STATISTICAL ANALYSIS PLAN

BBI-20231001

A Phase 2, Multi-Center, Randomized, Open-Label Trial of BDC-1001 as Single Agent and in Combination with Pertuzumab in Subjects with Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer Previously Treated with Trastuzumab Deruxtecan

Document Version: 1.0
Document Date: 14 November 2024

Statistical Analysis Plan Signature Page - Authors

The undersigned agree that all required reviews of this document are complete and approve this Statistical Analysis Plan v1.0. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

[redacted]

Signature Date

[redacted]

Signature Date

SAP Version History

Version #	Description of Changes	Version Date
1.0	Original	14 November 2024

Table of Contents

List of Tables

Glossary of Abbreviations

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
BI	before infusion
BLQ	Below limit of quantification
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CI	confidence interval
Cl	chloride
CL	clearance
CO_2	carbon dioxide
COVID-19	coronavirus disease 19
CR	complete response
CT	computerized tomography
CV	coefficient of variation
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EMA	European Medicines Agency
EOI	end of infusion
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FIH	first-in-human
F/U	follow-up
h	hour(s)
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	Immunohistochemistry
INR	international normalized ratio
ISH	in-situ hybridization
K	potassium
LDH	lactate dehydrogenase
LLN	lower limit of normal

Abbreviation	Term
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MPD	maximum protocol dose
MRI	magnetic resonance imaging
MSS/MSI	microsatellite stability/instability
MUGA	multigated acquisition scan
N	number of observations
Na	sodium
NCA	Non-Compartmental Analysis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Non-evaluable
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PDn	pharmacodynamic
PO4	phosphate
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
q2w	every 2 weeks
q3w	every 3 weeks
QTc	QT corrected
QTcF	QT corrected - Fridericia's correction formula
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCR	screening
SD	stable disease
SFU	safety follow-up
SI	International System of Units
SOC	System Organ Class
SoD	sum of diameters for all target lesions
SpO_2	peripheral capillary oxygen saturation
SRC	Safety Review Committee
STD	Standard deviation
T3	triiodothyronine
T4	thyroxine
TBILI	total bilirubin
TEAE	treatment emergent adverse events
TFLs	tables, figures and listings
TLR7/8	toll-like receptor 7/8

Abbreviation	Term
TMB	tumor mutational burden
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was updated based on the following documentation:

Document	Date	Version
Protocol	01Aug2024	V3.0
eCRF- Case Book	20Nov2023	V3.0

2. Protocol Details

2.1 Study Objectives

The objectives and endpoints to be evaluated in the study are outlined in Table 1.

Table 1: Objectives and Endpoints

Primary Objectives	Primary Endpoints
• Efficacy: To evaluate the preliminary anti-tumor activity of BDC-1001 as a single agent and in combination with pertuzumab in subjects with previously treated HER2+ MBC	• ORR according to RECIST v1.1
Secondary Objectives	**Secondary Endpoints**
• Efficacy: To evaluate the preliminary anti-tumor activity of BDC-1001 as a single agent and in combination with pertuzumab in subjects with previously treated HER2+ MBC	• DOR, DCR, PFS, OS
• Safety: To determine the safety and tolerability of BDC-1001 as a single agent and in combination with pertuzumab in subjects with previously treated HER2+ MBC	• Incidence of treatment-emergent AEs and SAEs graded according to NCI CTCAE v5.0 • Changes from baseline in vital signs, laboratory values, and ECGs
• PK: To evaluate the exposure profile of BDC-1001 as a single agent and in combination with pertuzumab in subjects with previously treated HER2+ MBC	• C_{min} and C_{max} values will be obtained throughout the study and compared to the PK data from the Phase 1 single agent BDC-1001 study utilizing a population approach
• ADA: To evaluate the immunogenicity of BDC-1001 as a single agent and in combination with pertuzumab in subjects with previously treated HER2+ MBC	• Incidence of ADAs

Exploratory Objectives	Exploratory Endpoints
• To explore potential baseline biomarkers in blood and tumor tissue associated with efficacy or safety of BDC-1001 as a single agent and in combination with pertuzumab in subjects with HER2+ MBC • To evaluate exploratory pharmacodynamic biomarkers in blood and tumor and their association with biological activity, efficacy or safety of BDC-1001 as a single agent and in combination with pertuzumab in subjects with HER2+ MBC	• [redacted] • [redacted] • [redacted]

Abbreviations: ADA = anti-BDC-1001 antibody; AE = adverse event; C_{max} = maximum (or peak) serum concentration; C_{min} = minimum (or trough) serum concentration; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; HER2+ = human epidermal growth factor receptor 2-positive; MBC = metastatic breast cancer NCI = National Cancer Institute; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event; TLR = toll-like receptor

2.2 Overall Study Design

This is an open label, Phase 2 study to evaluate preliminary anti-tumor activity, safety, tolerability, PK, pharmacodynamics, and immunogenicity of BDC-1001 administered as a single agent and in combination with pertuzumab in subjects with HER2+ metastatic breast cancer (MBC) previously treated with trastuzumab deruxtecan (ENHERTU®).

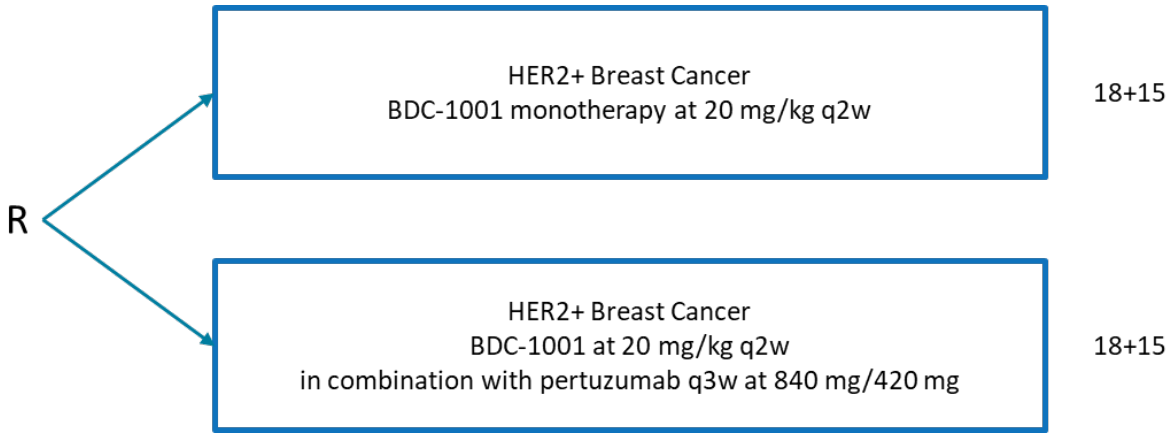
Eligible subjects will be randomly assigned in a 1:1 ratio to receive BDC-1001 as a single agent or BDC-1001 in combination with pertuzumab. Within each treatment arm, a Simon 2-stage design will be applied for enrollment (see Section 2.3).

All subjects in both treatment arms will be monitored for AEs and SAEs, see protocol for further details. Study data will be provided to the Safety Review Committee (SRC) for ongoing safety monitoring and detection of potential safety concerns (Section 2.2.1)

Subjects will return to the site for study assessments at the visits listed in the Schedule of Assessments in the protocol. In the event of study treatment discontinuation, subjects will be asked to complete an End of Treatment (EOT) visit 14 days (± 7 days) after the last dose of study treatment (EOT), and then return for a Safety Follow-Up visit, 28 days (+ 7 days) after last treatment. Subjects who discontinue treatment will have long-term follow-up every 12 weeks (± 14 days) after last treatment.

An overview of the study is displayed in Figure 1.

