Sumitomo Dainippon Pharma Oncology

Protocol BBI608-224

A Phase II Clinical Study of BBI608 in Adult Patients with Advanced Colorectal Cancer

Statistical Analysis Plan (SAP)

Version: Amendment 3

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Date: 9 September 2020

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Protocol BBI608-224

STATISTICAL ANALYSIS PLAN APPROVAL

Approved by:

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Contents

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the amendment 1 of the statistical analysis plan (SAP).

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	17SEP2018	Yue Chang	Statistical Analysis Plan
Amendment 1	15Nov2019	Yanqiu Weng	Clarification of statistical methods
Amendment 2	02Mar2020	FMD	Address biostat comments
Amendment 3	09Sep2020	Jay Hu	Address some internal comments

2. 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 BBI608-224.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 up to Protocol amendment 2 dated 09Oct2014.

2.1. Study Design

This is an open label, multi-center, Phase II study of napabucasin (BBI608) administered in combination with either cetuximab, or panitumumab, or capecitabine to patients with advanced colorectal cancer. The study is designed to explore the safety, tolerability, preliminary anti-tumor activity and pharmacokinetics of napabucasin when administered in combination with each one of the above regimens.

Six patients would be initially enrolled in each combination arm at a napabucasin dose level of 500 mg BID (1000 mg total daily using 50 mg capsules) before protocol amendment 2 or 480 mg twice daily (960 mg total daily dose) using 80 mg capsules after protocol amendment 2. If ≤ 1 out of 6 patients had an observable dose limiting toxicity (DLT) in the combination regimen, then that arm of the study would continue to enroll patients at 500 mg BID (1000 mg total daily) using 50 mg capsules or 480 mg BID (960 mg total daily) using 80 mg capsules following a Simon 2-stage design. If a DLT occurred in ≥ 2 of the 6 patients in a combination arm, then that arm of the study would be closed and no further patients would be enrolled. A given arm of napabucasin in combination with cetuximab, or panitumumab, or capecitabine would continue to enroll patients if no more than 1 out of 6 patients in the combination arm had an observable DLT.

The number of colorectal cancer patients enrolled would be based on a two-stage Simon design and is presented in Section 4.1 of the protocol amendment 2 [5]. If any of the three arms reach a disease control rate (DCR) of 60% or higher at the end of the Simon Stage 2 portion of the study, a one-time option to expand accrual to a total sample size of up to 50 patients may be implemented for each arm.

To evaluate the tolerability of napabucasin, patients from each arm would be assigned to one of 4 sub-cohorts (with 6 patients in each sub-cohort: IA, IB, IIA, IIB) from protocol amendment 2. The evaluation of tolerability would be done at selected centers for the study arm that was continuing patient accrual and in which a total of 50 evaluable patients had not been reached. For each

combination arm, patients assigned to sub-cohorts IA and IB would receive napabucasin at 240 mg twice daily (480 mg total daily dose) starting on Day 1 of Cycle 1. Intra-patient dose escalation of napabucasin to 480 mg twice daily (960 mg total daily dose) was allowed for patients in these cohorts as tolerated. Patients assigned to sub-cohorts IIA and IIB would receive napabucasin at 480 mg twice daily (960 mg total daily dose) starting on Day 1 of Cycle 1. In the event of toxicity, dose adjustment of napabucasin was permitted, as recommended in dose modification guidelines. Additionally, patients assigned to sub-cohorts IA and IIA would receive prophylactic anti-diarrheal treatment starting the day prior to Day 1 of Cycle 1. Patients assigned to sub-cohorts IB and IIB would receive anti-diarrheal treatment on an as-needed basis starting with development of diarrhea (ie, any occurrence greater than the patient's baseline). For each combination regimen, patients would be sequentially assigned to each of the 4 sub-cohorts in the following order until 6 patients were accrued in each of the sub-cohorts: IA, IB, IIA, and IIB. If required, up to an additional 20 patients might be assigned to selected sub-cohorts to validate the observations in the initial 6 patients.

Table 1 Tolerability Analysis of Napabucasin

Sub-cohort	Napabucasin Starting Dose Level	Anti-diarrheal Administration*
IA	240 mg bid (480 total daily dose)[1]	Prophylactic
IB	240 mg bid (480 total daily dose)[1]	As needed
IIA	480 mg bid (960 total daily dose)[2]	Prophylactic
IIB	480 mg bid (960 total daily dose)[2]	As needed

[1]Intra-patient dose escalation of napabucasin to 480 mg po twice daily (960 mg total daily dose) is allowed as tolerated.

