Rate (ORR)), progression free survival (PFS) and overall survival (OS) data will be analyzed by arm. Response data summary for Arm B will be provided only when the number of patients in that arm is at least 5. The same rule applies to Arm A data. Otherwise, only response data listing will be provided.

Summary for survival data (including PFS and OS) will follow the rule of 'at least 10' as described in Section 8.2.2.2.

DCR is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RANO. The primary estimate of DCR will be based on the FAS population. DCR will be summarized for each treatment arm along with the corresponding exact 2-sided 95% CI using the Clopper Pearson method.

ORR is defined as the proportion of patients with a documented complete response and partial response (CR + PR) based on RANO. The primary estimate for ORR will be based on the FAS population.

ORR will be analyzed similarly as DCR. Best Overall Response (BOR) will also be summarized in a similar fashion.

PFS in the full analysis set is defined as the time from exposure to any study drug to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of analysis, PFS will be censored on the date of the last tumor assessment. PFS is calculated as described in section 8.2.2.2.

PFS will be reported as the median event time (and other quartiles) and the corresponding 2-sided 95% CI for each treatment arm. Estimates of the PFS curves obtained from the Kaplan-Meier method will be presented along with a graphical presentation of PFS curves.

OS is defined as the time from exposure to any study drug to death from any cause. Patients who are alive at the time of analysis or who have dropped out will be censored at their last date known to be alive. OS in months is calculated as (date of death/Last known to be alive date – date of first dose of any study drug + 1)/30.4375.

The survival experience of patients will be summarized by the Kaplan-Meier method.

8.2.3.2. PK Analysis

Nuventra Pharma Sciences will compute PK parameters by noncompartmental analysis using Phoenix WinNonlin version 6.3 (Certara, L.P., Princeton, NJ), and generate TLFs using a validated version of R version 3.4.0 or later (R Foundation for Statistical Computing, Vienna, Austria).

Demographics for patients included in the PK Analysis Set will be summarized in the PK report, summarized by Arm.

8.2.3.2.1. PK Concentrations

Plasma concentrations will be listed and summarized by BBI608 dose, concomitant treatment, Arm, day, and nominal timepoint using descriptive statistics, including N, mean, standard deviation (SD), coefficient of variation (CV), minimum, maximum, and median. Imputation of concentration data BLQ is described in Section 7.5.

Actual elapsed time from dosing and the difference between actual and nominal time will be included in individual subject listings. Individual subject plasma concentrations versus actual elapsed time will be presented on spaghetti plots on linear scale and semi logarithmic scale. Mean plasma concentrations versus nominal time will be plotted on both linear and semi-logarithmic scales by day, BBI608 dose, concomitant therapy and Arm, as appropriate.

8.2.3.2.2. Pharmacokinetic parameters

Following pharmacokinetic parameters will be calculated for Cycle 1 Day 1 and Cycle 1 Day 5 as data allow:

- The maximum plasma concentration (Cmax)
- The time to reach maximum plasma concentration (Tmax)
- The area under the plasma concentration-time curve from zero to infinity (AUCinf) [Cycle 1, Day 1 only]
- The percentage of the AUC extrapolated beyond the last measurable concentration (AUCext)
- The AUC from time zero to time of the last measured concentration above the limit of quantification (AUClast)
- Time of last measurable (positive) observed concentration (Tlast)
- The AUC during a dosing interval at steady state (AUCtau) [Cycle 1, Day 5 only]
- The elimination rate constant (λz)
- Upper limit on time for values to be included in the calculation of λz (λz_upper)
- Lower limit on time for values to be included in the calculation of λz (λz_lower)
- Number of points used in computing λz (λz_No)
- Apparent systemic clearance (CL/F)
- Apparent total volume of distribution in the terminal phase (Vz/F)
- Terminal phase half-life ($t_{½}$)

Additionally for Cycle 1 Day 5, parameters listed below will be calculated where possible:

- Minimum concentration at steady state (Cmin,ss)
- Total body clearance at steady state (CLss/F)
- The acumulation ratio for Cmax and AUCtau will also be calculated (Racc Cmax and Racc AUCtau).

Derived plasma PK parameters will be summarized by day, BBI608 dose, concomitant treatment and Arm, as appropriate, using descriptive statistics including N, mean, SD, CV, geometric mean, geometric CV, minimum, maximum, and median. For Tmax and Tlast, N, minimum, maximum, and median will be reported.

