Sumitomo Dainippon Pharma Oncology

Protocol BBI608-503-103HCC

A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma

Statistical Analysis Plan (SAP)

Version: 2.5

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Date: 10SEP2020

STATISTICAL ANALYSIS PLAN APPROVAL

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VERSION HISTORY

This is the amendment version 2.4 of the statistical analysis plan (SAP).

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	14SEP2018	Yue Chang	Statistical Analysis Plan
Amendments 2.0-2.3	30AUG2019	Susan Wu	1. Entire document: Updated study drug name BBI608 to napabucasin; BBI503 to amcasertib 2. Section 2: Updated efficacy endpoints: ORR, DCR and PFS will be derived using both RECIST 1.1 and mRECIST 1.1. 3. Section 5: Deleted Enrolled population. Added response evaluable analysis set and dose escalation evaluable analysis set. 4. Section 7: Specified that data will be summarized by phase, arm, and assigned dose level. 5. Section 7: Updated the duration of follow-up. 6. Section 7: Deleted the "treatment compliance" in the exposure summaries, because it will be covered by the analysis of relative dose intensity. 7. Section 7: Added "Adverse Events of Clinical Relevance" in the Adverse Event summaries. 8. Section 7: Laboratory data will not be summarized by visit level. Data will be presented in listings. 9. Section 7: Added physical exam. 10. Section 7: Added separate AE summaries for the Run-in period.
Amendment 2.4	27MAR2020	Michael Dowd	Minor revisions to Section 5.3 (definition of Response Evaluable Set) to make wording more clear. Added a new summary table for concomitant medication using preferred base.

Amendment 2.5	10SEP2020	Michael Dowd	Clarification of presentation of PK/PD data (Section 7.2.3.1). Specified the method used to identify AEs leading to study drug discontinuation (Section 7.2.4.2).

List of Abbreviations

Abbreviation	Term
AEs	Adverse Events
AECR	Adverse event of clinical relevance
AFP	Alpha-feto protein
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CO_2	Carbon dioxide
CR	Complete response
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DCP	des-gamma-carboxy prothrombin
DCR	Disease control rate

DI	Dose intensity
DLT	Dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRFs	Electronic case report forms
EOT	End of treatment
HCC	Hepatocellular carcinoma
INR	International normalized ratio
ITT	Intent to Treat
LDH	Lactate Dehydrogenase
KM	Kaplan-Meier
LLQ	Low limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response evaluation criteria in solid tumors
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not Evaluable
OS	Overall survival
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RBC	Red Blood Cell
RD	Relative dose
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase II dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SMQ	Standardized MedDRA Query

SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods that will be used for the analyses of the clinical study report (CSR) for Boston Biomedical Protocol BBI608-503-103HCC. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP has been developed using Protocol amendment 4, dated 03Apr2018 [1].

1.1. Study Design

Phase Ib

This is an open label, phase 1b dose escalation study of napabucasin (BBI608) administered in combination with sorafenib (Arm 1), and amcasertib (BBI503) administered in combination with sorafenib (Arm 2) to patients with advanced hepatocellular carcinoma (HCC). Eligible patients will be randomized to either Arm 1 or Arm 2. The study is designed to explore the safety, tolerability and pharmacokinetics (PK) of napabucasin and amcasertib, and to define a recommended Phase II dose (RP2D) of napabucasin and amcasertib when administered in combination with sorafenib.

In Arm 1, initially 3 patients will be enrolled at napabucasin Dose-Level 1. Dose escalation will proceed with cohorts of 3 to 6 patients according to the criteria for dose escalation and the criteria for determining dose-limiting toxicity (DLT).

Napabucasin Dose Level	Napabucasin Dose & Schedule
Napabucasin Dose-Level I	160 mg Twice Daily
Napabucasin Dose-Level II	240 mg Twice Daily

In Arm 2, initially 3 patients will be enrolled at amcasertib Dose-Level 1. Dose escalation will proceed with cohorts of 3 to 6 patients according to the criteria for dose escalation and the criteria for determining DLT.

