SAP BBI608-246

A Phase Ib/II Clinical Study of BBI608 in Combination with Standard Chemotherapies in Adult Patients with Advanced Gastrointestinal Cancer

Statistical Analysis Plan (SAP)

Version: 4.0

Author: [redacted]

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	August 2, 2017	[redacted]	Statistical Analysis Plan
Version 2.0	August 30, 2018	[redacted]	• Laboratory variables and analysis have been edited. • Censoring rules have been edited for PFS
Version 3.0	July 10, 2019	[redacted]	• Analysis sets have been edited • Study Day has been added • Methods for handling missing data has been edited • Details regarding the efficacy endpoint analyses have been added • Details regarding the TEAE analysis have been edited • Analysis for AECRs have been added • Laboratory analysis has been edited • Karnofsky performance status analysis has been added • ECG analysis has been edited • Physical exam analysis has been added • PFS censoring hierarchy has been edited

Version 3.1	February 24, 2020	[redacted]	• BBI608 has been changed to napabucasin • Extent of Exposure section has been edited • Analysis for treatment discontinuation due to TEAE has been added • Two additional AECRs have been added • Additional summarization of concomitant medications has been added • Prior therapy analysis has been edited • E-dish plot has been added • Concurrent medical conditions summary has been added
Version 4.0	October 12, 2020	[redacted]	• Removed mixed effects model assessing the effect of bevacizumab on napabucasin PK with the coadministration of FOLFOX6 or FOLFIRI

STATISTICAL ANALYSIS PLAN APPROVAL

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Contents

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AECR	Adverse Event of Clinical Relevance
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate transaminase (SGOT)
AUC	Area under the time-concentration curve
BID	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
BLQ	Below the limit of quantification
CBC	Complete blood count
CDER	Center for Drug Evaluation and Research
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CRC	Colorectal Cancer
CRF	Case report form
CT	Computed tomography
CV	Coefficient of variation
CTCAE	Common terminology criteria for adverse events
DCR	Disease Control Rate
DLT	Dose limiting toxicity
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular Carcinoma

Hct	Hematocrit
HED	Human equivalent dose
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIPAA	Health Information Portability and Accountability Act
IC_{50}	Inhibitory concentration, 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
LDH	Lactic dehydrogenase
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not Evaluable
NOAEL	No observable adverse effect level
NOEL	No observable effect level
ORR	Objective response rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RBC	Red blood cell (count)
SAE	Serious adverse event
SD	Stable disease
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (AST)

SGPT	Serum glutamic pyruvic transaminase (ALT)
SMQ	Standard MedDRA Query
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to maximum plasma concentration
TNM Scale	Tumor node metastases scale
ULN	Upper limits of normal
WBC	White blood cell (count)

1. AMENDMENTS FROM PREVIOUS VERSION(S)

This is the fourth version of the statistical analysis plan, based on the BBI608-246 protocol dated June 23rd, 2017. The major changes in this amendment are replacing BBI608 with napabucasin, the analysis sets, addition of study day, details regarding the efficacy endpoint analyses, methods for handling missing data, extent of exposure analysis, details regarding the TEAE analysis, addition of analysis for AECRs and adding two additional AECRs, editing of lab analyses, addition of Karnofsky performance status analysis, addition of physical exam analysis, editing ECG analysis, editing of PFS censoring hierarchy, adding in treatment discontinuation due to TEAE analysis, adding a new summary table for concomitant medication using preferred base, editing the summarization of prior therapies, adding concurrent medical conditions summary, removing mixed effects model assessing the effect of bevacizumab on napabucasin PK with the coadministration of FOLFOX6 or FOLFIRI, and adding an E-DISH plot.

2. INTRODUCTION

2.1. Study Design

Phase Ib

Phase Ib is an open-label study of oral napabucasin administered with either FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan to patients with advanced GI malignancy. The study is designed to explore the safety, tolerability and pharmacokinetics of napabucasin, and to define a recommended Phase 2 dose (RP2D) of napabucasin when administered in combination with each one of the above regimens (except for irinotecan study arm for which RP2D in combination with napabucasin has been established).

Initially, 3 patients will be enrolled in each combination arm (except for the irinotecan study arm for which enrollment will begin with the expansion phase skipping dose-limiting toxicity (DLT) period assessment since the RP2D for napabucasin in combination with irinotecan has been established) at a napabucasin dose level of 240 mg twice daily (480 mg total daily dose—Cohort I). If 0 out of 3 patients experience a DLT, then the napabucasin dose will be escalated to 480 mg twice daily (960 mg total daily dose—Cohort II) and 6 patients will be enrolled at this dose level. If 1 out of 3 patients in the 240 mg twice daily cohort experience a DLT, then an additional 3 patients will be enrolled in that arm. If a DLT occurs in ≥2 of the 6 patients in an arm, then the napabucasin dose will be reduced to 160 mg twice daily (320 mg total daily dose—Cohort Ib) and 6 patients will be enrolled at this does level.