All PK parameters will be estimated using actual elapsed time from dosing.

8.2.3.3. PD/Biomarker Analysis

BBI is exploring several biomarkers in tumor tissues. Tumor archival tissue and biopsies will be collected as described in the Laboratory Manual. The correlations between the biomarker results, pharmacokinetic parameters, and measures of anti-tumor/anti-cancer efficacy signals or safety signals will be explored if data allows and it is deemed appropriate.

8.2.4. Analysis for Other Safety Endpoints

All adverse events, lab, vital signs, physical exam, and ECG data analyses will be summarized based on the full analysis set. These data will be summarized by arm.

8.2.4.1. Adverse Events

Overall Summary of AEs

An AE will be regarded as **treatment-emergent**, if

- it occurs for the first time on or after the first dose date of either BBI 608 or TMZ up to 30 days after the last dose of study treatment; or
- it occurs prior to first dose date of either BBI 608 or TMZ and worsens in severity on therapy or up to 30 days after the last dose of study treatment

Last dose of study treatment will be obtained from either drug administration or end of treatment CRF, whichever comes later.

Concurrent conditions from CRF collecting Adverse Event include any event or condition that was active at the time of starting on study. Entries have a start date and a severity grade. This will be considered a baseline AE and be used to derive treatment-emergent AE.

Adverse events will be coded by SOC and PT using the MedDRA® version 19.0. The severity of AEs will be graded by the investigator using NCI CTCAE Version 4.0. The verbatim term will be included in the AE listings.

An overview of treatment-emergent adverse events (TEAEs) will be provided. The number and percentage of subjects with following will be summarized for:

1. Subjects with at least one TEAE
2. Subjects with TEAE of CTCAE grade 3 or higher
3. Subjects with serious TEAE
4. Subjects with serious TEAE related to BBI608
5. Subjects with serious TEAE related to TMZ
6. Subjects with BBI 608 related TEAE
7. Subjects with BBI 608 related TEAE of CTCAE grade 3 or higher
8. Subjects with TMZ related TEAE
9. Subjects with TMZ related TEAE of CTCAE grade 3 or higher
10. Subjects with TEAE related to study drug (BBI608 or TMZ)
11. Subjects with study drug (BBI608 or TMZ) related TEAE of CTCAE grade 3 or higher
12. Subjects with TEAEs leading to BBI-608 being held
13. Subjects with TEAE leading to dose reduction BBI-608
14. Subjects with TEAE leading to BBI-608 dose discontinuation
15. Subjects with TEAE leading to TMZ being held
16. Subjects with TEAE leading to dose reduction of TMZ

Summary of AEs by System Organ Class and Preferred Term

The number and percentage of subjects with TEAEs by SOC and PT and maximum CTCAE grade will be summarized. A summary of TEAEs of CTCAE grade 3 or higher (Grade 3, 4, 5) will be presented by SOC and PT and maximum CTCAE grade. A summary of TEAEs by SOC, PT and maximum grade will be presented in the descending order of frequency counts for all grades. The most commonly reported AEs using different cutoffs (e.g., 2%, 5% or 10% or more of patients in either arm) may also be summarized by PT as needed for various reporting purposes. Adverse events associated with dose held/dose reduction of either BBI608 and/or Temozolomide will also be summarized by SOC and PT and maximum CTCAE grade.

Treatment Related TEAE

AEs reported with a relationship to a treatment considered by the investigator to be 'possible', 'probable' or 'definite' will be considered "Related" to study treatment or combination drug, respectively. AEs reported with a relationship to a treatment considered by the investigator to be "unlikely" or "unrelated" will be considered as "Not Related" to study treatment or TMZ, respectively. Missing relationship will be considered as "Related". Similar summaries of all causality AEs will be provided along with TEAEs leading to dose modification, reduction, or discontinuation.

Serious AE and Death

Treatment emergent SAEs and treatment related SAEs will be summarized by MedDRA SOC and PT and Maximum CTCAE grade.

Patients who experienced a SAE during AE reporting period will be listed for all safety patients. The number and percentage of patients who experience any treatment emergent SAE will be summarized by SOC, PT and maximum CTCAE grade. Similar summary for treatment related TESAE will be provided as well.

Deaths that occur on or after the first dose of study treatment and within 30 days of last dose of any study treatment will be summarized. The number and percentage of subjects who died during the study treatment and within 30 days after the last dose will be presented.