Amcasertib Dose Level	Amcasertib Dose & Schedule
Amcasertib Dose-Level I	100 mg Once Daily
Amcasertib Dose-Level II	200 mg Once Daily

Prior to initiation of combination therapy in each arm, sorafenib will be administered as monotherapy starting on Cycle 1, Day 1 for 14 days. Sorafenib will be administered at a fixed dose of 400 mg twice daily (800 mg total daily dose) for each arm and for each dose-level cohort. Dose-adjustment of sorafenib according to the approved product label is allowed. Following the sorafenib run-in period, the combination regimen will begin on Cycle 1, Day 15. Protocol therapy will continue in repeating 28-day cycles until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

For both arms, PK assessments will be performed on Cycle 1, Day 15 and Cycle 2, Day 15. An additional PK assessment may be performed to confirm exposure following dose modification. Once the RP2D is determined for both study arms, the phase II portion will begin.

Phase II

The phase II portion is an open-label, 3-arm, randomized phase II trial of patients with advanced HCC who have not received prior systemic treatment. Patients will be randomized to receive either Arm 1: sorafenib administered in combination with napabucasin (at the RP2D determined for napabucasin plus sorafenib during the phase Ib portion); Arm 2: sorafenib in combination with amcasertib (at the RP2D determined for amcasertib plus sorafenib during the phase Ib portion), or Arm 3: sorafenib alone at a starting dose of 400 mg twice daily. The starting dose for sorafenib is the same for all study arms.

When protocol amendment 3 [2] is in effect, Arm 2 in the Phase II portion was closed for enrollment due to amcasertib portfolio priorities and to increase efforts in enrolling patients to Arms 1 and 3.

At the time amendment 3 was in effect, there were approximately 10 patients already enrolled in Arm 2. Therefore, the actual sample size in Phase II by the end of the study is projected to be approximately 70 patients after amendment 3. Protocol therapy will continue in repeating 28-day cycles until disease progression, unacceptable toxicity, or another discontinuation criterion is met. Pharmacodynamic assessments will be performed in patients with readily accessible tumors through an optional on-study tumor biopsy. Archival tissue, if available, will be collected from all patients. Throughout the study, safety and tolerability of napabucasin in combination with sorafenib and of amcasertib in combination with sorafenib will be assessed for the duration of study treatment and up to 30 days after discontinuation of study drug (either napabucasin or amcasertib).

Evaluation of anti-tumor activity will be performed at regular 8-week intervals, with the first assessment 8 weeks (56 days) after Cycle 1, Day 1. The radiologic assessments will be evaluated according to response evaluation criteria in solid tumors (RECIST) 1.1 and modified RECIST (mRECIST) for patients with HCC. Alpha-feto protein (AFP) measurements will be performed at baseline, at the end of the 2-week sorafenib monotherapy Run-In, and at the start of each subsequent study cycle.

1.2. Study Objectives

1.2.1. Primary Objectives

Phase Ib

To determine the safety, tolerability, and RP2D of napabucasin administered in combination with sorafenib and of amcasertib administered in combination with sorafenib in adult patients with advanced HCC who have not received prior systemic chemotherapy.

Phase II

To evaluate the tolerability, safety, and preliminary anti-tumor activity in patients with advanced HCC randomized to receive treatment with sorafenib in combination with napabucasin, sorafenib in combination with amcasertib, or sorafenib alone; napabucasin and amcasertib would be administered at their respective RP2D dose levels for combination administration with sorafenib, which were determined during phase Ib.

1.2.2. Secondary Objectives

The secondary objectives of this study are as follows:

- To determine the PK profile of napabucasin administered in combination with sorafenib and of amcasertib administered in combination with sorafenib.
- To perform biomarker studies for napabucasin administered in combination with sorafenib and for amcasertib administered in combination with sorafenib.

2. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

2.1. Primary Endpoint(s)

Phase Ib

- Dose-Limiting Toxicities (DLTs): For definition of DLT, see section 3.10 of the Protocol [1].