If <1 of 6 patients experience a DLT at the 240 mg twice daily dose level, then napabucasin dose will be escalated to 480 mg twice daily (960 mg total daily dose) and 6 patients will be enrolled at this dose level. If ≤1 out of 6 patients experiences a DLT at 480 mg twice daily, this dose level will be considered the RP2D for napabucasin in that combination.

If ≥2 out of 6 patients experience a DLT at 480 mg twice daily, then RP2D will be declared as the next lowest dose level at which ≤1 out of 6 patients experiences a DLT.

Cycles of therapy will consist of the patient taking napabucasin daily in combination therapy for 28 days. Tumor assessments will be performed every two cycles (8 weeks), or as otherwise clinically indicated.

Dose escalation would be performed using patient cohorts as shown in Table 1.

Table 1: Dose Escalation Scheme for Napabucasin

Cohort	Total Daily Dose[a] (mg)	Number of Patients
I	480 mg	3 [b,c]
Ib	320 mg	3 [b,d]
II	960 mg	6

[a.] Daily dose must be taken one hour prior to or two hours after meals

[b] If a napabucasin-related DLT is seen in a 3-patient cohort an additional 3 patients will be enrolled at the same dose

[c]If ≥2 of 6 patients experience a napabucasin-related DLT, then the napabucasin dose will be reduced to 160 mg twice daily (total daily dose of 320 mg—Cohort Ib) and 6 patients will be enrolled at this dose level.

[d]If ≥2 patients experience a napabucasin-related DLT at this dose level, the arm will be closed to accrual.

The RP2D 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. Once the RP2D has been reached for a given combination arm based on DLT assessment rules outlined above, up to 15 additional evaluable patients may be enrolled at RP2D. If a patient drops-out another patient may be enrolled such that there are 15 evaluable patients available for analysis. An additional 20 evaluable patients will be enrolled on the hepatocellular carcinoma, cholangiocarcinoma, gastric/GEJ, esophageal or pancreatic adenocarcinoma disease cohorts. Up to an additional 50 evaluable FOLFIRI/XELIRI-refractory colorectal cancer (CRC) patients will be enrolled on the FOLFIRI (with bevacizumab if clinically indicated) study arm as an expansion cohort.

Phase II

In Phase II, 50 evaluable FOLFIRI/XELIRI-refractory CRC patients will be enrolled on the FOLFIRI study arm (with bevacizumab if clinically indicated) as an expansion cohort. FOLFIRI/XELIRI-refractory CRC patients will have failed treatment with FOLFIRI/XELIRI with or without bevacizumab regimen with failure defined as progression of disease during or ≤3 months after the last dose of FOLFIRI/XELIRI with or without bevacizumab. For the FOLFIRI/XELIRI-refractory CRC patients enrolled on the expansion cohort for whom bevacizumab is clinically indicated, bevacizumab 5 mg/kg will be administered intravenously following irinotecan/leucovorin infusion. In case of toxicity, dose adjustment is permitted.

In both Phase Ib and Phase II, a study cycle will consist of 28 days of daily administration of napabucasin in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. Pharmacokinetic (PK) and pharmacodynamic assessments will be performed in the first cycle only for each drug combination. If there is an indication of drug accumulation, PK assessment can be performed for more than two cycles. Safety and tolerability of napabucasin in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan will be assessed for the duration of study treatment and for 30 days after the last dose of napabucasin. Evaluation of anti-tumor activity of napabucasin in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan will be performed at 8 week intervals while patients remain on study according to RECIST 1.1. Patients will have confirmatory radiographic scanning within approximately 4 weeks of initial results of partial response (PR) or complete response (CR) according to RECIST 1.1.

2.2. Study Populations

This study is conducted in patients with advanced solid gastrointestinal malignancies for whom treatment with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan is an appropriate treatment option in the judgment of physician investigators. Examples of gastrointestinal cancers eligible for protocol therapy include the following:

- Colorectal Cancer (CRC)
- Hepatocellular Carcinoma (HCC)
- Pancreatic Adenocarcinoma
- Cholangiocarcinoma
- Gastro-esophageal Carcinoma

The study will be conducted at sites in the United States, Canada, and Europe.

2.3. Determination of Sample Size

Phase Ib

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of 3 to 6 patients, if the true underlying rates of DLT 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 in the Phase II part of the study. The sample size for this phase will use an estimation approach for objective response rate (ORR). If an ORR

response rate with FOLFIRI (with bevacizumab if clinically indicated) in combination with napabucasin is observed to be 12% with evaluable number of patients of N=50, the 95% confidence interval (CI) for the true ORR will be (4.5%, 24.3%) using exact method and the corresponding confidence interval length will be 19.8%. The following table provides some examples of the 95% CIs of the true ORR when various ORRs are observed with different evaluable numbers of patients.