TEAE or TESAEs leading to death will also be summarized by MedDRA, SOC, PT, and Maximum CTCAE grade.

A listing of death data will also be provided and it will include all deaths that occurred during the reporting period for deaths, which starts from the signing of informed consent to the end of the follow up period. The listing will include date of death, and the number of days relative to the administration of first and last dose.

Adverse Events of Clinical Relevance

Selected adverse events are specified for additional focus due to the potential clinical significance of the event and/or the potential association with the investigational product. These events include those in the standard MedDRA query (SMQ) terms (narrow or broad, as noted):

Table 1. Adverse Events of Clinical Relevance SMQ terms

MedDRA v20.0 Term	SMQ class
Myocardial infarction	Broad
Supraventricular tachycardia	Narrow
Non-infectious diarrhea	Broad
Gastrointestinal haemorrhage	Narrow
Gastrointestinal obstruction	Narrow
Acute kidney injury	Narrow (acute renal failure)

Tables listing the incidence and maximum severity of these events in the safety population will be generated.

8.2.4.2. Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables. The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, RBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and white blood cell (WBC) count

- Serum chemistry: electrolytes (sodium, potassium, and chloride), CO_2, calcium, phosphorus, magnesium, total protein, albumin, glucose, serum creatinine, urea, AST, ALT, LDH, alkaline phosphatase, total and direct bilirubin, and uric acid.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity (version 4.0) from baseline to post baseline worst CTC grade. Parameters to be tabulated will include:

- Hematology: hemoglobin, platelets, WBC, ANC
- Serum chemistry: ALT, AST, alkaline phosphatase, creatinine, total bilirubin, calcium, magnesium, potassium, sodium, and phosphate.

Summary statistics will also be presented for shift from baseline urinalysis values.

- Urinalysis: protein, specific gravity, glucose, and occult blood

Listings to be presented include hematology, serum chemistry, and urinalysis. These will include the test result, units, normal range (H and L), change from baseline, and CTCAE grades if graded.

8.2.4.3. Electrocardiograms

12-lead ECG with categorical results (Normal, Abnormal [Not clinically significant], Abnormal [clinically significant]) will be summarized by treatment and visit. The shift from baseline to worst post baseline will be produced. A patient listing will also be provided.

8.2.4.4. Physical Exam

Physical examination abnormalities will be summarized for each visit by body system and by treatment group. Patients with clinically significant abnormal findings will be flagged in the data listing.

8.2.4.5. ECOG

ECOG will be summarized in a shift table from baseline to worst post baseline for Full analysis set.

8.2.4.6. Vital Signs

Vital sign data will be summarized by treatment and by visit. Change from baseline will be additionally summarized by treatment group and visit.

Summaries of markedly abnormal vital signs parameters, including blood pressure (BP) and pulse, will be presented by treatment group. Values for vital signs for all patients will be presented in a listing, and patients with markedly abnormal values will be flagged.

Markedly abnormal ranges for vital signs parameters are given in the table below.

Vital Sign Parameter	Markedly Abnormal (Low)	Markedly Abnormal (High)
Systolic BP	Absolute value $\leq$ 90 mmHg, or a decrease from baseline $\geq$ 20 mmHg	Absolute value $\geq$ 180 mmHg, or an increase from baseline $\geq$ 20 mmHg
Diastolic BP	Absolute value $\leq$ 50 mmHg, or a decrease from baseline $\geq$ 15 mmHg	Absolute value $\geq$ 105 mmHg, or an increase from baseline $\geq$ 15 mmHg

Pulse	Absolute value $\leq$ 50 bpm, or a decrease from baseline $\geq$ 15 bpm	Absolute value $\geq$ 120 bpm, or an increase from baseline $\geq$ 15 bpm
BMI	Absolute value $\leq$ 18 kg/m^2	Absolute value $\geq$ 25 kg/m^2

9. REFERENCES

1. Protocol BBI608-201GBM A Phase Ib/II Clinical Study of BBI608 in Combination with Temozolomide in Adult Patients with Recurrent or Progressed Glioblastoma, March 9th, 2017

2. Blyth C.R., Still H.A. [1983]. Binomial Confidence Intervals *Journal of the American Statistical Association 78*, 381.