Phase II

- Objective Response Rate (ORR) and Disease Control Rate (DCR).

ORR is defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR), using both RECIST and mRECIST assessment data.

DCR is defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) or stable disease (SD), using both RECIST and mRECIST assessment data. Response Criteria by RECIST and mRECIST is provided in Appendix 1.1 and 1.2, respectively. The categorizations of response (CR, PR, SD, progressive disease [PD], and not evaluable [NE]) and the derivations of BOR are provided in Appendix 1.3.

2.2. Secondary Endpoints

- Plasma concentration of napabucasin administered in combination with sorafenib.
- Plasma concentration of amcasertib administered in combination with sorafenib.
- Pharmacodynamics parameters (or biomarkers level in archival tissues) of napabucasin administered in combination with sorafenib.
- Pharmacodynamics parameters (or biomarkers level in archival tissues) of amcasertib administered in combination with sorafenib.

- Progression-Free Survival (PFS) by both RECIST and mRECIST in phase II.

  PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first.

  PFS censoring rules are provided in Appendix 1.4: Censoring for Time-to-Event Data.

- Overall Survival (OS)

  OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive.

2.3. Other Endpoints

2.3.1. Adverse Events

- Adverse events (AEs) characterized by type, frequency, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE version 4.0]), timing, seriousness, and relationship to study therapy.

- Laboratory abnormalities characterized by type, frequency, severity (graded by NCI CTCAE version 4.0), and timing.

2.4. Covariates

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

3. HYPOTHESES AND DECISION RULES

3.1. Statistical Hypotheses

There is no hypothesis testing in this study.

3.2. Statistical Decision Rules

3.2.1 Dose Escalation and De-escalation

Dose escalation decisions are based on the observed number of patients with a DLT.

Table 1 Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these additional 3 patients experience a DLT, proceed to the next dose level • If 1 or more of these additional 3 patients experience a DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the maximally tolerated dose. RP2D will not exceed the maximum tolerated dose (MTD).

3.2.2. MTD and RP2D

The maximum tolerated dose (MTD) for a given combination arm is defined as the dose level at which no more than 1 patient with a DLT is observed among 6 patients for each combination. RP2D will be determined according to safety, tolerability, and pharmacokinetics.

3.2.3. Sample Size Justification

Phase Ib

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of 3 to 6 patients during phase Ib, if the true underlying rates of DLT at a given dose-level are 0.1, 0.2, 0.3, 0.4, and 0.5, there will be 91%, 71%, 49%, 31%, and 17% chances, respectively, of escalating to the next full dose.

Phase II

There is no statistical hypothesis testing and the sample size of the phase II part of the study is considered to be clinically adequate to assess tolerability, safety, and preliminary anti-cancer activity of the study drug of interest. Estimation and 95% confidence intervals will be provided for the proportion of patients with Grade 3 AEs by treatment, as well as for the proportion of patients who are alive and progression-free at 4 months (PFS-4) after randomization for each arm. Other anti-cancer activity parameters will also be estimated.

4. INTERIM ANALYSES

No formal interim analyses are planned for this study.

5. ANALYSIS SETS

5.1. Intent to Treat (ITT) Analysis Set

The ITT population includes all randomized patients.

5.2. Safety Analysis Set

The safety population is defined as all patients who receive at least 1 dose of napabucasin, amcasertib, or sorafenib. The safety population will be used for all safety-related analyses such as AEs, laboratory tests, and vital signs.

5.3. Response Evaluable Analysis Set

The response evaluable set is defined as patients who have received at least one cycle of study treatment unless discontinued early due to death or PD and have had at least one disease assessment following the initiation of therapy. A subject completes a cycle if the daily treatment compliance of napabucasin/amcasertib/sorafenib for Arm1/Arm2/Arm3 respectively is 80% or higher in that cycle (cycle 1 or cycle 2). The response evaluable set will be used for analyses of DCR and ORR, as a sensitivity analysis to ITT analysis.