N	Observed ORR	95% CI of True	95% CI length
40	10%	(2.8%, 23.7%)	20.9%
40	12%	(3.9%, 26.2%)	22.3%
40	14%	(5.1%, 28.6%)	23.6%
50	10%	(3.3%, 21.8%)	18.5%
50	12%	(4.5%, 24.3%)	19.8%
50	14%	(5.8%, 26.7%)	20.9%
60	10%	(3.8%, 20.5%)	16.7%
60	12%	(5.0%, 23.0%)	17.9%
60	14%	(6.4%, 25.4%)	19.0%

2.4. Study Objectives

2.4.1. Primary Objectives

Phase Ib:

To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of napabucasin when administered in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan in adult patients with advanced gastrointestinal (GI) cancer.

Phase II:

To assess the objective response rate (ORR) of napabucasin administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory metastatic colorectal cancer (mCRC).

2.4.2. Secondary Objectives

Phase Ib:

- To determine the pharmacokinetic profile of napabucasin administered in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab or regorafenib

- To assess the preliminary anti-tumor activity of napabucasin when administered in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan.

- To determine the pharmacodynamics (i.e., identify biomarkers) of napabucasin administered in combination with FOLFOX6 with and without bevacizumab or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan.

Phase II:

To assess the disease control rate (DCR), progression free survival (PFS), and overall survival (OS) of napabucasin administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory mCRC.

3. ENDPOINTS AND COVARIATES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Phase Ib

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

3.1.2. Phase II

Objective response rate (ORR) of napabucasin administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory mCRC, which is defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RECIST 1.1 as determined by the investigator assessment collected in the CRFs, relative to the Response Evaluable analysis set (see Table 4 in Appendix 1.1 for Response Criteria).

3.2. Secondary Endpoints

3.2.1. Phase Ib

- PK parameters of napabucasin administered in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab or regorafenib.

- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (8.1).

- Pharmacodynamics parameters (or biomarkers in archival tumor tissues), if identified appropriately, of napabucasin administered in combination with FOLFOX6 with and without bevacizumab or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan.

3.2.2. Phase II

- Disease control rate (DCR), progression free survival (PFS), and overall survival (OS) of napabucasin administered in combination with FOLFIRI (with

bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory mCRC (see 8.1 for Response Criteria and PFS/OS definitions).

3.3. Safety Endpoints

3.3.1. Adverse Events, Laboratory Test Results, and Other Safety Endpoints in Phase Ib and Phase II

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

- Laboratory test results as characterized by type, change from baseline, and severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0)

- Other safety endpoints include physical examination, Karnofsky performance score, electrocardiogram (ECG) and vital signs data.

3.4. Covariates

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

4. INTERIM ANALYSES

No formal interim analyses are planned for this study

5. ANALYSIS SETS

5.1. Full Analysis Set

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

5.2. Response Analysis Set

The response data will be summarized for all patients who receive at least one cycle of study drug, have measurable disease at baseline, and at least one post baseline response assessment. Initiation of therapy is defined as the date of the first dose of napabucasin. At least one cycle of study treatment is defined as at least 80% daily treatment compliance at targeted dose level during one cycle period prior to the first post-dosing imaging assessment.

5.3. PK Analysis Set

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

5.4. Pharmacodynamics/Biomarker Analysis Set

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

6. DATA HANDLING

6.1. Methods for Handling Missing Dates

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

Missing or Partial Death Dates

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

Date of Last Dose of All Study Drugs

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

- If the last date of study drug is completely missing and the End of Treatment eCRF page has not been completed and no death date has been entered, the patient should be considered ongoing and the cutoff date for the analysis should be used as the last dosing date.
- If the last date of study drug is completely or partially missing and there is EITHER a completed End of Treatment eCRF page OR a death date available (within the data cutoff date), then impute this date as the last dose date:

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

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

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

Missing Dates in Adverse Events/Concomitant Therapies

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

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

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

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

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

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

Missing 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 set to:
  - 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 set to:

  - July 1 of the year or date of informed consent, whichever is earlier

- If date is completely missing, then no imputation will be done

Missing Efficacy Endpoints

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

Missing Age

Age will be computed from birth date to the date of Informed Consent, as (Date of Informed Consent – Date of Birth +1)/365.25 rounded down to the nearest integer.

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

6.2. Definition of Baseline Values

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

6.3. Study Day

Study day is calculated as:

- Assessment date – first dose date + 1; if the assessment was performed on or after the first dose date.
- Assessment date – first dose date; if the assessment was performed prior to the first dose date.