[2]In case of toxicity, dose adjustment of napabucasin is permitted.

*See protocol amendment 2 [5] section 7.1.4 for details

A study cycle would consist of 28 days of daily administration of napabucasin in combination with cetuximab or panitumumab, or capecitabine. Cycles would continue until unacceptable toxicity, disease progression (clinical or radiological) or another discontinuation criterion is met. Pharmacokinetic (PK) assessments would be performed on the first 6 patients enrolled in each combination arm. Pharmacodynamic assessments would be performed in patients with readily accessible tumor tissue through an optional tumor biopsy. Evaluation of anti-tumor activity would be performed at 8-week intervals per RECIST 1.1 while patients remain on study.

2.2 Study Objectives

2.1.1. Primary Objectives

To determine the safety and preliminary anti-tumor activity of napabucasin when administered in combination with cetuximab, or panitumumab, or capecitabine in adult patients with advanced colorectal cancer who have failed first- and second-line treatment.

The primary endpoint is disease control rate, defined as the proportion of patients with a documented complete response, partial response and stable disease (CR + PR + SD) based on

RECIST 1.1. The secondary endpoints include progression-free survival (PFS) and overall survival (OS).

2.1.2. Secondary Objectives

The secondary objectives of this study are as follows:

- To determine the pharmacokinetic profile of napabucasin and cetuximab, or panitumumab, or capecitabine when administered in combination.
- To determine the pharmacodynamics (biomarkers) of napabucasin.
- To evaluate tolerability of two dosing regimens of napabucasin by comparing administration of napabucasin at a 240 mg twice daily starting dose and escalating to 480 mg twice daily after Cycle 1 versus administration of napabucasin at a 480 mg twice daily starting dose with dose adjustment permitted.
- To evaluate tolerability of napabucasin by comparing prophylactic administration of anti-diarrheal medication versus as-needed administration of anti-diarrheal medication. The tolerability will be assessed using the adverse event profile and achieved dose intensity.

3. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Disease Control Rate (DCR), defined in section 2.1.1

3.2. Secondary Endpoints

- PK parameters of napabucasin administered in combination with cetuximab, or panitumumab, or capecitabine.

- PK parameters of capecitabine and metabolite (5-FU).

- Pharmacodynamics parameters (or biomarkers) of napabucasin administered in combination with cetuximab, or panitumumab, or capecitabine. Response (increase or decrease) of several biomarkers of napabucasin from biopsied tumors following napabucasin administration will be examined in patients with accessible tumors who consent to an optional biopsy.

- Objective Response Rate (ORR)

  ORR is defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR). The categorizations of response (CR, PR, SD, PD, and NE) and the derivations of BOR is provided in Appendix 1.1 and 1.2.

- Progression Free Survival (PFS) and Overall Survival (OS)

PFS is defined as the time from the date of first treatment (or date of enrollment in sensitivity analysis) to the date of first documentation of progressive disease (PD) or death due to any cause, whichever occurs first.

OS is defined as the time from the date of treatment (or date of enrollment in sensitivity analysis) 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.

- Dose Limiting Toxicities (DLTs): For definition of DLT, see Section 4.5 of the protocol amendment 2 [5].

3.3. Other Endpoints

- 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.

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. DLT Decision Rule

DLT decisions are based on the observed number of patients with DLT at 480 mg BID napabucasin.

Number of Patients with DLT at 480 mg bid	DLT Decision Rule
$\leq$ 1 out of 6	Continue patient enrollment in combination arm
$\geq$ 2 out of 6	Close combination arm of the study

4.2.2. Simon's Design Decision Rule

The Simon's design decision rule is described in Section 4.1 of protocol amendment 2 [5], but the study was not conducted following the Simon two-stage design and no Simon's design decision rule was applied.

4.3. Sample Size Justification

The sample size for this study was determined by clinical rather than statistical considerations. The exact number of patients estimated for this trial is dependent on the number of patient cohorts investigated based on the toxicity encountered. It is expected that up to a total of approximately 50 response evaluable patients will be enrolled in each combination arm during the study. Patients who have received at least one cycle of study treatment unless discontinued due to death or PD and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response.

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 enrolled patients.

6.2. Safety Analysis Set

The safety population is defined as all patients who receive at least 1 dose of any study drug. The safety population will be used for all safety-related analyses such as AEs, concomitant medications, laboratory tests, and vital signs.