3. Brookmeyer R, Crowley JJ. [1982]. A confidence interval for the median survival time. *Biometrics*. 38:29-41.

4. Wen P.Y., Macdonald, D.R., Reardon, D.A., et al [2010]. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. *Journal of Clinical Oncology*. 28: 1963-1972.

10. APPENDICES

10.1. Appendix 1.1 Further Definition of Endpoints

Table 2 Response Criteria

Evaluation of lesions	
Complete Response (CR):	Requires ALL of the following: 1. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. 2. No new lesions. 3. Stable or improved non-enhancing (T2/FLAIR) lesions. 4. Patients must be off corticosteroids (or on physiologic replacement doses only). 5. Patients must be stable or improved clinically[£]
Partial Response (PR):	Requires ALL of the following: 1. Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. 2. No progression of non-measurable disease. 3. No new lesions. 4. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. 5. The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan. 6. Patients must be stable or improved clinically.[£]
Progressive Disease (PD):	Defined by ANY of the following: 1. Greater than 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.** 2. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects). 3. Any new lesion. 4. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. [£] 5. Failure to return for evaluation due to death or deteriorating condition. 6. Unequivocal progression of non-measurable disease.

Stable Disease (SD):	Requires ALL of the following: 1. Does not qualify for complete response, partial response, or progression. 2. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. IN the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid use was equivalent to the baseline dose. 3. Patients must be stable clinically.£

*Patients with non-measurable disease only cannot have a complete or partial response. The best response possible is stable disease.
**Stable doses of corticosteroids include patients not on corticosteroids.
£ Clinical status will be assessed via ECOG Performance Score.

The table below provides the summary of the RANO response criteria.

Table 3 Overall Response

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1/Gd enhanced lesions	None	>50% decrease	<50% decrease to <25% increase	>25% increase*
T2/FLAIR	Stable or decreasing	Stable or decreasing	Stable or decreasing	Increasing*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decreasing	Stable or decreasing	NA**
Clinical Status#	Stable or improving	Stable or improving	Stable or improving	Worsening*
Requirement for Response	ALL	ALL	ALL	Any*

*Progressive Disease occurs when any of the criteria marked by * are present.

**Increase in corticosteroid dose in isolation of other criteria will not be taken into account in the assessment of progressive disease in the absence of persistent clinical status deterioration.

#Clinical status will be assessed via ECOG Performance Score

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression. Patients will have confirmatory radiographic scanning within approximately 4 weeks of initial results of partial or complete response (PR or CR) according to RANO. If not confirmed, response will be SD.

BOR rules are described as below based on the requirement of confirmed responses per RANO criteria.

BOR Based on Confirmed Responses

CR: Two objective statuses of CR a minimum of four weeks apart documented before progression and start of new anti-cancer therapy.

PR: Two objective statuses of PR or better (PR followed by PR or PR followed by CR) a minimum of four weeks apart documented before progression and start of new anti-cancer therapy, but not qualifying as CR. Sequences of PR- SD- PR are considered PRs as long as the two PR responses are observed at a minimum of 4 weeks apart.

SD: At least one objective status of stable or better documented at least 8 weeks after start date and before progression and the start of new anti-cancer therapy but not qualifying as CR or PR.

PD: Progression documented within 16 weeks after start date and not qualifying as CR, PR or SD.

Not Evaluable (NE): All other cases. Note that reasons for NE should be summarized and the following reasons could be used:

- Early death (Note: death prior to 8 weeks after start date)
- No post-baseline assessments
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD too early (<8 weeks after start date)
- PD too late (>16 weeks after start date)

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

Derivation of BOR

The following table provides the derivation of BOR.

Table 3 Derivation of Best Overall Response when confirmation of response is required

Objective status at:

Assessment 1	Assessment 2	Assessment 3	Assessment 4	Overall Response
Death				NE
CR	CR	PD		CR
CR	NE	CR	PD	CR
PR	CR	CR	PD	CR
PR	CR	PD		PR
PR	PR	PD		PR
PR	SD or NE	PR	PD	PR
PR	PR	CR	PD	PR
CR	PR			Not allowed. Reappearance is progression
CR	PD or No or NE			SD
PR	PD or No or NE			SD
SD or NE	CR	PD		SD
SD or NE	PR	PD		SD
SD	PD			SD
PD				PD
No or NE assessment				NE
NE	PD			PD
NE	No or NE assessment			NE
NE	NE	PD		NE

Objective response rate (ORR) is defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RANO criteria as determined by the investigator assessment collected in the CRFs, relative to the Full Analysis Set.