6.4. Visit Windows

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

6.5. Dropouts

Time to event parameters will be censored if patients drop out (withdraw from consent or lost to follow-up) before documentation of the events (progressive disease / death). Rules for censoring for PFS are detailed in Appendix 1.2 Censoring for Time to Event Data

6.6. Pharmacokinetics

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

· If a BLQ value occurs in a profile before the first quantifiable concentration, it will be assigned a value of zero.

· If a BLQ value occurs after a quantifiable concentration in a profile and is

immediately followed by a value above the LLQ, then the BLQ value should be treated as missing.

· If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration) it will be treated as missing.

· If two BLQ values occur in succession after Cmax, the profile will be deemed to have terminated at the first BLQ value and any subsequent quantifiable concentrations will be omitted from PK calculations by treating them as missing.

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

6.7. Pharmacodynamic Parameters

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

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 and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each time-to-event endpoint (3) will be provided. The 6 month, 1 year, and 18 month survival probability will be estimated using the Kaplan-Meier method and a 2-sided 95% CI will be calculated using the normal approximation to the log transformed cumulative hazard rate.

7.1.2. Analysis for Binary Data

Descriptive statistics (frequency and percentage) of binary endpoints for each treatment arm will be provided along with the corresponding 2-sided 95% confidence intervals using the Exact Method based on the F distribution (Clopper-Pearson method) (2).

7.1.3. Analysis for Continuous Data

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

7.2. Statistical Analyses

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 patients ongoing. All percentages will be based on the number of patients in the full analysis dataset (FAS) and will be summarized by arm, disease cohort, and dose level.

Demographic and Baseline Characteristics

Demographics will be summarized by arm, disease cohort, and dose level in a descriptive fashion in the FAS. Baseline demographic data to be evaluated will include age, sex, race, height, weight, smoking history, and other parameters as appropriate.

BMI will be calculated as weight (kg) / [height (m)]^2.

Age will be computed from birth date to the date of Informed Consent, as (Date of Informed Consent – Date of Birth +1)/365.25 rounded down to the nearest integer.

Baseline disease characteristics will also be summarized by arm, disease cohort, and dose level. Since each disease cohort has specific disease characteristics pertaining to that cohort, each baseline disease characteristics table will vary dependent on the disease.

Prior and Concomitant Medications

Prior and concomitant medications will be coded to ATC (Anatomical Therapeutic Chemical) classification and Drug Class using WHO Drug Dictionary (WHO-DD) March 2015 and will be summarized by arm, disease cohort, and dose level.

Medications that start and stop prior to the date of first treatment administration (napabucasin or chemotherapy 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 name using frequencies and percentages for the FAS. A separate concomitant medications table using preferred base and level 4 ATC classification will also be provided using frequencies and percentages for the FAS.

Prior and Concomitant Treatment

Prior treatment will be summarized by arm, disease cohort, and dose level and listed for each patient in the FAS.

Prior cancer surgery will be summarized by the number and percentage of patients who underwent each type of prior cancer surgery. Procedures will be listed in alphabetical order.

The total dose of prior cancer radiotherapy will be summarized.

Prior cancer therapies will be summarized by the number of unique agents per patients, the number and percentage of patients reporting each agent, time from start of first anticancer therapy to first dose date of napabucasin, and time from end of last anticancer therapy to first dose date of napabucasin. Prior cancer therapies will be coded to Agent Received using WHO Drug Dictionary (WHO-DD) March 2015.

The reasons for all concomitant procedures will be summarized, and the procedures will be displayed alphabetically in the FAS.

Medical History

Medical history will be coded by SOC and PT using MedDRA 18.0. Medical history will be summarized by SOC and PT using the number and percentage of patients for the FAS and will be summarized by arm, disease cohort, and dose level.

Concurrent Medical Conditions

Concurrent medical conditions will be summarized by SOC and PT and maximum grade using the number and percentage of patients for the FAS and will be summarized by arm, disease cohort, and dose level.

Extent of Disease

All target lesions at baseline will be analyzed for the FAS. The number of target lesions, the length of the largest target lesion, and sum of target lesions will be summarized by arm, disease cohort, and dose level.

Extent of Exposure

Exposure will be summarized as dose received (cumulative dose and actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

Cycle 1 dosing intensity will be summarized separately from Cycle 2 onwards for Arm C (CAPOX) and Arm F (Regorafenib) as capecitabine and regorafenib are permitted to have protocol-specified dose increases after cycle 1.

The information that will be summarized depends on how the study drug is dosed (e.g., infusion cyclical, oral daily, oral cyclical). All information regarding dosing will be obtained from the drug administration CRF.