6.3. Response Evaluable 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. At least one cycle of study treatment is defined as at least 80% daily treatment compliance at targeted dose level during one cycle (cycle 1 or cycle 2) period prior to the first post-dosing imaging assessment. The response evaluable set will be used for analyses of disease control rate and overall response.

6.4. PK Analysis Set

The napabucasin PK analysis dataset will include all patients who received at least one dose of napabucasin and have at least one quantifiable concentration.

The capecitabine and 5-fluorouracil PK analysis datasets will include all patients who received at least one dose of capecitabine and have at least one quantifiable concentration.

7. DATA HANDLING

7.1. Methods for Handling Missing Dates

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

Missing or Partial Death Dates

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

A death date missing 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 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. 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 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 treatment failure/relapse/PD, or the end date of new anti-cancer therapy if available, whichever comes first
- Start date missing both 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 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 adverse events/concomitant therapies will be imputed as follows:

- Completely missing start date will not be imputed .
- Start date missing both month and day will be imputed as:
    - the date of 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 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 adverse events/concomitant therapies will be imputed as follows:

- Completely missing stop date will not be imputed.
- Stop date missing both month and day will be imputed as Dec 31st of the year of stop date.
- Stop date missing 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. In any cases above, if the imputed start date is after the end date, then set the start date the same as the end date.

7.2. Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but on or prior to, the start of study drug administration. CT and MRI scans may be considered for baseline assessment only if they were performed within 30 days of the first dose of napabucasin.

7.3. 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.

7.4. Withdrawals, Dropouts, 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 (progressive disease / death). Rules for censoring for PFS are detailed in Appendix 1.3.

7.5. Pharmacokinetics

For individual concentration-time plots and the calculation of PK parameters using noncompartmental analysis, individual below the limit of quantification (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 lower limit of quantification (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 additional exploratory analyses are 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 (KM) method [3] and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint [2] will be provided. KM analysis will only be performed if the number of events is no less than 5.

8.1.2. 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 [1].

8.1.3. 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.

8.2. Statistical Analyses

In general, all data will be summarized by arm and sub-cohort, unless otherwise specified.

8.2.1. 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 study, and primary reason to discontinue from the study. The summary will be based on the FAS.

Demographic and Baseline Characteristics

Baseline characteristics such as demographics, prior medication, medical history, Eastern Cooperative Oncology Group (ECOG) performance status, and primary diagnosis will be tabulated for the safety set and listed for the FAS.

- Demographics: Demographics will be summarized in a descriptive fashion. Baseline demographic data to be evaluated will include age, sex, race, height, weight, and other parameters as appropriate. Patient enrollment by region and country may be summarized.
- Baseline disease characteristics: ECOG performance status, stage at study entry, and K-RAS mutation status.

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 2015).

Medications that start and stop prior to the date of first treatment administration (either napabucasin or backbone chemotherapy, whichever is administered first) will be classified as 'prior' medications. If a medication starts on or after the date of first treatment administration, 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 safety analysis set. Additional summary of concomitant medication will be provided by preferred name base and drug class.

Prior Cancer Treatment

Prior cancer treatment included surgery plus radiotherapy and hormone /biologic/ chemotherapy /other treatments, where the former will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 18.0 and the latter will be coded using WHO Drug.

Prior cancer treatment may be summarized by System Organ Class (SOC) and Preferred Term (PT) as appropriate for each patient in the safety analysis set.

Medical History

Medical history will be coded by SOC and PT using the MedDRA version 18.0 prior to the analysis. Medical history will be summarized by SOC and PT using the number and percentage of patients

for the safety analysis set.

Duration of Overall Survival Follow-up

The duration of overall survival (OS) follow-up is defined as time from the date of first treatment to death or the last known alive visit. 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 (ie, 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 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 (eg, infusion cyclical, oral daily, oral cyclical).

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

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

- For napabucasin and Capecitabine, the actual end of treatment date is the last dosing date
- For cyclic combination drugs in Arms A and B, actual end of treatment date = last dose of cyclic dosing + interval - 1, where interval = 7 for Arm A and interval =14 for Arm B.