The DCR is the proportion of patients whose best overall response is CR, PR or SD based on RANO full analysis set. The best response of SD can be assigned if SD criteria were met at least once after first dose date at a minimum interval of 8 weeks from BBI608. New anti-cancer treatment will be derived based on Concomitant Medication if available.

Progression free survival (PFS) is defined as the time from the date of the first dose of any study drug to the date of PD, or death due to any cause, whichever comes first. If neither event has been observed, then the patient will be considered as censored. PFS (in months) will be calculated as (first event date – first dose date of any study drug + 1) / 30.4375. Sensitivity analyses for PFS may be conducted if deemed necessary.

Overall survival (OS) is defined as the time from the date of the first dose of any study drug to the date of death from any cause. Patients who are still alive at the time of the final observation, or who have become lost to follow-up will be censored at their last date of contact. OS in month is calculated as (date of death – first dose date of any study drug +1) / 30.4375.

10.2. Appendix 1.2 Censoring for Time to Event Data

Table 4 summarizes the censoring rules for the PFS analysis and displays censoring hierarchy for this study. Table 5 shows the general reasons for PFS censoring and where the censoring hierarchy in **Table 4** came from.

Table 4 Event or Censor Time for PFS and Censoring Hierarchy

Censoring Hierarchy	Situation	Date of Event or Censor	Event / Censor
1	**No baseline** radiological tumor assessment available	Date of First Dose	Censored
2	**New anticancer treatment** started and no tumor progression	Date of previous adequate radiological assessment immediately prior to start of new therapy or Date of first dose, whichever comes later	Censored
3	**Tumor progression** (per RANO) documented after 2 scan intervals following previous adequate radiological tumor assessment	Date of previous adequate radiological assessment or Date of first dose, whichever comes later	Censored
4, 5	**No tumor progression** (per RANO) and subject lost to follow-up or withdrawal of consent	Date of last adequate radiological Assessment or Date of first dose, whichever comes later	Censored
6	**No post baseline** radiological tumor assessment available and no death reported within 2 scan intervals following the date of the first dose of study drug (BBI608)	Date of First Dose	Censored
7	**No post baseline** radiological tumor assessment available but death reported within 2 scan intervals following the date of the first dose of study drug (BBI608)	Date of Death	Event

	No tumor progression (per RANO) and no death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of last adequate radiological tumor assessment or Date of first dose, whichever comes later	Censored
	No tumor progression (per RANO) but death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of death	Event
	Tumor progression (per RANO) documented within 2 scan intervals following previous adequate radiological tumor assessment	Earliest of the target, non-target and new tumor assessment dates	Event

Notes: (1) Symptomatic deteriorations (i.e. symptomatic progressions, which are not radiographically confirmed) will not be considered as progressions.

(2) If target, non-target and new lesion assessments have different dates within a visit, then the earliest of those dates will be considered as the date of the tumor assessment if the assessment for that visit is progressive disease (PD); otherwise the latest date will be used.

(3) Adequate radiographical tumor assessment refers to an assessment with overall response of CR, PR, SD or PD.

(4) Comparing date of last tumor assessment to date of first dose is necessary if the last tumor assessment is baseline assessment

Table 5 PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event more than *2 weeks* from last adequate post-baseline tumor assessment/start date	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ start date OR End of study (EOS) = Subject refused further FU]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up

6	No event and [EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

For OS, patients last known to be alive are censored at date of last contact.

Date of Last Contact

The date of last contact will be derived for patients not known to have died at the analysis data cutoff date using the latest complete date (non-imputed) among the following:

- All patient assessment dates (e.g., blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, concomitant radiation, surgery)
- Start and end dates of follow-up anti-cancer therapies
- AE start and end dates
- Last date of contact where "Subject Remains in Follow-up" collected on the "Survival Follow-up" eCRF (do not use date of survival follow-up assessment unless status is alive)
- Study drug start and end dates
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Note:

1. This list is not all inclusive and should be agreed upon by the study team according to the data collected in the CRF
2. Only dates associated with patient visits or actual examinations of the patient should be used. Dates associated with a technical operation unrelated to patient status (e.g., the date a blood sample was processed) should not be used.
3. Assessment dates after the cutoff date will not be applied to derive the last contact date.