A FOLFOX6 regimen includes four agents: Oxaliplatin, leucovorin, 5-FU bolus, and 5-FU drip. A CAPOX regimen includes two agents: capecitabine and oxaliplatin. A FOLFIRI regimen includes four agents: Irinotecan, leucovorin, 5-FU bolus, and 5-FU drip. A regorafenib regimen consists of just regorafenib. The same applies for an irinotecan regimen.

Any regimen that also includes bevacizumab includes the agents needed for that regimen along with the single agent of bevacizumab.

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

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

1. For napabucasin, capecitabine in Arm C, and regorafenib in Arm F, the actual end of treatment date is the last dosing date
2. For all other IV cyclic combination drugs in Arms A, B, C, D, E, and G, the actual end of treatment date = Last dosing date + interval - 1, where interval = 14 for Arms A, B, D, E, and G, and interval = 21 for oxaliplatin in Arm C (CAPOX).

Note that the actual end of treatment date in this analysis is not the collected end of treatment date in the eCRFs. The actual end of treatment date in this analysis is being derived and may be different from what was recorded by sites.

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]:

- Overall actual DI (*dose unit*/*week*) = [overall cumulative dose] / [actual treatment duration in *weeks*].

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) overall
    - Intended DI (*dose unit*/*time unit*) = [intended cumulative dose per cycle] / [intended number of *time units* in a cycle]
    - 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 capecitabine in Arm C and regorafenib in Arm F. For capecitabine, dose level is permitted to increase from 850 mg/m^2 to 1000 mg/m^2 after cycle 1. For regorafenib, dose level is permitted to increase from 120 mg to 160 mg after cycle 1. So if dose level increases for regorafenib between 20-35 days after first dose date, then updated increased dose level is the new intended dose level for cycle 2 onwards. If dose level increases for capecitabine between 15-22 days after first dose date, then updated increased dose level is the new intended dose level for cycle 2 onwards.*
  - *Second exception is for all backbone therapies except for regorafenib. All other backbone therapies incorporate BSA or weight to calculate each dose. Bevacizumab incorporates weight to calculate each dose—all other therapies incorporates 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 bevacizumab, 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 a combination drug per cycle is constant for all cycles*
  - *One exception is for capecitabine in Arm C and regorafenib in Arm F. If dose levels change as mentioned above within the specified window after first dose date, this updated intended dose level should be considered when calculating intended cumulative dose of this particular drug per cycle after cycle 1.*
  - *Second exception is for all backbone therapies except for regorafenib after the updated BSA or weight calculation prior to each infusion. The updated dose level based on changing BSA or weight should be considered when calculating intended cumulative dose of these drugs per cycle*
- *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 should be obtained from dose cohort information*
- *Dose unit of napabucasin and regorafenib is mg, dose unit of other combination drugs (except bevacizumab) is mg/m^2, dose unit of bevacizumab is mg/kg*

Treatment Compliance

Napabucasin compliance will be summarized by overall.

1. Overall: Treatment compliance for napabucasin is defined as follows:
   (Cumulative actual total dose / total planned or intended dose) × 100 = %

compliance

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

- The % of days the patient received a total dose of at least 960 mg napabucasin out of actual treatment duration in days.
- The % of days the patient received a total dose of at least 480 mg napabucasin 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.

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

These summaries will also be repeated for cycle 1 compliance.

Combination drugs compliance overall

1. Overall:
   For any IV combination drug, compliance will be calculated using the following equation:
   (Number of treatments administered / number of treatments that should have been administered) × 100 = % compliance

   For any oral combination drug, compliance will be calculated using the following equation:
   (Cumulative actual total dose / total planned or intended dose) × 100 = % compliance

7.2.2. Analysis for Primary Endpoint

7.2.2.1. DLT (Phase Ib)

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. A listing of the DLTs will be provided.

7.2.2.2. Objective Response Rate (ORR, Phase II)

The objective response rate (ORR) is defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) based on RECIST 1.1. The categorizations of response (CR, PR, stable disease [SD], progressive disease [PD], and not evaluable [NE]) and the derivations of BOR is provided in Section 8.1. The primary estimate of ORR will be based on the Response Analysis Set (RAS).

ORR will be summarized for each treatment arm, disease cohort, and dose level along with the corresponding Exact 2-sided 95% CI using the Clopper Pearson method (2).

7.2.3. Analyses for Secondary Endpoints

7.2.3.1. Other Efficacy Endpoints Analysis

The following secondary outcomes will also be assessed.

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

The survival of patients in all treatment groups, disease cohorts, and dose levels will be summarized by the Kaplan-Meier method and will be displayed graphically. The 95% CI will be calculated based on the Brookmeyer and Crowley method [3]. The survival probability at 6 months, 1 year, and 18 months will also be summarized using the Kaplan-Meier method and the 95% CI will be calculated using the normal approximation to the log transformed cumulative hazard rate. The OS summary for each arm within each disease cohort and dose level will only be provided when the number of events in that arm is at least 5.