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

Actual Dose Intensity [DI]

- By cycle actual DI (*dose unit*/*week*) = [cumulative dose in the cycle]/ [actual cycle duration in *weeks*]
- Overall actual DI (*dose unit*/*week*) = [overall cumulative dose] / [actual treatment duration in *weeks*]
- *Note that actual DI for cyclical dosing is calculated based on actual cycle duration in all but the last cycle where it is fixed at the intended duration.*

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*/*time unit*) = [intended cumulative dose per cycle] / [intended number of *time units* in a cycle]
- By cycle RDI (%) = 100 × [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

- One exception is for Cetuximab. For Cetuximab, dose level is permitted to change from 400 mg/m^2 on day 5 in cycle 1 to 250 mg/m^2 for each subsequent infusion. If dose level decreases for Cetuximab 4-7 days after first dose date, then updated dose level is the new intended dose level for Cetuximab.
- Second exception is for all backbone therapies. All backbone therapies incorporate BSA or weight to calculate each dose. Panitumumab incorporates weight to calculate each dose—all other therapies incorporate BSA. Therefore, the BSA to be used for calculating each dose of the backbone therapies will be using the Mosteller method (see below) based on the last available weight and height prior to each infusion. For Panitumumab, the last available weight prior to each infusion will be used for calculating each dose.
- *BSA [m^2] = ((Height [cm] × Weight [kg])/3600) × 0.5*
- Calculated doses will be rounded to the nearest integer
- Cumulative dose, actual dose intensity and relative dose intensity will remain missing if they cannot be derived due to missing weight, or BSA. Height from the most recent earlier visit can be used if height is missing.

The intended cumulative dose of napabucasin per cycle is calculated by (intended dose level per day) × (intended cycle duration in days)

- Intended dose level per day for napabucasin is 500mg po BID

Dose unit of napabucasin is mg, dose unit of other combination drugs (except Panitumumab) is mg/m^2, dose unit of Panitumumab is mg/kg.

Treatment compliance

Treatment compliance for napabucasin is defined as follows:

(Cumulative actual total dose / total planned or intended dose) × 100 = % compliance

For any IV combination drug (Cetuximab and Panitumumab), compliance will be calculated using the following equation:

(Number of treatments administered / number of treatments that should have been administered) × 100 = % compliance

For oral combination drug (Capecitabine), compliance will be calculated using the following equation:

(Cumulative actual total dose / total planned or intended dose) × 100 = % compliance

Daily treatment compliance will be reported for each patient by dose level cohort.

- The % of days the patient received full daily dose of napabucasin or higher out of actual treatment duration in days.
- The % of days the patient received a non-zero dose of napabucasin out of actual treatment duration in days.
- The % of days the patient received full daily dose of napabucasin or higher out of the first 56 days from treatment start.
- The % of days the patient received a non-zero dose of napabucasin out of the first 56 days from treatment start.

Daily treatment compliance will be grouped according to the following categories: < 60%, ≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90%, and will be summarized for all arms.

8.2.2. Analysis for Primary Endpoint

The primary endpoint is DCR, which is defined as the proportion of patients with a documented complete response (CR), partial response (PR), and stable disease (SD). The categorization of response (CR, PR, SD, PD, and NE) and the derivations of BOR are provided in Appendix 1.1.

DCR will be summarized by arm and sub-cohort for the response evaluable set. DCR point estimates will be provided along with the corresponding 2-sided 95% confidence intervals using an exact method [1]. Sensitivity analysis of DCR will be performed for all patients in the safety set.

8.2.3. Analysis for Secondary Endpoints

8.2.3.1. PK Analysis

Nuventra Pharma Sciences will compute PK parameters by noncompartmental analysis using Phoenix WinNonlin version 8.1 (Certara, 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 and cohort.

8.2.3.1.1. PK Concentrations

Plasma concentrations will be listed and summarized by napabucasin dose, concomitant treatment, and nominal timepoint using descriptive statistics, including N, mean, standard deviation, coefficient of variation (CV), minimum, maximum, and median.

Figures of individual and mean drug concentrations vs actual or nominal elapsed time will be presented on linear and semi logarithmic scales by day, napabucasin dose, and concomitant therapy, as appropriate.

8.2.3.1.2. Pharmacokinetic parameters

PK parameters for napabucasin, including maximum concentration at steady state (Cmax,ss), the timepoint when Cmax was observed (Tmax), area under the plasma concentration time curve during a dosing interval at steady state (AUCtau), minimum concentration at steady state (Cmin,ss), total body clearance at steady state (CLss/F), volume of distribution during terminal elimination phase at steady state (Vz/F), and terminal elimination half-life (t1/2) will be listed and summarized using descriptive statistics, including N, mean, standard deviation, CV, geometric mean, geometric CV, minimum, maximum, and median. For Tmax, N, minimum, maximum, and median will be reported. Parameters will be summarized by day, napabucasin dose, concomitant therapy and cohort.