Figure 1: Study Schema



HER2+ = human epidermal growth factor receptor 2-positive; q2w = every 2 weeks q3w=every 3 weeks; R = randomization

2.2.1 Study Oversight

An SRC, with membership including Investigators or sub-Investigators from sites that have enrolled a subject under active investigation, Medical Monitor, and Statistician, or designees, will be established to oversee the safety of the study. The SRC will review safety data, with a focus on SAEs and use of the Toxicity Monitoring Safety Stopping Rules (see Section 8.6).

The SRC will be responsible for safeguarding the interests of trial subjects and assessing the risk-benefit of the study including the safety of the interventions during the trial.

The SRC will meet periodically based on enrollment, the meeting frequency will be at least every 6 months. Ad-hoc meetings may be conducted to address additional safety or study conduct issues.

Details of the membership, responsibilities, and procedures of the SRC will be included in an SRC Charter.

2.2.2 Study Periods

The study periods or visits include the Screening Period, treatment period, end of treatment (EOT), safety follow-up (SFU) and long-term follow-up (LTFU)/end of study. Study day from Screening Period through LTFU is calculated from cycle 1 day 1 (C1D1).

- During the **Screening Period** subjects will be screened for eligibility to participate in the study. The Screening Period is 28 days, beginning with the day of the first eligibility assessment. If screening assessments are performed on Study Day 1, they can be considered as Day 1 data and there is no need to repeat them.

- The **treatment period** will begin on C1D1 and conclude at the latest date of the last study treatment administered. Scheduled intervals of the treatment period will be identified by cycle and day (e.g., C1D15 or C3D8). Cycles will be identified by the study day of treatment based on dosing windows (Table 2) or the nearest number of x-day intervals from C1D1 where x=14 for q2w schedule.

Table 2: Time Windows Allowed for Administration of Study Drugs

Dosing Schedule	Cycles	Allowed Dosing Window
q2w Dosing	Cycle 1	-
	Cycle 2 onwards	14 ± 2 days
q3w Dosing	Cycle 1	-
	Cycle 2 onwards	21 ± 2 days

- The **SFU1** visit should occur 28 days (+7 days) after the last administration of BDC-1001 or pertuzumab. If the subject begins another anticancer therapy before the end of the 28 days (-7 days), every effort will be made to complete all the SFU assessments prior to beginning the new therapy. In case of unresolved adverse events (AEs), the Investigator will follow the AEs until the event has resolved or the condition has stabilized as possible. If assessments at EOT or treatment period are performed within this period, they can be considered as the SFU data, and there is no need to repeat them.
- **Long-Term Follow-Up/ End of Study**

  All subjects that discontinue study treatment will be followed for:

  - Assessment of treatment-related SAEs until their resolution to baseline or Grade ≤ 1
  - Survival via a clinic visit or telephone call until any of the following: death, withdrawal of consent, lost to follow-up, the Sponsor notifies sites that survival follow-up is no longer required, or termination of the trial by the Sponsor

  Subjects discontinuing treatment for reasons other than radiographic progression will continue to have tumor assessments using the same modality that was used during study treatment. These should occur every 12 weeks (± 14 days) for up to 2 years after the last treatment visit, until any of the following occur): the subject has progressive disease, the subject starts a new therapy for their cancer, the subject is lost to follow-up, the subject dies, the subject withdraws consent, the Sponsor notifies sites that tumor assessment is no longer required during LTFU, or the trial is terminated by the Sponsor.

- **Maintenance Phase**

  As of this protocol Version 3.0 (01 Aug 2024), any subject(s) still receiving study treatment (BDC-1001) will transition to the Maintenance Phase and are to be followed as described in the protocol, Table 2. Subjects remaining on study treatment will continue to receive the study drug until a criterion for discontinuation has been met (see Section 4.3 of the protocol). Subjects are to undergo periodic safety assessments; the nature and frequency of these assessments are to be performed per local standard of care. It is the Investigator's responsibility to ensure that subject visits occur frequently enough and adequate assessments are performed to ensure subject safety.
  The study clinical database will be closed after the last subject remaining on treatment enters the Maintenance Phase. All data collected prior to implementation of the Maintenance Phase will be reported in a clinical study report.

2.2.3 Study Assessments, Screening Period

Prior to obtaining any assessments a signed and dated informed consent must be obtained from the subject. In general, the Screening assessments are to be done 28 days prior to first dose administration. Please see schedule of assessment for exception to this window and for further details. The following will be performed during the Screening Period:

- Assign a subject and site- specific identifier
- Review eligibility criteria. Record primary cancer history, demographic information (e.g., race, birth year, sex, ethnicity), significant medical history and prior cancer treatment history
- Assess subject for AEs
- Perform a complete physical examination and record height and weight
- Assess functional status using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) Scale
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature)
- Perform a 12-lead electrocardiogram (ECG) in triplicate
- Obtain a serum and urine sample
- Obtain blood samples for safety laboratory tests
- Conduct pregnancy testing in women of childbearing potential
- Perform either echocardiogram (ECHO) or multigated acquisition scan (MUGA) to evaluate left ventricular ejection fraction (LVEF)

- Perform tumor assessment by computerized tomography (CT) or magnetic resonance imaging (MRI) scans of the brain, chest, abdomen, pelvis, and any other sites of disease
- Obtain a pre-treatment biopsy if required

2.2.4 Study Assessments, through End of Study

AEs and concomitant medications will be recorded from Screening Period through SFU visits.

Pregnancy testing of female subjects of child-bearing potential will consist of a serum pregnancy test performed at Screening, C1D1, C4D1, C7D1 etc. and at EOT

Other safety assessments will be performed from Screening Period through SFU:

- Physical examination and weight.
- Functional status using the ECOG PS Scale
- Vital sign measurements
- Chemistry and hematology
- Urinalysis with urine dipstick
- 12-lead ECG in triplicate
- ECHO or MUGA to evaluate LVEF
- Peripheral capillary oxygen saturation (SpO_2)
- Thyroid-stimulating hormone (TSH)/ thyroxine (T4)

Serum will be collected from all subjects enrolled in the study for assessment of BDC-1001 pharmacokinetics (PK)

Serum will be collected from all subjects enrolled in the study for assessment of anti-drug antibody (ADA)

Samples for assessment of biomarkers will be collected as outlined in the Schedule of Assessment in the protocol: plasma, serum, whole blood – peripheral blood mononuclear cells (PBMC), whole blood-RNA, and whole blood-DNA.

Tumor assessments will be performed every 6 weeks (±7 days) during first 24 weeks after C1D1, and then every 12 weeks (±7 days)

Survival information will be collected from screening through LTFU.

2.3 Sample Size and Power

Approximately 66 evaluable subjects will be randomized 1:1 to either the BDC-1001 monotherapy arm or the BDC-1001 plus pertuzumab arm. Within each arm, a Simon 2-stage design will be used to evaluate ORR. It is assumed under the null hypothesis, that ORR will be ≤ 20% (not considered clinically compelling) for both arms. Based on the probability of accepting the poor drug (one-sided alpha level) at 5%, 80%

power, P0 and P1 at 20% and 40% respectively, 18 subjects will be enrolled into the first stage. If at least 5 objective responses (confirmed CR or PR) are observed in an arm, the study will continue to enroll additional 15 subjects for a total of 33 evaluable subjects to that arm. The null hypothesis will be rejected if at least 11 objective responses are observed out of the 33 subjects in an arm.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

The following endpoint will be based on tumor assessments by CT or magnetic resonance imaging (MRI) scans:

- ORR of confirmed CR or confirmed PR

The ORR will be calculated as the proportion of subjects with best overall response of confirmed CR or PR as determined by the treating Investigator using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) see Appendix A Assessment of Disease Response Using RECIST V1.1, Confirmed CR or PR will be defined as a repeat assessment performed no less than 4 weeks after the criteria for response is first met.