5.4. Dose Escalation Evaluable Analysis Set of Phase Ib

Patients are considered evaluable for the determination of dose escalation if they:

a) Experience a DLT

b) Complete 28 days of combination dosing at the assigned dose level

6. DATA HANDLING

6.1.1. Methods for Handling Missing Dates

For patient data listings, no imputation of incomplete dates will be applied. The listings will present incomplete dates, if applicable, without any change.

<u>Missing or Partial Death Dates</u>

Completely missing death dates will be imputed as the day after the date of last contact.

A death date missing the month and day will be imputed as Jan 1st of the year or the date after the date of last contact, whichever comes last.

A death date missing the day will be imputed as the 1st of the month or the day after the date of last contact, whichever comes last.

Date of Last Dose of Study Drug

No imputation will be done for first dose date. No imputation will be done for the date of last dose for patients off study. The date of last dose will be imputed by the analysis cutoff date for ongoing patients.

Date of Start of New Anti-Cancer Therapy

Incomplete dates for the start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses:

- Completely missing start date will be imputed as the day after study failure/relapse/PD, or the end date of new anti-cancer therapy if available, whichever comes first
- Start date missing both the month and day will be imputed as Dec 31st of the year, or the end date of new anti-cancer therapy if available, whichever comes first
- Start date missing the day will be imputed as the last date of the month, or the end date of new anti-cancer therapy if available, whichever comes first

Missing Dates in Adverse Events/Concomitant Therapies

Every effort will be made to avoid missing/partial dates in on-study data. Start dates of AEs/concomitant therapies will be imputed as follows:

- Completely missing start date will not be imputed.

Start date missing both the month and day will be imputed as:

- The date of the first dose if the year of the start date is the same as the date of first dose;
- otherwise, Jan 1st of the year of the start date will be used.

Start date missing the day will be imputed as:

- The date of first dose if the year and month of the start date are the same as the date of first dose;
- otherwise, the 1st of the month of the start date will be used.

Stop dates of AEs/concomitant therapies will be imputed as follows:

- Completely missing stop date will not be imputed.

- Stop date missing both the month and day will be imputed as Dec 31st of the year of stop date.
- Stop date missing the day will be imputed as the last date of the month of the stop date.

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead.

Missing Dates in Prior Therapies

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

- The missing day of start or end date of prior therapy will be imputed as:
  - the 15th of the month or date of informed consent, whichever is earlier.
- If the start or end date of a prior therapy is missing both the day and month, the date will be imputed as:
  - July 1 of the year or date of informed consent, whichever is earlier.
- If date is completely missing, then no imputation will be done.

6.2. Definition of Baseline Values

- Efficacy: The last measurement on or prior to the date of randomization will serve as the baseline measurement. In the event such a value is missing, the last assessment completed prior to the first study drug administration will be used as the baseline assessment.
- Safety: The last measurement prior to the first study drug administration will be used as the baseline assessment.

6.3. Windowing of Visits

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

6.4. Withdrawals, Dropouts, and Loss to Follow-up

Time-to-event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (PD / death). Rules for censoring for PFS are detailed in Appendix 1.4.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. Statistical Methods

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

7.1.1. Analysis for Time-to-Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method [5] and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint [4] will be provided.

7.1.2. Analysis for Binary Data

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

7.1.3. Analysis for Continuous Data

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

7.2. Statistical Analyses

In general, all data will be summarized by phase, arm, and assigned dose level (Phase Ib only), unless otherwise specified.

7.2.1. Standard Analysis

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, and primary reason to discontinue from the treatment. All percentages will be based on the number of patients in the ITT analysis set.

Demographic and Baseline Characteristics

- Demographics: Demographics will be summarized in a descriptive fashion in the ITT population. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, alcohol history, smoking history, and other parameters as appropriate. Patient enrollment by region and country may be summarized.
- Baseline disease characteristics: Eastern Cooperative Oncology Group [ECOG] performance status, cancer diagnosis and tumor stage at time of first pathologic diagnosis and at time of study entry.

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) (March 2016).