PK parameters for capecitabine and metabolite 5-FU, including maximum concentration after a single dose (Cmax), the timepoint when Cmax was observed (Tmax), area under the plasma concentration time curve from zero to the last quantifiable concentration (AUClast), area under the plasma concentration time curve from zero extrapolated to infinity (AUCinf), total body clearance (CL/F) volume of distribution during the terminal elimination phase (Vz/F), and t½, will be listed and summarized using descriptive statistics, including N, mean, standard deviation, CV, geometric mean, geometric CV, minimum, maximum, and median. For Tmax, N, minimum, maximum, and median will be reported. Parameters will be summarized by day and napabucasin dose.

Napabucasin PK parameters will be estimated using actual elapsed time from napabucasin dosing. PK parameters of capecitabine and metabolite 5-FU will be estimated using actual elapsed time from capecitabine dosing. Imputation of concentration data for BLQ is described in Section 7.5.

8.2.3.2. PD/Biomarker Analysis

Tumor archival tissues and biopsies will be collected as described in the protocol amendment 2 [5] Section 6.5. A listing of tumor biomarkers may be provided if data are available.

Additional analyses of safety and/or efficacy may be performed in subsets defined by biomarker status as determined by evaluation of archival tissue.

8.2.3.3. Other Efficacy Endpoints Analysis

Summary tables of Objective Response Rate (ORR), Progression Free Survival (PFS), and Overall Survival (OS) will be provided by arm and sub-cohort. The ORR will be summarized for the response evaluable set and safety set. The PFS and OS will be summarized with KM method for all patients in the safety set with start day calculated from the date of first treatment. Sensitivity analysis may be considered for PFS and OS based on the FAS with start day calculated from the date of patient enrollment if data are available. KM analysis will not be conducted if the number of events is less than 5.

Efficacy listings to be provided include 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 and last tumor assessment date, etc. Swimmer plots for individual response and time on treatment, waterfall plots for individual tumor size percent change from baseline, and spider plots for individual tumor size percent change from baseline over time may also be presented.

The following table provides an overview of the efficacy analysis.

Endpoint	Analysis Set	Statistical Method	Missing Data
Response (DCR, ORR, CR, PR)	Efficacy	Exact CI	Observed case
Overall Survival (OS)	Efficacy	Kaplan-Meier	Censored at date of last contact (Appendix 1.3)
Progression Free Survival (PFS)	Efficacy	Kaplan-Meier	Censored per Table **A.1.3.1** (Appendix 1.3)
Overall Survival and PFS follow-up time)	Efficacy	Reverse Kaplan-Meier	Event and censor in the original KM analysis are reversed.

8.2.3.4. DLT

A listing of the DLTs will be provided by arm and cohort.

8.2.4. Safety Analyses

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

8.2.4.1. 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 either napabucasin 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 either napabucasin 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 version 18.0 prior to the analysis. The severity of AEs will be graded by the investigator using 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 TEAE of CTCAE Grade 3 or higher
- Patients with serious TEAE
- Patients with napabucasin related TEAE
- Patients with napabucasin related TEAE of CTCAE Grade 3 or higher
- Patients with Cetuximab related TEAE
- Patients with Cetuximab related TEAE of CTCAE Grade 3 or higher
- Patients with Panitumumab related TEAE
- Patients with Panitumumab related TEAE of CTCAE Grade 3 or higher
- Patients with Capecitabine related TEAE
- Patients with Capecitabine related TEAE of CTCAE Grade 3 or higher
- Patients with napabucasin related serious TEAE
- Patients with napabucasin related serious TEAE of CTCAE Grade 3 or higher
- Patients with Cetuximab related serious TEAE
- Patients with Cetuximab related serious TEAE of CTCAE Grade 3 or higher
- Patients with Panitumumab related serious TEAE
- Patients with Panitumumab related serious TEAE of CTCAE Grade 3 or higher
- Patients with Capecitabine related serious TEAE
- Patients with Capecitabine related serious TEAE of CTCAE Grade 3 or higher
- TEAE as the primary reason leading to end of study

Summary of AEs by System Organ Class and Preferred Term

The number and percentage of patients with AEs 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 PT and maximum grade will be presented in the descending order of frequency counts for all grades.

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 BBI608 or a combination drug, respectively. Missing relationship will be considered as "Related". Summaries similar to those for the "all causality AEs" will be provided.