3.2 Secondary Efficacy Endpoints

The following endpoints using RECIST v1.1 will be evaluated as secondary endpoints:

- Duration Of Response (DOR)
- Disease Control Rate (DCR) of confirmed CR, confirmed PR, SD lasting ≥ 23 weeks following the initiation of BDC-1001. Note that the scheduled tumor assessment at week 24 can be performed as early as week 23 hence SD lasting ≥ 23 weeks is considered in the definition of DCR
- Progression-Free Survival (PFS)
- Overall survival (OS)

Duration of response (DOR) will be calculated only for subjects who achieve confirmed CR or PR. For such subjects, DOR is defined as the number of months from the start date of CR or PR (whichever response status is observed first) and subsequently confirmed, to the first date that recurrent or progressive disease is objectively documented or death. Subjects who start a subsequent therapy prior to progressing will be censored at the last evaluable tumor assessment date prior to initiating the subsequent therapy. Subjects who do not progress or die will be censored at their last evaluable tumor assessment date.

DOR = (Date of progression or death or censoring – date of response + 1)/30.4375.

The DCR will be calculated as the proportion of subjects with at least one assessment of confirmed CR, PR or SD that is at ≥ 23 weeks after start of treatment.

Progression-free survival (PFS) is defined as the duration from the date of first study drug administration (Cycle 1, Day 1) to the earliest of documented PD or death from any cause:

PFS (months) = (Date of progression/death – Date of first dose +1)/30.4375.

For subjects who do not progress or die at the time of analysis will be censored per the censoring rules defined in Table 3.

Table 3: Date of Progression or Censoring for DOR and PFS

Scenario	Date of Progression or Censoring	Event or Censored
Death or disease progression between planned tumor assessments	Date of death or first tumor assessment showing disease progression, whichever occurs first	Event
Subsequent systemic anti-cancer treatment started before disease progression or death	Date of last evaluable tumor assessment prior to the start of subsequent systemic anti-cancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled tumor assessments	Date of last evaluable tumor assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last evaluable tumor assessment	Censored

Abbreviations: DOR = duration of response; PFS = progression-free survival.

Overall Survival (OS) is defined as the duration from first study drug administration (Cycle 1, Day 1) to death due to any cause. For subjects who are still alive as of the data cut-off date, OS time will be censored on the date when the subject was last known to be alive.

Overall Survival (months) = (Date of death or last known to be alive – Date of first dose +1)/30.4375.

3.3 Exploratory Efficacy Endpoints

[redacted]

3.4 Safety Variables

3.4.1 Primary Endpoints

- Incidence of AEs and SAEs graded according to NCI CTCAE v5.0
- Changes from baseline in clinical safety laboratory values and vital signs
- Incidence of potential immune-related toxicities

  To monitor for potential immune-related toxicities, the following additional assessments will be taken at baseline and throughout the study:

  - Observation of immune-related clinical signs and symptoms
  - Thyroid-stimulating hormone (TSH), thyroxine (T4) at every other cycle
  - Pulse oximetry at every cycle

3.4.2 Other Safety Assessments

- ECG
  Standard parameters including RR, PR, QT intervals, and QRS duration will be measured in triplicate. The mean of each parameter and assessment time will be calculated and rounded to the nearest integer
- ECHO or MUGA to monitor LVEF
- ECOG PS numerical grade (0 through 4) will be recorded

4. Pharmacokinetic/Pharmacodynamic variables

4.1 Pharmacokinetic Variables

Pharmacokinetics (PK) data will be analyzed using the PK Analysis Set as defined in Section 5.5 . Subjects with protocol deviations will be assessed on a subject-by-subject basis for inclusion in the PK population.

4.2 Pharmacodynamic and Biomarker Variables

- [redacted]

5. Analysis Populations

5.1 Enrolled Subjects

Subjects who meet all inclusion and exclusion criteria will be enrolled in the study and this will be considered as the Enrolled Subjects set.

In general, the enrolled subjects set will be used for all listings and for subject disposition summaries.

5.2 Safety Analysis Set

The Safety Analysis Set will consist of all enrolled subjects who receive any dose of BDC-1001 monotherapy or in combination with pertuzumab.

The Safety Analysis Set will be used primarily for the analysis of safety data and for PFS and OS analysis.

5.3 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who meet the following criteria:

- Receive any dose of BDC-1001 monotherapy or in combination with pertuzumab
- Have one or more measurable lesions at baseline as assessed using RECIST v1.1

The FAS will be used primarily for the analysis of anti-tumor activity-related data such as tumor response.

5.4 Per Protocol Analysis Set - Not Applicable

5.5 PK Analysis Set

The PK Analysis Set (PKAS) will consist of all subjects in the Safety Analysis Set with any PK concentration assessed and deemed valid by the PK analyst.

The PK Analysis Set will be used for summary tables and figures representing PK concentrations and parameters.

5.6 Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set (PDAS) will consist of all subjects in the Safety Analysis Set with at least one set of postbaseline Biomarker data.

The PDAS will be used for summary tables and figures representing all biomarker analysis.

6. Data Handling Conventions

6.1 Time Points and Visit Windows

Study Day 1 is defined as the day of first dose of study treatment. This is Cycle 1, Day 1 (C1D1) in the schedule of assessments. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

Summaries of study treatment dosing and exposure will be based on treatment cycle and allowed dosing windows as outlined in Table 2. If dose interval from the previous dose to the current dose exceeds the allowed dosing windows in Table 2 then this will be considered as a dose delay.

Scheduled safety assessments will be analyzed using nominal study visits and time points as defined in the Study Schedule and electronic case report form (eCRF). No visit windows will be applied for summary and analysis of these endpoints. In case of multiple assessments at a scheduled visit, the first will be considered as the scheduled assessment and later assessments will be repeat or unscheduled. Repeat or unscheduled assessments will be listed and excluded from summaries by visit and time point.

All scheduled and unscheduled tumor assessments will be considered when evaluating the efficacy endpoints. Every assessment, including any outside of the schedule visit window will be grouped to nominal visit as represented in Table 4. In case two assessments are grouped to one nominal visit then the one closest to the target day will be mapped to the nominal visit and the other will be mapped to the actual week the assessment was done.

Table 4: Tumor Assessment Time Points

Visit	Target Day[a]	Interval to include in summary by visit[b]
Screening		Prior to treatment on Day 1
Week 6	Day 43	Day 2 to Day 50
Week 12	Day 85	Day 51 to Day 92
Week 18	Day 127	Day 93 to Day 134
Week 24	Day 169	Day 135 to Day 183
Week 36	Day 253	Day 184 to Day 267
Week 48	Day 337	Day 268 to Day 351

[a] Schedule visit window is ±7 day.
[b] relative to the date of first dose of IMP.

6.2 Handling of Dropouts, Missing Data, and Outliers

6.2.1 Dropouts

Enrolled subjects who receive no dose of study treatment may be replaced.

Subjects who discontinue treatment prior to the first on-treatment tumor assessment (minimum of 4 weeks after C1D1) will be replaced.

6.2.2 Missing Data

In general, missing values for data points will remain as missing unless otherwise specified. Missing values will not be imputed and only observed values will be used in data analyses and presentations unless otherwise stated.

Subjects missing baseline and or all post-baseline tumor assessment data will be scored as non-responder for analysis of ORR and DCR, will not be included in the analysis of DOR and will be censored at Day 1 for analysis of PFS.

6.2.3 Unevaluable Values

For laboratory and biomarker analysis, results of a non-numeric qualifier (e.g., '< x' - below the lower limit of quantification or '> x' - above the upper limit of quantification) will be displayed in the data listings as shown in the data. In these cases, the numerical value of "x" will be used for calculation of summary statistics.