PFS in the Full Analysis Set
PFS in the FAS is defined as the time from first dose of any study drug to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of analysis, PFS will be censored on the date of the last tumor assessment. PFS in months is calculated as (first event date / censored date – date of first dose of any study drug + 1) / 30.4375.

PFS will be reported as the median event time (and other quartiles) and the corresponding 2-sided 95% CI for each treatment arm within each disease cohort and dose level. The 95% CI will be calculated based on the Brookmeyer and Crowley method. Estimates of the PFS curves obtained from the Kaplan-Meier method will be presented along with a graphical presentation of PFS curves. The survival probability at 6 months, 1 year, and 18 months will also be summarized using the Kaplan-Meier method and the 95% CI will be calculated using the normal approximation to the log transformed cumulative hazard rate. The PFS summary for each arm within each disease cohort and dose level will only be provided when the number of events in that arm is at least 5.

DCR in the Response Analysis Set
DCR is 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 primary estimate of DCR will be based on the Response Analysis Set (RAS).

DCR will be summarized for each treatment arm within each disease cohort and dose level along with the corresponding Exact 2-sided 95% CI using the Clopper-Pearson method [2].

7.2.3.2. **PK Analysis**

Nuventra Pharma Sciences will compute PK parameters by noncompartmental analysis using Phoenix WinNonlin version 6.3 (Certara, L.P., Princeton, NJ), and generate results 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 napabucasin dose and concomitant treatment.

7.2.3.2.1. 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. Imputation of concentration data BLQ is described in Section 6.6.

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 treatment, as appropriate.

7.2.3.2.2. Pharmacokinetic Parameters

Pharmacokinetic parameters, including maximum concentration at steady state (Cmax,ss), time of maximum concentration (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 accumulation ratios for Cmax (Racc Cmax) and AUCtau (Racc AUCtau) will be listed and summarized by day, napabucasin dose, and concomitant treatment using descriptive statistics, including N, mean, SD, CV, geometric mean, geometric CV, minimum, maximum, and median. For Tmax, N, minimum, maximum, and median will be reported.

All PK parameters will be estimated using actual elapsed time from dosing. Imputation of concentration data BLQ is described in Section 6.6.

7.2.3.3. **Pharmacodynamic/Biomarker Analysis**

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

7.2.4. Analyses for Other Endpoints

All adverse events, laboratory parameters, vital signs, Karnosky performance status, physical examinations, and ECG data analyses will be summarized based on the FAS. These data will be summarized by arm, disease cohort, and dose level.

7.2.4.1. Adverse Events

Overall Summary of AEs

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

- it occurs for the first time on or after the first dose date of either napabucasin or FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, or regorafenib or irinotecan up to 30 days after the last dose of study treatment; or
- it occurs prior to the first dose date of either napabucasin or FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, or regorafenib or irinotecan and worsens in severity on therapy or up to 30 days after the last dose of study treatment

The date of the last dose of study treatment will be determined from either drug administration data or the end of study CRF, whichever date is later.

Adverse events will be coded by SOC and PT using the MedDRA® version 18.0. The severity of AEs will be graded by the investigator using NCI CTCAE Version 4.0. The SOC, PT, and 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 the following:

1. Patients with at least one TEAE
2. Patients with TEAEs of CTCAE grade 3 or higher
3. Patients with serious TEAEs
4. Patients with serious TEAEs related to napabucasin
5. Patients with serious TEAEs related to regorafenib
6. Patients with serious TEAEs related to backbone therapy
7. Patients with serious TEAEs related to study drug (napabucasin or FOLXFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, or regorafenib, or irinotecan)
8. Patients with napabucasin-related TEAEs
9. Patients with napabucasin-related TEAEs of CTCAE grade 3 or higher
10. Patients with any study drug-related TEAEs
11. Patients with any study drug-related TEAEs of CTCAE grade 3 or higher

12. Patients with regorafenib-related TEAEs
13. Patients with regorafenib-related TEAEs of CTCAE grade 3 or higher
14. Patients with backbone therapy-related TEAEs
15. Patients with backbone therapy-related TEAEs of CTCAE grade 3 or higher
16. Patients with TEAEs leading to any napabucasin dose modification
17. Patients with TEAEs leading to any napabucasin dose reduction
18. Patients with TEAEs leading to napabucasin dose stoppage
19. Patients with TEAEs leading to any oxaliplatin* dose modification
20. Patients with TEAEs leading to any oxaliplatin* dose reduction
21. Patients with TEAEs leading to any oxaliplatin* dose stoppage

*Repeated for leucovorin, 5-FU, irinotecan, regorafenib, capecitabine, and bevacizumab

Summary of TEAEs by System Organ Class and Preferred Term

The number and percentage of patients with TEAEs by SOC and PT and maximum CTCAE grade will be summarized. A summary of TEAEs of CTCAE grade 3 or higher (Grade 3, 4, 5) will be presented by SOC and PT and maximum CTCAE grade. A summary of TEAEs by PT and maximum CTCAE grade in descending order of frequency will be presented, and this same summary table will be repeated for TEAEs of at least grade 3. The most commonly reported TEAEs using different cutoffs (e.g., 2%, 5% or 10% or more of patients in either arm) will also be summarized by PT. TEAEs associated with dose reduction/dose stoppage of napabucasin will also be summarized by SOC and PT and maximum CTCAE grade.