Medications that start and stop prior to the date of first treatment administration (either napabucasin or backbone, whichever is administered first) will be classified as 'prior' medications. If a medication starts on or after the date of first treatment administration up to the last dose date of study medication (inclusive), then the medication will be classified as 'concomitant'. If a medication starts before the date of first treatment administration and stops on or after the date of first treatment administration, then the medication will be categorized as both a 'prior' and 'concomitant' medication.

Summaries of prior and concomitant medications will be provided by level 3 ATC classification and preferred term using frequencies and percentages for the ITT analysis set. A separate concomitant medications table using preferred base and level 4 ATC classification will also be provided using frequencies and percentages for the ITT analysis set.

Prior Cancer Treatment

Prior cancer treatment, including surgery, radiotherapy and hormone/biologic/chemotherapy/ other treatments will be summarized and/or listed for the ITT analysis set if available.

Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) v19.0. Medical history will be summarized by system organ class (SOC) and preferred term (PT) using the number and percentage of patients for the ITT analysis set.

Duration of Overall Survival (OS) Follow-up

The duration of overall survival (OS) follow-up is defined as time from the date of randomization to either death or the last known visit alive. The median follow-up time for OS and the corresponding 95% confidence interval (using the method of Brookmeyer and Crowley, 1982 with the log-log transformation) will be summarized using the reverse Kaplan-Meier (KM) method for the safety set. The analysis involves the event and censoring rules to be switched (i.e., the patients who die become 'censored', and the censored patients are treated as the 'event').

Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be also provided.

Extent of Exposure

Exposure may be summarized (per cycle and/or overall) as dose received (cumulative dose or actual dose intensity) or as dose received relative to the 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).

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

- For napabucasin, amcasertib, and sorafenib, the actual end of treatment date is the last dosing date

Cumulative dose in a cycle or overall is the sum of the actual doses received in a cycle or overall, respectively.

Intended cumulative dose in a cycle or overall is the sum of the intended dose level doses in a cycle or overall, respectively.

Actual Dose Intensity [DI]

- By cycle actual DI (*dose unit*/*day*) = [cumulative dose in the cycle] / [actual cycle duration in days]
- Overall actual DI (*dose unit*/*day*) = [overall cumulative dose] / [actual treatment duration in days]

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

Relative dose intensity (RDI) by cycle and overall:

- Intended DI (*dose unit/day*) = [intended cumulative dose per cycle] / [intended number of days in a cycle]
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]

Daily treatment compliance

Daily treatment compliance will be reported for each patient by phase, treatment arm and dose level cohort.

- The % of days the patient received full daily dose of napabucasin/amcasertib or sorafenib or higher out of actual treatment duration in days.
- The % of days the patient received a non-zero dose of napabucasin/amcasertib or sorafenib out of actual 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 all arms.

These summaries will be performed for cycle 1 and overall.

7.2.2. Analysis for Primary Endpoint

7.2.2.1. Dose-Limiting Toxicity (Phase Ib)

7.2.2.2. Dose-Limiting Toxicity is the primary endpoint of the dose escalation component of the study, which will be summarized by treatment groups using the safety analysis set for patients in the dose escalation portion of the study. A listing of the DLTs will be provided. Objective Response Rate and Disease Control Rate

The ORR is defined as the percentage of patients with a BOR of CR or PR, and the DCR is defined as the percentage of patients with a BOR of CR or PR or SD. The categorizations of response (CR, PR, SD, PD, and NE) and the derivations of BOR are provided in Appendix 1.3.

ORR/DCR will be summarized for the ITT analysis set and repeated for the response evaluable analysis set as sensitivity analysis. ORR/DCR point estimates for each treatment arm will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method [3].

7.2.3. Analysis for Secondary Endpoints

7.2.3.1. PK and PD Analysis

Plasma concentration of napabucasin and amcasertib will be listed. Nominal times, actual PK sample collection times and dose will be included in the listing.

PD data will be listed if available.