6.2.4 Outliers

No rules for outlier detection are planned.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using SAS Version 9.4 (or later) of the SAS® statistical software package.

For statistical analyses, baseline is defined as the most recent measurement on or prior to initiation of first study drug administration. All observations and derived endpoints presented in summary tables may be listed.

7.1.1 Multicenter Studies

The center effect will not be considered for this study.

7.1.2 Multiplicity Adjustments

No multiplicity adjustment is planned for the hypothesis testing.

8. Statistical Summaries

8.1 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment arm and overall. The following subject disposition categories will be summarized:

Treatment

- Subjects who were enrolled and not treated
- Subjects who were enrolled and treated
- Subjects in each analysis set (Safety, FAS)
- Subjects who discontinued BDC-1001 and the primary reason for discontinuation
- Subjects who discontinued pertuzumab and the primary reason for discontinuation

Safety follow up and Long-term follow up

- Subjects who completed safety follow up
- Subjects who entered long-term follow up

Study

- Subjects who discontinued from study and the primary reason for study discontinuation

A listing for screen failures with available demographic data may be generated.

8.2 Protocol Deviations

A listing of all protocol deviations, including the description of the deviation, deviation category and date of deviation will be provided.

Important protocol deviations that could potentially affect the interpretation of the safety, efficacy, PK, or PD data will be identified prior to database lock and summarized by treatment arm for the Safety Analysis Set. Examples of such deviations are as shown below:

- Inclusion/Exclusion criteria not met
- Study procedures performed prior to obtaining consent
- Subject developed withdrawal criteria during the study but was not withdrawn
- Incorrect dose administered
- Subject received any excluded concomitant treatment
- Missing assessments that may affect the safety and efficacy for a subject

8.3 Baseline Characteristics

Descriptive summaries of baseline characteristics will be tabulated for both Safety Analysis Set and FAS. Subjects will be tabulated by treatment arm and overall.

8.3.1 Demographics and Other Baseline Characteristics

The following characteristics are summarized:

Standard descriptive statistics will be presented for the continuous variables of:

- Age (years) (If birthdate is given then age (years) = (informed consent date – birthdate)/365.25)

- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)

The total count and percentage of subjects will be presented for the categorical variables of:

- Sex (Female)
- Female of childbearing potential (Yes, No)
- Race
- Ethnicity
- ECOG PS (0,1)
- Historical HER2 status at enrollment per CRF
    - IHC3+
    - IHC2+
    - IHC1+
    - IHC0
- NGS Status
    - Amplified positive
    - Equivocal
    - Not detected
    - Other
    - Assay not done
- HER2 Gene Amplification by ISH assay
    - Amplified positive
    - Equivocal
    - Not detected
    - Other
    - Assay not done
- PD-L1 Status at Screening (Positive, Negative, Unknown)
- PIK3CA Mutation status (Yes, No)
- Microsatellite Stability/Instability Status at Screening (MSI, MSS, Unknown)
- Baseline target lesion sum of diameters (mm)

8.3.2 Primary Cancer History

Primary cancer history including site of primary tumor, histological grade, nuclear grade, diagnosis staging at screening, locally advanced or metastatic, TNM staging

and dates of first diagnosis and last recurrence will be listed. For tumor history, results of tumor mutational burden (TMB), PD-L1 (by IHC), mutational analysis and microsatellite stability/instability (MSS/MSI) testing should be recorded if known.

The baseline characteristics summary will include the following:

- Site of primary tumor
- Months since initial cancer diagnosis (Date of informed consent – date of initial diagnosis)/30.4375
- Staging at screening (Pathological, Clinical)
- Diagnosis staging at screening (0, I, II, III, IV)
- Diagnosis sub-stage at screening (A, B, C)
- Metastatic status (Locally Advanced, Distant Metastatic)
- Months since first diagnosis of locally advanced or Metastatic disease (Date of informed consent – date of locally advanced or Metastatic disease diagnosis)/30.4375
- Months since last recurrence or progression (Date of first dose date – date of last recurrence or progression)/30.4375

8.3.3 Medical and Surgical History

Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All medical history may be listed.

8.3.4 Cancer Treatment History

All cancer treatment history will be coded by the World Health Organization (WHO) Drug Dictionary, to Anatomical Therapeutic Classification (ATC) and preferred drug name.

The following characteristics are summarized:

- Received prior radiotherapy (Yes, No)
- Received prior cancer-related surgery/Procedures (Yes, No)
- Received prior anti-neoplastic therapies (Yes, No)
- Number of lines of prior anti-neoplastic therapies received (descriptive summary)
- Best response to most recent prior anti-neoplastic therapy (CR, PR, SD, PD, Not Assessed, Not Evaluable, Unknown)
- Duration in days since most recent prior anti-neoplastic therapy ended date to first dose date (descriptive summary)
- Discontinuation reason for most recent prior anti-neoplastic therapy (Progressive disease, Toxicity, Completed Regimen, Other, Unknown)

Prior Anti-HER2 therapy summaries include the following:

- Received prior anti-HER2 therapy (Yes, No)
- Days since most recent prior anti-HER2 therapy ended to first dose date (descriptive summary)
- Reason for discontinuing most recent prior anti-HER2 therapy (Progressive Disease, Toxicity, Completed Regimen, Other, Unknown)

Prior immunotherapy summaries include the following:

- Received prior immunotherapy (Yes, No)
- Days since most recent prior immunotherapy ended date to first dose date (descriptive summary)
- Reason for discontinuing most recent prior immunotherapy (Progressive Disease, Toxicity, Completed Regimen, Other, Unknown)

Details of cancer treatment history including start and end dates and total cumulative dose will be listed.

8.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded by the WHO Drug Dictionary, to Anatomical Therapeutic Classification (ATC) and preferred drug name. Prior and concomitant medications will be summarized separately by ATC level 4 and preferred drug name.

Prior medications are those with a stop date prior to Day 1 of Cycle 1.

Concomitant medications are those with a start date on or after the first dose date of IMP, or those with a start date before the first dose date of study treatment and a stop date on or after the first dose date of study treatment or medication status is indicated as 'ongoing'.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed.

Any use of prohibited prior and concomitant medications will be recorded as protocol deviations.

8.4 Efficacy

8.4.1 Primary Efficacy Analysis, Anti-Tumor Activity Analysis

Anti-tumor activity measures are primary endpoints for this study. The analysis of anti-tumor activity will be performed for subjects in the FAS and summarized descriptively by treatment arm and overall.

Tumor Response

Best overall response, DCR and ORR as determined by the treating Investigator using RECIST v1.1 will be summarized. Point estimates of the ORR and the 2-sided 95%

exact binomial CI will be presented by treatment arms and overall.

Time to Event Analysis

Progression-free survival (PFS), OS and if applicable time to response and DOR will be summarized descriptively using the Kaplan-Meier method with 95% CIs calculated using Greenwood's formula.

8.4.2 Exploratory Analysis

[redacted]

8.5 Safety

Safety will be assessed by clinical review of all relevant parameters including extent of exposure, AEs, SAEs, laboratory values, vital signs, and ECG results. Unless specified otherwise, safety analyses will be conducted for all subjects in the safety analysis set.

8.5.1 Extent of Exposure

Descriptive statistics will be used to summarize study treatment exposure for each treatment arm and will include the following:

- Duration of treatment in months will be calculated as:

  (date of last infusion – date of first infusion+1)/30.4375
- Number of BDC-1001 infusions received
- Number of pertuzumab infusions received
- Actual BDC-1001 cycles of treatment completed (≥1, ≥2, ≥3 etc.)
- Actual pertuzumab cycles of treatment completed (≥1, ≥2, ≥3 etc.)