The number and percentage of patients with TEAEs leading to end of treatment for napabucasin by SOC and PT and maximum CTCAE grade will be summarized. These TEAEs will be obtained from the End of Study CRF, as AEs leading to napabucasin treatment discontinuation were not collected in the AE CRF.

Treatment-Related TEAEs

TEAEs reported with a relationship to a treatment or combination drug considered by the investigator to be ‘possible’, ‘probable’ or ‘definite’ will be considered “Related” to study treatment or combination drug, respectively. TEAEs reported with a relationship to a treatment considered by the investigator to be 'unlikely' or 'unrelated' will be considered as “Not Related” to study treatment. Missing relationships will be considered as “Related”. Similar summaries of all causality TEAEs will be provided.

Serious TEAEs 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. 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 TESAEs will be provided as well.

Deaths that occur on or after the first dose of study treatment will be summarized. The number and percentage of patients who died during and after the study treatment will be presented, along with time to death from the last dose.

TEAEs leading to death will also be summarized by MedDRA, SOC, PT, and maximum CTCAE grade.

A listing of death data will also be provided and will include all deaths that occurred during the reporting period for deaths that started 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 of study drug.

Adverse Events of Clinical Relevance

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

Table 2: Adverse Events of Clinical Relevance SMQ Terms

MedDRA v18.0 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 and maximum severity of these events in the full analysis set will be generated.

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 lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Baseline is defined as the last non-missing value prior to the date of first dose of any study drug. All records on or after first dose date (scheduled or unscheduled visit) will be considered as post-baseline. For all lab parameters collected in the CRF, summary statistics for baseline values and maximum change from baseline will be presented for each arm, disease cohort, and dose level based on the FAS. Figures of maximum post-baseline vs baseline values will be plotted 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.

The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, ANC, ALC, monocytes, eosinophils, basophils, platelets, red blood cell and white blood cell (WBC) count

- Serum chemistry: blood urea nitrogen, creatinine, total and direct bilirubin, LDH, albumin, alkaline phosphatase, AST, ALT, glucose, calcium, sodium, potassium, total protein, chloride, CO_2 (bicarbonate), magnesium, and phosphorous

The results of laboratory parameters will be graded according to NCI CTCAE v4.0 and summarized at baseline and post baseline by maximum CTC grade. The CTCAE grading will be performed based on only observed values without considering any clinical symptoms or findings. Shift tables summarizing baseline grade to maximum CTCAE grade post baseline will be provided. The CTCAE terms to be graded are listed in Table 3.

Table 3: CTCAE Grading for Laboratory Parameters

Hematology	**Biochemistry**
White blood cell decreased	Creatinine increased
Leukocytosis	Blood bilirubin increased
Anemia	Alanine aminotransferase increased
	Aspartate aminotransferase increased
Hemoglobin increased	Alkaline phosphatase increased
Platelet count decreased	Hypoalbuminemia
Neutrophil count decreased	Hyperkalemia
Lymphocyte count decreased	Hypokalemia
Lymphocyte count increased	Hypermagnesemia
	Hypomagnesemia
	Hypophosphatemia
	Hyponatremia

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

- Urinalysis: protein, glucose, and occult blood

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

7.2.4.3. Electrocardiograms

12-lead ECG with categorical results (Normal, Abnormal [Not clinically significant], Abnormal [clinically significant]) will be summarized at baseline and any time post baseline by treatment, disease cohort, and dose level. Shift tables showing results from baseline to worst post baseline will be provided. A patient listing will also be provided.

7.2.4.4. Physical Examination

Physical examination abnormalities will be summarized for baseline and worst values any time post baseline by treatment group, disease cohort, and dose level. Patients with clinically significant abnormal findings will be flagged in the data listing.

7.2.4.5. Karnofsky Performance Status

Karnofsky Performance Status will be summarized in a shift table from baseline to worst post baseline for the FAS by treatment group, disease cohort, and dose level.

7.2.4.6. Vital Signs

Vital signs maximum change from baseline will be summarized by treatment group, disease cohort, and dose level.