7.2.3.2. Other Efficacy Endpoints Analysis

PFS and OS will be summarized and listed as appropriate. Efficacy parameters that involve disease progression as an endpoint will be derived by using both RECIST and mRECIST assessment data. The PFS and OS will be summarized with Kaplan-Meier method in the ITT analysis set with start day calculated from the date of randomization. KM analysis will not be conducted if the number of event is less than 5. Estimation and 95% confidence intervals will be provided for the proportion of patients who are alive and progression-free 4 months (PFS-4) after randomization for each arm.

Efficacy listings will be provided for best response, first CR/PR date, last date with CR or PR, most recent date without progression, progression date, death date, date of first response, date of last tumor assessment, etc.

Table 2 provides an overview of the efficacy analysis.

Table 2 Analysis Method Efficacy Endpoints

Endpoint	Analysis Set	Statistical Method	Missing Data
Response (ORR and DCR)	ITT/response evaluable analysis set	Exact CI	Observed case
Overall Survival (OS)	ITT	Kaplan-Meier	Censored at date of last contact (Appendix 1.4)
Overall Survival Follow-up Time	ITT	Reverse Kaplan-Meier	Event and censor in the original KM analysis are reversed.
Progression-Free Survival (PFS)	ITT/response evaluable analysis set	Kaplan-Meier	Censored per Table A.1.4.1 (Appendix 1.4)

7.2.4. Safety Analyses

All safety analyses will be summarized based on the safety analysis set.

7.2.4.1. Adverse Events

Overall Summary of AEs

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

- it occurs on the day of or after the first dose of napabucasin or amcasertib or a combination drug and up to 30 days after the last dose of any study drug; or
- it occurs prior to first dose date of napabucasin or amcasertib or a combination drug and worsens in severity on therapy and up to 30 days after the last dose of study drug.

Adverse events will be coded by SOC and PT using the MedDRA v19.0. The severity of AEs will be graded by the investigator using (NIH 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 patients will be summarized for:

- Patients with at least one TEAE
- Patients with TEAEs of CTCAE Grade 3 or higher
- Patients with serious TEAEs
- Patients with napabucasin-related TEAEs

- Patients with napabucasin-related TEAEs of CTCAE Grade 3 or higher
- Patients with amcasertib-related TEAEs
- Patients with amcasertib-related TEAEs of CTCAE Grade 3 or higher
- Patients with sorafenib-related TEAEs
- Patients with sorafenib-related TEAEs of CTCAE Grade 3 or higher
- Patients with napabucasin-related serious TEAEs
- Patients with napabucasin-related serious TEAEs of CTCAE Grade 3 or higher
- Patients with amcasertib-related serious TEAEs
- Patients with amcasertib-related serious TEAEs of CTCAE Grade 3 or higher
- Patients with sorafenib-related serious TEAEs
- Patients with sorafenib-related serious TEAEs of CTCAE Grade 3 or higher
- Patients with TEAEs leading to napabucasin dose hold
- Patients with TEAEs leading to dose reduction of napabucasin
- Patients with TEAEs leading to amcasertib dose hold
- Patients with TEAEs leading to dose reduction of amcasertib
- Patients with TEAEs leading to sorafenib dose hold

Patients with TEAEs leading to dose reduction of sorafenib

Summary of AEs during Run-in Period

Besides overall summary of AEs as described above, the analysis of AEs during Run-in period will be summarized separately. Run-in Period is defined from the first sorafenib dose date to one day prior to patient administrated the napabucasin/amcasertib, or to the end of treatment if patient discontinued the study treatment before the napabucasin/amcasertib administration. For Phase II sorafenib monotherapy arm patients, run-in period is defined as the first 14 days of sorafenib administration.

An overview of TEAEs during Run-in period will be provided. The number and percentage of patients will be summarized for:

- Patients with at least one TEAE
- Patients with TEAEs of CTCAE Grade 3 or higher
- Patients with serious TEAEs
- Patients with serious TEAEs of CTCAE Grade 3 or higher
- Patients with sorafenib-related TEAEs
- Patients with sorafenib-related TEAEs of CTCAE Grade 3 or higher
- Patients with sorafenib-related serious TEAEs
- Patients with sorafenib-related serious TEAEs of CTCAE Grade 3 or higher
- Patients with TEAEs leading to sorafenib dose hold
- Patients with TEAEs leading to dose reduction of sorafenib

Summary of Overall AEs and AEs during Run-in Period by System Organ Class and Preferred Term

The number and percentage of patients with overall AEs and AEs during run-in period 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.