In the combination arm calculation of overall duration of treatment will use date of last infusion as later of the date of last BDC-1001 and last pertuzumab infusion. Duration of treatment will not be adjusted for missed cycles

- Cumulative dose of BDC-1001 in mgs received
- Cumulative dose of pertuzumab in mgs received
- Percent Dose intensity will be calculated as follows:

  For BDC-1001:

$$\frac{100 * (cumulative\ dose\ in\ mg/kg)}{[(Last\ infusion\ date\ -\ First\ infusion\ date\ + 14)\ *\ (20/14)]}$$

For pertuzumab:

$$\frac{100 * (cumulative\ pertuzumab\ dose\ in\ mgs)}{840 + [(Last\ infusion\ date\ -\ First\ infusion\ date) * \left(\frac{420}{21}\right)]}$$

- The number and percentage of subjects who receive 85 to 115% of intended BDC-1001 dose will be presented. Similar calculations will be reported for pertuzumab, as applicable.

Dose reductions were not permitted for either BDC-1001 or pertuzumab. Hence only dose delays as reported on the respective eCRFs record of infusion will be listed for each treatment arm:

8.5.2 Adverse Events

An AE is any unfavorable and unintended sign /symptom sign (including an abnormal laboratory finding), or disease (new or exacerbated) temporally associated with the use of an investigational product or other protocol-imposed intervention whether or not considered related to the investigational product. AEs and SAEs will be collected from first dose of study drug to the end of the SFU period. SAEs that occur during screening will be collected only if the event is related to a study mandated procedure from Screening to the first dose of study drug.

Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 5.0). Each AE will be recorded using NCI-CTCAE 5.0 terminology and the NCI-CTCAE Grade recorded. Any change in the grade or seriousness of an AE if worsening or improvement occurs will be recorded to a separate AE record.

All adverse events (AEs) recorded on the eCRF will be coded using MedDRA dictionary and classified as either treatment–emergent AEs (TEAEs) or not treatment–emergent as follows:

- Treatment-emergent AEs (TEAEs) are defined as AEs that start or those that worsen on or after the first administration of study drug
- All other AEs will be classified non treatment–emergent

The relationship between an AE and study treatment is assessed separately for BDC-1001 and pertuzumab as related or not related by the treating investigator. For subjects with relationship missing for an AE will be considered as related to BDC-1001 and or pertuzumab as applicable.

All AE data will be listed. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of, serious AEs (SAEs) and study treatment related AES may be produced.

In summaries for TEAES, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity grade, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

For summaries of AEs by SOC, PT and severity, AEs with missing severity will be included in the overall count of subjects with AEs and in the counts of subjects with AEs within a SOC, PT and severity displayed on a row titled 'Missing Grade'.

An overview table will summarize the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- Any AE
- Any grade 3-5 AEs
- Any AE by severity grade 1,2,3,4,5
- Repeat the above 3 bullets for AEs related to BDC-1001, pertuzumab, related to either or both of the study drugs
- AE leading to BDC-1001 discontinuation
- AEs leading to BDC-1001 interruption
- AEs leading to pertuzumab discontinuation
- Any AE leading to pertuzumab interruption
- Any AE leading to discontinuation of either BDC-1001 or pertuzumab
- Any AE leading to interruption of either BDC-1001 or pertuzumab
- Any SAEs
- Any SAEs related to BDC-1001
- Any SAEs related to pertuzumab
- Any SAE leading to BDC-1001 discontinuation
- Any SAE leading to BDC-1001 interruption
- Any SAE leading to pertuzumab discontinuation
- Any SAE leading to pertuzumab interruption
- Any SAE leading to discontinuation of either BDC-1001 or pertuzumab
- Any SAE leading to interruption of either BDC-1001 or pertuzumab
- SAE leading to death

All TEAEs will be summarized for the Safety Analysis Set based on the number and percentage of subjects experiencing the event. Summaries will display subject count for each treatment arm and for overall arm that includes all subjects in the 2

treatment arms. Summaries by SOC and PT will be sorted alphabetically and those by PT will be sorted by descending frequency of the TEAEs in the overall arm.

Tabular summaries of AEs will be provided for:

- All TEAEs by SOC and PT
- All TEAEs by SOC, PT, and maximum severity
- TEAEs with action of study drug interrupted, separately for either study drugs and for BDC-1001 and/or pertuzumab by SOC and PT
- TEAEs with action of study drug discontinued, separately for either study drugs and for BDC-1001 or pertuzumab by SOC and PT
- TEAEs by PT sorted by descending frequency of PT in the overall arm
- TEAEs by severity grade and by PT and sorted by descending frequency of PT in the total column
- TEAEs related to study treatment by SOC and PT
- TEAEs related to study treatment by SOC, PT and maximum severity grade
- TEAEs related to study treatment by PT and sorted by descending frequency of PT in the total column
- TEAEs related to study treatment by PT and maximum severity grade and sorted by descending frequency of PT in the overall arm
- SAEs by SOC and PT
- SAEs related to the study drug by SOC and PT
- SAEs by PT and sorted by descending frequency of PT in the overall arm

No statistical comparisons of AEs between treatment arms will be performed.

8.5.3 Deaths

All deaths may be reported in a subject listing and will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

8.5.4 Possible Immune-related Treatment Emergent Adverse Events

The Sponsor has identified SOC and PTs for evaluation of possible immune related TEAEs (IRTEAEs) based on data collected thus far. These include Pneumonitis, Colitis; Nephritis; Endocrinopathies; Hepatitis; Skin reactions; Other immune-related adverse reactions; Infusion-related reactions; Cytokine release syndrome. The IRAEs will be summarized as follows:

- Possible IRTEAEs Reactions by SOC, PT and maximum severity

8.5.5 Laboratory Evaluations

Data for hematology, blood chemistry, and urinalysis analytes recorded in the eCRF are shown in Appendix C Laboratory Tests, Standard International Units (SIU). The following laboratory analytes will be summarized:

Table 5: Laboratory Analytes to Be Summarized

Category	Lab Abnormality	PARAMCD	Grading System
Hematology	WBC increased WBC decreased	WBC	CTCAE
	ANC decreased	NEUT	CTCAE
	Platelets decreased	PLAT	CTCAE
	Hemoglobin increased Hemoglobin decreased	HGB	CTCAE
Serum Chemistry	Albumin decreased	ALB	CTCAE
	ALP increased	ALP	CTCAE
	ALT increased	ALT	CTCAE
	AST increased	AST	CTCAE
	Amylase increased	AMYLASE	CTCAE
	Calcium increased Calcium decreased	CA	CTCAE
	Creatinine increased	CREAT	CTCAE
	Glucose increased Glucose decreased	GLUC	CTCAE
	LDH increased	LDH	CTCAE
	Magnesium increased Magnesium decreased	MG	
	Phosphate decreased	PHOS	
	Potassium increased Potassium decreased	K	CTCAE
	Sodium increased Sodium decreased	NA	CTCAE
	Total bilirubin increased	BILI	CTCAE
Endocrinology	Thyroid Stimulating Hormone increased Thyroid Stimulating Hormone decreased	TSH	HLN

All laboratory data will be reported in SI units as shown in: Appendix C Laboratory Tests, Standard International Units (SIU). Values out of reference range will be flagged as high (H) or low (L) in the listings and the Investigator assessment of not clinically significant (NCS) or clinically significant (CS). Laboratory results that are regarded as clinically significant will be recorded as adverse events.

For analysis purposes values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively. In case any value has been converted from conventional to SI units the decimal precision will be set so that the number of significant figures on the SI value is consistent with original reporting.