Grade II or above Diarrhea

Number of days of Grade II or above diarrhea will be summarized. For patients who had a Grade II or above diarrhea TEAE ongoing at the time of analysis, the duration of TEAE will be censored at data cutoff or safety follow-up completion date, whichever is earlier. The safety follow-up completion date is the defined as the earlier day of the last treatment plus 30 days and death day (if applicable).

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 an SAE during the AE reporting period will be listed for all safety patients.

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 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 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 standard MedDRA (narrow or broad, as noted) query terms of: non-infectious diarrhea (broad SMQ), gastrointestinal haemorrhage (narrow SMQ), gastrointestinal obstruction (narrow SMQ), acute kidney injury (narrow acute renal failure SMQ) and preferred term of ventricular fibrillation and ventricular tachycardia. Tables listing the incidence, maximum severity and drug relationship 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 laboratory 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 follow:

- Hematology: CBC including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell, and platelet count.

- Blood chemistry: CO_2, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, lactate dehydrogenase (LDH), uric acid, blood urea nitrogen (BUN), AST, ALT, alkaline phosphatase, total and direct bilirubin, and total protein, sodium, potassium, and chloride.

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: ALC, ANC, hemoglobin, platelet count, WBC
- 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 blood.

By-patient listings to be presented include hematology, serum chemistry, and urinalysis results.

A listing of all laboratory parameters, including hematology, biochemistry, and urinalysis, will be provided, including the test result, units, normal range (H and L) and change from baseline, and CTCAE grades (if available). Patients who developed toxicities of Grade ≥ 3 will also be listed.

Figures of maximum post-baseline vs baseline values will be produced for key lab parameters, including but not limited to ANC, platelets, and liver function tests (ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin) as well as E-DISH scatter plots.

8.2.4.3. Electrocardiograms

12-lead 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.

8.2.4.4. Vital Signs

For systolic blood pressure, diastolic blood pressure, pulse, and respiration 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.

Summaries of markedly abnormal vital signs parameters, including blood pressure (BP) , pulse, and BMI,will be presented.

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 following table.

Table Vital Sign Threshold of Interest

Vital Sign Parameter	Markedly Abnormal (Low)	Markedly Abnormal (High)
Systolic BP	Absolute value ≤ 90 mmHg, or a decrease from baseline ⩾20 mmHg	Absolute value ≥ 180 mmHg, or an increase from baseline ⩾20 mmHg
Diastolic BP	Absolute value ≤ 50 mmHg, or a decrease from baseline ⩾15 mmHg	Absolute value ≥ 105 mmHg, or an increase from baseline ⩾ 15 mmHg
Pulse	Absolute value ≤ 50 bpm	Absolute value ≥ 120 bpm
BMI	Absolute value ≤ 18 kg/m^2	Absolute value ≥ 25 kg/m^2

9. REFERENCES

[1] 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.

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[5] Boston Biomedical, Inc, 2014. A Phase II Clinical Study of BBI608 Adult Patients with Advanced Colorectal Cancer. Amendment 2

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10. APPENDICES

Appendix 1.1. Response Criteria

	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 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

Patients with an imaging assessment that meets criteria for either complete response (CR) or partial response (PR) must have a repeat radiologic assessment approximately 4 weeks after the assessment in which CR or PR criteria were met.

Appendix 1.2. 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 and 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 – 1 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 + 1 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 – 1 days) after start date)*
- No post-baseline assessments
- All post-baseline assessments have overall response of NE
- New anti-cancer therapy started before first post-baseline assessment
- SD too early (< (8 weeks – 1 days) after start date)
- PD too late (> (16 weeks + 1 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 1.3. Censoring for Time to Event Data

Table A.1.3.1 summarizes the censoring rules for the PFS analysis and displays censoring hierarchy for this study. Table A.1.3.2 shows the general reasons for PFS censoring and where the censoring hierarchy in Table A.1.3.1 came from.

Table A.1.3.1 PFS Censoring Reasons and 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	Censored
3	**Tumor progression** (per RECIST 1.1) 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) 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 the first dose of study drug (napabucasin)	Date of First Dose	Censored
	No post baseline radiological tumor assessment available but death reported within 2 scan intervals following the date of the first dose of study drug (napabucasin)	Date of Death	Event
7	**No tumor progression** (per RECIST 1.1) 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) but death reported within 2 scan intervals	Date of death	Event

	following last adequate radiological tumor assessment		
	Tumor progression (per RECIST 1.1) 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 (ie, 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 A.1.3.2 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+1 day)* 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+1 day)* 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 (eg, 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 "Patient 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/enrollment date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Note:

- *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 (eg, 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.*