Treatment-Related TEAEs

TEAEs reported with a relationship to a treatment considered by the investigator to be 'possible', 'probable' or 'definite' will be considered "Related" to either the study treatment or a combination drug. Missing relationships will be considered as "Related".

Serious AEs and Death

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

Patients who experience an SAE during the 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. A similar summary for treatment-related treatment-emergent SAEs will be provided also.

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

A listing of death data will also be provided and will include all deaths that occurred during the reporting period for deaths, which starts from the signing of the 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 the first and last dose.

Adverse Events of Clinical Relevance

Selected AEs were pre-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 standardized MedDRA query (SMQ) (narrow or broad, as noted):

Table 3 Adverse Events of Clinical Relevance SMQ Terms

MedDRA v19.0 Term	SMQ class
Ventricular fibrillation	NA (individual PT)
Ventricular tachycardia	NA (individual PT)
Non-infectious diarrhea	Broad
Gastrointestinal haemorrhage	Narrow

Gastrointestinal obstruction	Narrow
Acute kidney injury	Narrow (acute renal failure)

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

Adverse Events Leading to a Study Drug Discontinuation

Adverse Events leading to a study drug discontinuation will be identified based on any AEs collected on CRF End of Treatment page along with study drug hold action on Adverse Events page.

7.2.4.2. Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a laboratory value is reported using a non-numeric qualifier (e.g., 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.

By-patient listings to be presented include hematology, serum chemistry, urinalysis, and tumor marker for HCC AFP. Laboratory test results (units), normal range (H and L), with change from baseline (baseline value will be flagged in the listing), and CTCAE grades if applicable will be presented in laboratory listings. Patients who developed toxicities of Grade ≥ 3 will be flagged in the listings. The parameters to be listed are as follows:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC), white blood cell (WBC), platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, prothrombin time, and International Normalized Ratio (INR)

- Chemistry: sodium, potassium, chloride, carbon dioxide (CO_2), glucose, magnesium, calcium, phosphorus, total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, lactate dehydrogenase (LDH), total protein, albumin, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and uric acid.

- Urinalysis: specific gravity, protein, glucose, urinary sodium, urinary phosphate, and urinary creatinine.

- Tumor markers: AFP, AFP-L3%, des-gamma-carboxy prothrombin (DCP), CA242

Shift tables will be constructed for toxicity gradable laboratory parameters to tabulate changes in NCI CTCAE for toxicity (version 4.0) from baseline to post baseline worst CTCAE grade for gradable laboratory tests. Unscheduled laboratory test results will be included in laboratory shift tables.

For all lab parameters collected in the CRF, summary statistics for baseline values and maximum change from baseline will be presented by phase, treatment arm and dose level cohort based on the safety analysis set . Figures of maximum post-baseline vs baseline values will be plotted along with E-DISH scatter plots for key lab parameters, including but not limited to neutrophils, platelets, and liver function tests (ALT, AST, ALP, and total bilirubin).

7.2.4.3. Electrocardiograms

12-lead electrocardiogram (ECG) with categorical results (Normal, Abnormal [Not clinically significant], Abnormal [Clinically significant]) will be summarized. Shift tables showing results from baseline to worst post baseline will be provided. A patient listing will also be provided.

7.2.4.4. Vital Signs

For weight, temperature, heart rate, respiration rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), summary statistics for baseline values and maximum change (maximum increase, maximum decrease and no change) from baseline will be summarized based on the safety analysis set. A patient listing will also be provided.

7.2.4.5. Physical Exams

Physical examination findings (Normal, Abnormal, or Not Done) will be collected per protocol schedule. Data will be presented in a by-patient listing.

8. REFERENCES

[1] Boston Biomedical, Inc, 2018. A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma.