Hematology and serum chemistries may be summarized by treatment arm and visit using standard descriptive statistics for the Safety Analysis Set. Changes from baseline will also be summarized. For each laboratory analyte, the baseline value will be defined as last scheduled or unscheduled value collected on or prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the study treatment administration, if the corresponding times have not been recorded. In case of unscheduled or repeat assessments at a post-baseline visit, only the first result will be included in the summary by visit.

Laboratory values will be assigned toxicity grades, when available, using criteria based on the NCI CTCAE v5.0 (Appendix D CTCAE Version 5.0 Toxicity Grades for Clinical Laboratories). These criteria are derived using only the numeric laboratory measurement, baseline measurement and normal range limits. Where defined, low and high shifts will be summarized separately. Directional shifts in hematology and serum chemistry toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of subjects and their maximum grade shift.

Separate laboratory shift tables will present directional shifts from baseline to above the laboratory standard upper limit of normal (ULN) or below the lower limit of normal (LLN) using the maximum increase and/or decrease observed throughout the course of treatment and including the SFU visit. Scheduled and unscheduled assessments will be included in this analysis.

A summary for assessment of Hy's law may be presented for all ALT, AST, TBILI and ALP assessments of subjects with any ALT ≥ 3 x ULN, AST ≥ 3xULN, or TBILI ≥ 2 x ULN.

8.5.6 Vital Signs

The following vital signs were assessed and collected during the study:

- systolic and diastolic blood pressure (mmHg)

- height (only collected at screening visit)
- oxygen saturation
- pulse rate (bpm)
- respiration rate (breaths/min)
- body temperature (°C)
- weight

Weight will be summarized by treatment arm and visit using standard descriptive statistics for the Safety Analysis Set. All vital signs may be listed.

8.5.7 Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- RR interval (msec)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- Fridericia corrected QT (QTcF) interval (msec)
- An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant")

The ECG collected in triplicate will be summarized as follows for all listings and tables: The mean over the triplicate of each quantitative measurement will be reported to the nearest integer.

The ECG measurements and changes from baseline in ECG may be listed.

For post-baseline, only data from scheduled visits will be included in the summary tables.

A categorical summary of maximum post-baseline ECG will present number of percent of subjects with QTcF >450 msec in males and >480 msec in females, QTcF >480 msec (male or female subjects), and QTcF change from baseline increased >30 msec. All mean of triplicate post-baseline QTcF will be included in this analysis.

8.5.8 Echocardiogram or Multigated Acquisition Scan

Left ventricular ejection fraction (LVEF) and change from baseline will be listed and summarized by treatment arm and visit using standard descriptive statistics for the Safety Analysis Set.

8.5.9 Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History or Adverse Events as appropriate and may be listed and summarized as such [See Section 8.3.3 (Medical History) and 8.5.2 (Adverse Events)].

8.5.10 Other Safety Variables

All ADA assessments will be listed.

8.6 Interim Analysis – Safety Data Monitoring

8.6.1 Safety Review and Potential Early Stopping

A Safety Review Committee (SRC) will be established to oversee the safety aspects for this component of the study. Specifically, the SRC will perform ongoing review on the rate of SAEs attributable to study treatment. Details of the SRC conduct are provided in the SRC Charter.

A Bayesian toxicity monitoring rule will be implemented. Specifically, if the probability (true study treatment related SAE rate > 30% data) > 70% in any given treatment arm, the enrollment to that treatment arm will be temporarily halted pending the SRC review. A Beta (0.5, 0.5) prior for the true study treatment related SAE rate is utilized. Table 6 shows the stopping boundaries for this safety monitoring rule in up to 33 subjects per treatment arm.

Table 6: Bayesian Toxicity Monitoring Safety Stopping Rules

Number of Subjects	Early Stop if Number of Subjects with Related SAEs
3-5	≥ 2
6-7	≥ 3
8-10	≥ 4
11-13	≥ 5
14-16	≥ 6
17-19	≥ 7
20-22	≥ 8
23-26	≥ 9
27-29	≥ 10
30-32	≥ 11
33	≥ 12

Number of Subjects	Early Stop if Number of Subjects with Related SAEs
	Reach Max N

SAEs = serious adverse events

An ad hoc review meeting will be conducted to review accumulated safety data, including SAEs, if a threshold on Table 6 is crossed and the timing doesn't fall in the regular SRC reviewing meeting schedules (as set forth in the SCR Charter). If the SRC considers the safety profile inadequate for BDC-1001 as monotherapy or in combination with pertuzumab, then enrollment to either of both treatment arms may be stopped. The SRC may also recommend stopping the entire study based on the safety review at any time.

In addition to the stopping rules, if any subject dies due to an event attributable by the Investigator or Sponsor to BDC-1001 and/or pertuzumab, enrollment will be interrupted in all treatment arms that include the implicated study treatment (i.e., BDC-1001 or BDC-1001+pertuzumab), pending review by the SRC.

The SRC may recommend that enrollment and/or study treatment be interrupted for either or both treatment arms should emerging safety data suggest an unacceptable risk.

Although the decision of whether to close a treatment arm will be made primarily based on the safety monitored continuously using Bayesian toxicity monitoring, the totality of data (including safety, efficacy, and PK, if available) will also be reviewed and considered in the final decision made by the Sponsor. The decision will be communicated to sites in writing if the Sponsor determines a treatment arm is to be closed.

8.7 Pharmacokinetic and Immunogenicity Analyses

8.7.1 General Data Handling Rules in Pharmacokinetic Analysis

If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.

8.7.2 Analysis

The following summaries are planned:

- Summary statistics of serum concentration data of BDC-1001 (n, arithmetic mean, standard deviation [STD], coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum and maximum) will be calculated for each nominal time point by cohort.

8.8 Public Health Emergency, Study Impact

The coronavirus disease 19 (COVID-19) public health emergency declared by United States Health and Human Services (Jan 31, 2020 to May 11, 2023) may have impacted study conduct resulting in contingency arrangements, protocol deviations, or protocol amendments. As specified in the Food and Drug Administration (FDA, United States) Guidance and by the European Medicines Agency Points to Consider, relevant site communications and notes to file related to the public health emergency will be reviewed and may be summarized in the clinical study report (or in a separate study-specific document):

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.

2. A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.

3. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Specific information was captured in the CRF and in protocol deviation records of any missing data and study discontinued events related COVID-19. Impact on the data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment. Summary and analysis of the study data, for DESC, or final reporting may include an assessment of data 'affected' or 'unaffected' by decisions and deviations related to the COVID-19 pandemic.

9. Changes in Planned Analysis

Not applicable.

10. Data Issues

Not applicable

11. References

1 Eisenhauer, E. A., P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe and J. Verweij (2009). *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer 45(2): 228-247.

2 European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP). *Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical 5 trials*`, 2020 https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials

3 FDA. *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, 2009 http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

4 FDA. *Guidance for Industry on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. 2020* https://www.fda.gov/regulatory-information/search-fda-guidance-documents

5 ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at http://www.emea.eu.int/pdfs/human/ich/036396en.pdf

6 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012. Available at http://www.ich.org/fileadmin/Public_Web_Study site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf

7 Koyama, T. and H. Chen (2008). *Proper inference from Simon's two-stage designs*. Stat Med 27(16): 3145-3154.

8 U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. November 27, 2017.

9 Schemper, M. and T. L. Smith (1996). *A note on quantifying follow-up in studies of failure time*. Control Clin Trials 17(4): 343-346.

10 Seymour, L., J. Bogaerts, A. Perrone, R. Ford, L. H. Schwartz, S. Mandrekar, N. U. Lin, S. Litiere, J. Dancey, A. Chen, F. S. Hodi, P. Therasse, O. S. Hoekstra, L. K. Shankar, J. D. Wolchok, M. Ballinger, C. Caramella, E. G. de Vries and R. w. group (2017). *iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.* Lancet Oncol 18(3): e143-e152.