Summaries of markedly abnormal vital signs parameters, including blood pressure (BP), pulse, and BMI will be presented along with their study day by treatment group, disease cohort, and dose level. Values for vital signs for all patients will be presented in a listing.

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

Vital Sign Parameter	Markedly Abnormal (Low)	Markedly Abnormal (High)
Systolic BP	Absolute value ≤ 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, or a decrease from baseline ≥ 15 bpm	Absolute value ≥ 120 bpm, or an increase from baseline ≥ 15 bpm
BMI	Absolute value ≤ 18 kg/m^2	Absolute value ≥ 25 kg/m^2

8. REFERENCES

1. Protocol BBI608-246 A Phase Ib/II Clinical Study of BBI608 in Combination with Standard Chemotherapies in Adult Patients with Advanced Gastrointestinal Cancer, June 23rd, 2017

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

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

APPENDICES

8.1. Appendix 1.1 Further Definition of Endpoints

Table 4: 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 <10 mm
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 5 mm. 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 (<10 mm 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

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence and is determined as indicated in Table 5. BOR is derived from the sequence of overall response. Assessments done after PD or after "new anti-cancer" treatment but prior to PD will not be considered evaluation of best overall response. Tumor assessments will be performed every 8 weeks. BOR derivation (based on unconfirmed response) is derived from the sequence of overall response 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 or start of new anti-cancer therapy, but not qualifying as CR.
- SD: At least 1 objective status of SD or better documented within at least 1 nominal scan interval (8 weeks – 5 days window = 51 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 2 nominal scan intervals (or 16 weeks + 5 days window = 117) after start date and not qualifying as unconfirmed CR, unconfirmed PR, 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 after start date)
    - No post-baseline assessments
    - All post-baseline assessments have overall response NE
    - New anti-cancer therapy started before first post-baseline assessment
    - SD too early (<8 weeks after first dose but before first scheduled response assessment)
    - PD too late (>16 weeks after first dose date)

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

Table 5: **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
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Objective response rate (ORR) is defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RECIST 1.1 as determined by the investigator assessment collected in the CRFs, relative to the Response Evaluable analysis set.

Disease Control Rate (DCR) is the proportion of patients with a documented CR, PR, or SD based on RECIST 1.1 as determined by the investigator assessment collected in the CRFs, relative to the RAS.

A patient will be considered as a non-responder until proven otherwise. Thus, the following patients are considered non-responders:

- Do not have CR or PR while on study; or
- Do not have a baseline or post-baseline tumor evaluation; or
- Do not have an adequate baseline tumor evaluation; or
- Receive anti-tumor treatment other than the study medication prior to reaching a CR or PR; or
- Die, progress, or drop out for any reason prior to reaching a CR or PR.

8.2. Appendix 1.2 Censoring for Time to Event Data

Table 6 summarizes the censoring rules for the PFS analysis and displays censoring hierarchy for this study. Table 7 shows the general reasons for PFS censoring and where the censoring hierarchy in Table 6 came from.

Table 6: Event or Censor Time for PFS and Censoring Hierarchy

Censoring Hierarchy	Situation	Date of Event or Censor	Event / Censor
1	**No baseline** radiological tumor assessment available	Date of First Dose	Censored
2	**New anticancer treatment** started before tumor progression or death	Date of previous adequate radiological assessment immediately prior to start of new therapy or Date of first dose, whichever comes later	Censored
3	**Tumor progression** (per RECIST 1.1) documented or death after 2 scan intervals following previous adequate radiological tumor assessment, no new anticancer treatment started	Date of previous adequate radiological assessment or Date of first dose, whichever comes later	Censored
4, 5	**No tumor progression** (per RECIST 1.1), no death reported and patient lost to follow-up or withdrawal of consent, no new anticancer treatment started	Date of last adequate radiological Assessment or Date of first dose, whichever comes later	Censored

6	**No tumor progression** (per RECIST 1.1) and no death reported within 2 scan intervals following last adequate radiological tumor assessment or first dose date (if no post baseline tumor assessment available), no new anticancer treatment started	Date of last adequate radiological tumor assessment or Date of First Dose, whichever comes later	Censored
7	**No tumor progression** (per RECIST 1.1) and no death reported and none of the conditions in the prior hierarchy are met	Date of last adequate radiological tumor assessment or Date of first dose, whichever comes later	Censored
	No tumor progression (per RECIST 1.1) but death reported within 2 scan intervals following last adequate radiological tumor assessment or first dose date (if no post baseline tumor assessment available)	Date of death	Event
	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 (i.e. symptomatic progressions, which are not radiographically confirmed) will not be considered as progressions.

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

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

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

Table 7: 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* from last adequate post-baseline tumor assessment/start date	Event after missing assessments [a]

4	No event and patient withdrawn consent	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event 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 after last adequate tumor assessment

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

Date of Last Contact

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

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

Note:

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