[2] Boston Biomedical, Inc, 2017. A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma.

[3] Clopper, C. J. and Pearson, E. S., 1934. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, 26, 404–413.

[4] Brookmeyer, R. and Crowley, J., 1982. A confidence interval for the median survival time. *Biometrics*, pp.29-41.

[5] Kaplan, E.L. and Meier, P., 1958. Nonparametric estimation from incomplete observations. *Journal of the American statistical association*, *53*(282), pp.457-481.

9. APPENDICES

Appendix 1.1. Response Criteria by RECIST 1.1

	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions Any pathological lymph nodes must have reduction in short axis of <10mm
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started. In addition to the increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Appendix 1.2. Response Criteria by mRECIST 1.1

	Evaluation of target lesions
Complete Response (CR):	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Progressive Disease (PD):	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Stable Disease (SD):	Any cases that do not qualify for either partial response or progressive disease

	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of intratumoral arterial enhancement
Stable Disease (SD):	Persistence of intratumoral arterial enhancement in one or more non-target lesions
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Patients with an imaging assessment that meets criteria for either complete response (CR) or partial response (PR) according to RECIST 1.1 or mRECIST should have a repeat, confirmatory, radiologic assessment approximately 4 weeks after the assessment in which CR or PR criteria were met.

Appendix 1.3. Evaluation of Best Overall Response

Target lesions	Non-Target lesions	Evaluation of New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The best overall response (BOR) is the best response recorded from start date until disease progression or start of new anti-cancer therapy. BOR is determined by the following order:

CR: One objective status of CR documented before progression or start of new anti-cancer therapy.

PR: One objective status of PR documented before progression and start of new anti-cancer therapy, but not qualifying as CR.

SD: At least one objective status of SD documented at least (8 weeks – 7 days) 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 + 7 days) after start date and not qualifying as uCR, uPR, or SD.

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 – 7 days) 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 – 7 days) after start date))
- PD too late (> (16 weeks + 7 days) 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’.

Appendix 1.4. 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 comes from.

Table 3 PFS (Primary Definition) Censoring Reasons and Hierarchy

Censoring Hierarchy	Situation	Date of Event or Censor	Event / Censor
1	**No baseline** radiological tumor assessment available	Date of Randomization	Censored
2	**New anticancer treatment** started and no tumor progression	Date of previous adequate radiological assessment immediately prior to start of new therapy	Censored
3	**Tumor progression** (per RECIST 1.1 or mRECIST) documented after 2 scan intervals following previous adequate radiological tumor assessment	Date of previous adequate radiological assessment	Censored
4, 5	**No tumor progression** (per RECIST 1.1 or mRECIST) and patient lost to follow-up or withdrawal of consent	Date of last adequate radiological assessment	Censored
6	**No post baseline** radiological tumor assessment available and no death reported within 2 scan intervals following the date of randomization	Date of Randomization	Censored
	No post baseline radiological tumor assessment available but death reported within 2 scan intervals following the date of randomization	Date of Death	Event
7	**No tumor progression** (per RECIST 1.1 or mRECIST) and no death reported within 2 scan intervals following last adequate radiological tumor assessment	Date of last adequate radiological tumor assessment	Censored
	No tumor progression (per RECIST 1.1 or mRECIST) but death reported within 2 scan intervals following last	Date of Death	Event

Censoring Hierarchy	Situation	Date of Event or Censor	Event / Censor
	adequate radiological tumor assessment		
	Tumor progression (per RECIST 1.1 or mRECIST) 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.

Table 4 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 (16 weeks+7 days*)* 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) = Patient 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

[a] More than (16 weeks+14 days) after last adequate tumor assessment. <Note: This should correspond to 2 or more missing assessments using the nominal schedule of assessments but best to describe directly as 16 weeks to match on how the analyses are performed as per the table above>

Date of Last Contact for Overall Survival

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
- Randomization date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Note:

- This list is not all inclusive and should be agreed upon by the study team according to the data collected in the CRF
- 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.
- Assessment dates after the cutoff date will not be applied to derive the last contact date.