11 Simon, R. (1989). *Optimal two-stage designs for phase II clinical trials*. Control Clin Trials 10(1): 1-10.

12. Appendix A Assessment of Disease Response Using RECIST V1.1

A summary of the best overall tumor response calculation is provided in Appendix A.3. For confirmation of CR and PR, the response criteria must be met again at least 4 weeks after the date of the initial documentation of response. Subjects with time point responses such as PR–NE–PR or PR–Stable–PR will be considered confirmed. Unless specified otherwise, tumor assessments will be excluded from the best overall response calculation if they occur after the start of any non-protocol anticancer therapy or surgical intervention. Stable disease will be measured from the date of the first dose of study drug until the criteria for disease progression is first met. A best overall response of stable disease will require a time point response of stable disease or better at least 4 weeks after the first dose of study drug. For example, a subject who has SD at the first assessment, PD at the second assessment and does not meet the minimum duration for SD, will have a best response of PD. The same subject lost to follow up after the first SD assessment would be considered non-evaluable (NE).

For subjects who discontinued from study drug due to worsening disease or early death and their tumor assessments were either incomplete or were never performed or not repeated, their best overall response cannot be determined (NE) due to the lack of objective evidence of disease progression.

Appendix A.1 RECIST v1.1 Criteria for Tumor Response

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	Stable, PD, or PR[a]
CR	Stable	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	CR[b]	PR
PR	PR	PR
PR	Stable	Stable
PR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
NE	NE	NE

Abbreviations: CR = complete response; LD = longest diameter PD = progressive disease; PR = partial response; SD = stable disease.

Source: Eisenhauer, Therasse et al. 2009.

Appendix A. 2 RECIST v1.1 Overall Response Criteria

Subjects with Target and Non-target Lesions			
Target Lesions	**Non-Target Lesions**	**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 evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Subjects with Non-target Lesions Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR / Non-PD	No	Non-CR / Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = unevaluable; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Eisenhauer, Therasse et al. 2009.

Appendix A. 3 Best Overall Response When Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	Stable, PD, or PR[a]
CR	Stable	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	CR[b]	PR
PR	PR	PR
PR	Stable	Stable
PR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
NE	NE	NE

CR = complete response; NE = non-evaluable; PD = progressive disease; PR = partial response

a. If a CR is truly met at a first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response will depend on whether minimum duration of Stable is met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject has PR, not CR, at the first time point. Under these circumstances, the original CR will be changed to PR and the best response is PR.

b. Every effort will be made to confirm the CR. For such cases where CR is not subsequently confirmed, then best overall response is PR.

Source: Eisenhauer, Therasse et al. 2009

13. Appendix B Date Imputation Rules

Missing or Partial Adverse Event and Prior/Concomitant Medication Start Dates

In cases of missing or incomplete dates for safety data (e.g., AE or concomitant medications), the actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings. The missing portion(s) will be assumed as the most conservative value possible, if deemed appropriate.

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as 15. For an AE, however, if the month and year are the same as the month and year of the date of the first dose of study medication, then the missing day will be imputed to be the day part of the first dose date.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01JUL. For an AE, however, if the year is the same as the year of the date of the first dose of study medication, then the missing day and month will be imputed to be the day and month parts of the first dose date.
- If the date is completely missing, then the start date will be imputed to be the earlier of the date of the first dose of study medication and the AE or medication end date. If the end date is partial, then impute the end date first before imputing the start date.

Missing or Partial Adverse Event and Prior/Concomitant Medication End Dates

If the AE or medication is reported as ongoing (or for an AE, not resolved/not recovered or recovering/resolving), then the end dates should be blank; otherwise, the following rules for imputation should be followed:

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as the last day of the month except for prior anticancer therapies where the day will be set to 15th of the month.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 31DEC. If it is a prior anticancer medication and the imputed date is on or after the informed consent date then set the imputed date to (informed consent date -15). For an AE, however, if the year is the same as the year of the date of the last dose of study medication, then the missing day and month will be imputed to be the day and month parts of the last dose date.
- If the date is completely missing, then the end date will be imputed to be the date of the first visit that is after the AE start date or the subject's last dose date, if there is no visit that is after the AE start date. If the start date is partial, then impute the start date first before imputing the end date.

If the imputation rules above result in an end date being earlier than the start date, where one or both dates are imputed, then end date will be set to start date + 1. If an imputed start date is after the end date, then the start date will be set to the end date – 1. Prior to database lock, all imputed adverse event dates will be reviewed by the study team and approved by the sponsor for clinical relevance. Imputed dates may be adjusted based on this review.

Missing or Partial Diagnosis Dates of Historical Conditions of Interest

- If the day is missing but both the month and year are non-missing, then the missing day will be imputed as 15.
- If both the day and month are missing but the year is non-missing, then the missing day and month will be imputed as 01JUL.
- If the date is completely missing, then it will not be imputed.

If the imputed date is after informed consent date then set it to one day prior to informed consent date.

14. Appendix C Laboratory Tests, Standard International Units (SIU)

Decimal Precision indicates number of decimal places to be used in laboratory listings.

Hematology	LBTESTCD	LBTEST	SIU (LBSTRESU)	Decimal Precision
Red Blood Cell (RBC) Count	RBC	Erythrocytes	10^12/L	2
Hemoglobin	HGB	Hemoglobin	g/L	0
Hematocrit	HCT	Hematocrit	RATIO	1
Platelet Count	PLAT	Platelets	10^9/L	0
White Blood Cell (WBC) Count	WBC	Leukocytes	10^9/L	1
WBC Differential (absolute)				
Neutrophils	NEUT	Neutrophils	10^9/L	2
Lymphocytes	LYM	Lymphocytes	10^9/L	2
Monocytes	MONO	Monocytes	10^9/L	2
Eosinophils	EOS	Eosinophils	10^9/L	2
Basophils	BASO	Basophils	10^9/L	2
WBC Differential (percent)				
Neutrophils	NEUTLE	Neutrophils/Leukocytes	%	1
Lymphocytes	LYMLE	Lymphocytes/Leukocytes	%	1
Monocytes	MONOLE	Monocytes/Leukocytes	%	1
Eosinophils	EOSLE	Eosinophils/Leukocytes	%	1
Basophils	BASOLE	Basophils/Leukocytes	%	1

Serum Chemistry	LBTESTCD	LBTEST	SIU (LBSTRESU)	Decimal Precision
Blood Urea Nitrogen (BUN)	UREAN	Urea Nitrogen	mmol/L	1
Uric acid	URATE	Urate	mmol/L	0
Total Bilirubin (TBILI)	BILI	Bilirubin	µmol/L *	2
Aspartate aminotranferase (AST)	AST	Aspartate Aminotransferase	U/L	0
Alanine aminotranferase (ALT)	ALT	Alanine Aminotransferase	U/L	0
Alkaline phosphatase (ALP)	ALP	Alkaline Phosphatase	U/L	0
Lactate dehydrogenase (LDH)	LDH	Lactate Dehydrogenase	U/L	0
Glucose **	GLUC	Glucose	mmol/L	1
Bicarbonate (total CO_2)	CO2	Carbon Dioxide	mmol/L	0
Sodium (Na)	SODIUM	Sodium	mmol/L	0
Potassium (K)	K	Potassium	mmol/L	1

Serum Chemistry	LBTESTCD	LBTEST	SIU (LBSTRESU)	Decimal Precision
Chloride (Cl)	CL	Chloride	mmol/L	0
Magnesium (Mg)	MG	Magnesium	mmol/L	2
Calcium (Ca)	CA	Calcium	mmol/L	1
Phosphate (PO4)	PHOS	Phosphate	mmol/L	1
Creatinine (Cr)	CREAT	Creatinine	µmol/L *	0
Amylase	AMYLASE	Amylase	U/L	0
Triglyceride **	TRIG	Triglycerides	mmol/L	1
Total Cholesterol **	CHOL	Cholesterol	mmol/L	0
Total protein	PROT	Protein	g/L	0
Albumin	ALB	Albumin	g/L	0

* µmol/L may print as umol/L
** Required only under Protocol Versions 1 and 2

Thyroid Function Testing	LBTESTCD	LBTEST	SIU (LBSTRESU)	Decimal Precision
Thyroid-stimulating hormone (TSH)	TSH	Thyrotropin	mIU/L	1
Free triiodothyronine (T3)†	T3FR	Triiodothyronine, Free	pmol/L	1
Free thyroxine (T4)	T4FR	Thyroxine, Free	pmol/L	0

Coagulation Tests	LBTESTCD	LBTEST	SIU (LBSTRESU)	Decimal Precision
Prothrombin time (PT)	PT	Prothrombin Time	sec	1
International normalized ratio (INR)	INR	Thyroxine, Free	RATIO	1
activated partial thromboplastin time (aPTT) **	APTT	Activated Partial Thromboplastin Time	sec	0

** Required only under Protocol Versions 1 and 2

Urinalysis (dipstick)	LBTESTCD	LBTEST	SIU (LBSTRESU)	Decimal Precision
pH	PH	pH	(no unit)	1
Specific gravity	SPGRAV	Specific Gravity	(no unit)	3
Glucose, Ketones, Protein, Leukocytes, Nitrites, and Bilirubin are qualitative assessments.				

†The test was not collected for the study

15. Appendix D CTCAE Version 5.0 Toxicity Grades for Clinical Laboratories

The following table of criteria to assign laboratory toxicity grade is based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017.

In the following tables, 'Clinical' indicates that the CTCAE definition includes clinical signs and symptoms. Assignment of toxicology grade by statistical programming will not evaluate clinical signs or symptoms.

Hematology	Hypo/ Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Red Blood Cell (RBC) Count	NA					
Hemoglobin	Hyper	Hemoglobin increased	>0 - 2 g/dL above ULN or above BL if BL is above ULN	>2 - 4 g/dL above ULN or above BL if BL is above ULN	>4 g/dL above ULN or above BL if BL is above ULN	NA
Hemoglobin	Hypo	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L; Clinical	Clinical
Hematocrit	NA					
Platelet Count	Hypo	Platelet count decreased	<LLN -75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9/L
White Blood Cell (WBC) Count	Hyper	Leukocytosis	NA	NA	>100,000/mm3	Clinical
White Blood Cell (WBC) Count	Hypo	White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophils	NA	Febrile neutropenia	NA	NA	ANC <1000/mm3, Clinical	Clinical
Neutrophils	Hypo	Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocytes	Hypo	Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Lymphocytes	Hyper	Lymphocyte count increased	NA	> 4 - 20 x10e9/L	> 20 10e9/L	NA
Monocytes	NA					
Eosinophils	Hyper	Eosinophilia	>ULN and >Baseline and NCS	NA	>ULN and >Baseline and CS	NA
Basophils	NA					

BL = baseline; CS = clinically significant; LLN = lower limit of normal range; NA = not applicable, no toxicology grade will be assigned; NCS = not clinically significant; ULN = upper limit of normal range.

Serum Chemistry	Hypo / Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Blood Urea Nitrogen (BUN)	Hyper [1]	not CTCAE	23 – 26 mg/dL 8.2 – 9.5 mmol/L	27 – 31 mg/dL 9.6 – 11 mmol/L	> 31 mg/dL > 11 mmol/L	Clinical
Uric acid	Hyper	Hyperuricemia	>ULN and NCS	NA	>ULN and CS	NA
Total Bilirubin (TBILI)	Hyper	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Aspartate aminotranferase (AST)	Hyper	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alanine aminotranferase (ALT)	Hyper	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase (ALP)	Hyper	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was Abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was Abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Lactate dehydrogenase (LDH)	Hyper	Blood lactate dehydrogenase increased	>ULN	NA	NA	NA
Bicarbonate (total CO_2)	Hypo	Blood bicarbonate decreased	<LLN	NA	NA	NA
Sodium (Na)	Hyper	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; Clinical	>155 - 160 mmol/L; Clinical	>160 mmol/L; Clinical
Sodium (Na)	Hypo	Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and NCS	125-129 mmol/L and CS; 120-124 mmol/L (and CS or NCS)	<120 mmol/L; Clinical
Potassium (K)	Hyper	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; Clinical	>6.0 - 7.0 mmol/L; Clinical	>7.0 mmol/L; Clinical
Potassium (K)	Hypo	Hypokalemia	<LLN - 3.0 mmol/L and NCS	<LLN - 3.0 mmol/L and CS; clinical	<3.0 - 2.5 mmol/L; Clinical	<2.5 mmol/L; Clinical

Serum Chemistry	Hypo / Hyper	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chloride (Cl)	NA					
Magnesium (Mg)	Hyper	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	NA	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; Clinical
Magnesium (Mg)	Hypo	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; Clinical
Calcium (Ca) [Corrected serum calcium] or {Ionized} [2]	Hyper	Hypercalcemia	[>ULN - 2.9 mmol/L] {>ULN - 1.5 mmol/L}	[>2.9 - 3.1 mmol/L] {>1.5 - 1.6 mmol/L} Clinical	[>3.1 - 3.4 mmol/L] {>1.6 - 1.8 mmol/L} Clinical	[>3.4 mmol/L] {>1.8 mmol/L} Clinical
Calcium (Ca) [Corrected serum calcium] or {Ionized} [2]	Hypo	Hypocalcemia	[<LLN - 2.0 mmol/L] {LLN - 1.0 mmol/L}	[<2.0 - 1.75 mmol/L] {<1.0 - 0.9 mmol/L} Clinical	[<1.75 - 1.5 mmol/L] {<0.9 - 0.8 mmol/L} Clinical	[<1.5 mmol/L] {<0.8 mmol/L} Clinical
Phosphate (PO4)	Hyper	Hyperphosphatemia	>ULN and NCS	>ULN and CS	Clinical	Clinical
Phosphate (PO4)	Hypo	Hypophosphatemia	< LLN and NCS	< LLN and CS	Clinical	Clinical
Creatinine (Cr)	Hyper	Creatinine increased	>ULN - 1.5 x ULN; >1 - 1.5 x baseline	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Amylase	Hyper	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and NCS	>2.0 - 5.0 x ULN and CS; >5.0 x ULN and NCS	>5.0 x ULN and CS
Total protein	Hypo [1]	not CTCAE	5.5 - 6.0 g/dL	5.0 - 5.4 g/dL	< 5.0 g/dL	NA
Albumin	Hypo	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Clinical

BL = baseline; CS = clinically significant; LLN = lower limit of normal range; NA = not applicable, no toxicology grade will be assigned; NCS = not clinically significant; ULN = upper limit of normal range.
[1] CTCAE grade is not defined. Source is FDA Guidance 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials'.
[2] Corrected serum calcium (mmol/L) = total calcium (mmol/L) + 0.02 [40 – albumin (g/L)]. Corrected calcium will be used for assignment of toxicology grade by statistical programming.

Urinalysis (dipstick)	Hypo/ Hyper	**CTCAE Term**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
pH	NA					
Specific gravity	NA					
NA = not applicable, no toxicology grade will be assigned. Glucose, Ketones, Protein, Leukocytes, Nitrites, and Bilirubin are qualitative assessments.						