# 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

| | |
|---|---|
| **Investigational Product:** | BDC-1001 |
| **INN Name:** | Trastuzumab imbotolimod |
| **Protocol Number:** | BBI-20231001 |
| **IND #:** | [redacted] |
| **ClinicalTrials.gov Identifier:** | NCT05954143 |
| **EU CTIS Number:** | 2023-506038-65-00 |
| **Development Phase:** | Phase 2 |
| **Sponsor:** | Bolt Biotherapeutics, Inc.<br>900 Chesapeake Drive<br>Redwood City, CA 94063 |
| **Protocol Version:** | 3.0<br>01 August 2024 |

# PROTOCOL SIGNATURE PAGE – AUTHORS

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|---|---|
| **Protocol Title:** | 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 |
| **Protocol Number:** | BBI-20231001 |
| **Protocol Version:** | 3.0<br>01 August 2024 |

This study protocol was subjected to critical review. The information it contains is consistent with the current benefit/risk evaluation of the test preparation. The study will be conducted in compliance with the protocol, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP), and any applicable regulatory requirements.

This protocol is approved by:

[redacted]

Refer to Veeva signature manifest at the end of the document

Signature Date

[redacted]

Refer to Veeva signature manifest at the end of the document

Signature Date

## PROTOCOL SIGNATURE PAGE – INVESTIGATOR

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| **Protocol Title:** | 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 |
| **Protocol Number:** | BBI-20231001 |
| **Protocol Version:** | 3.0<br>01 August 2024 |

I confirm that I have read and understood this protocol and agree to conduct the trial as outlined in the protocol and other information supplied to me. I agree to conduct the trial in accordance with the Declaration of Helsinki and its amendments, Good Clinical Practice (GCP) guidelines established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and applicable local legal and regulatory requirements.

Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes only.

The current version of the protocol has been reviewed and approved.

| | |
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| Principal Investigator's Signature | Date |
| Print Principal Investigator's Name | |

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# SYNOPSIS

**SPONSOR/COMPANY:**

Bolt Biotherapeutics, Inc.

**PROTOCOL:**

Title: 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

Number: BBI-20231001

Phase: 2

Investigational Medicinal Product: BDC-1001 (trastuzumab imbotolimod)

**STUDY SITES:**

Approximately 30 institutions across North America and the European Union were initially planned for participation in this study.

**NUMBER OF SUBJECTS PLANNED:**

Approximately 66 evaluable subjects

**OBJECTIVES AND ENDPOINTS:**

The objectives and endpoints to be evaluated in the study are as follows:

| 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<br>• 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 | • Evaluation of BDC-1001 activity in the context of additional exploratory predictive and/or prognostic biomarkers related to tumor and immune biology by such |

| | |
|---|---|
| combination with pertuzumab in subjects with HER2+ MBC<br>• 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 | methods as gene expression profiling, mutational, protein and tissue image analysis<br>• Changes in TLR7/8 pathway activation, myeloid and T cell content, and activation status by such methods as gene expression profiling, protein, and tissue image analysis.<br>• Evaluation of changes in additional exploratory biomarkers in tumor tissue and blood related to tumor and immune biology by such methods as gene expression profiling, mutational, protein and tissue image analysis |

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-positiveMBC = metastatic breast cancer; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; 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

**STUDY DESIGN/METHODOLOGY:**

This is an open label, Phase 2 study to evaluate preliminary anti-tumor activity, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and immunogenicity of BDC-1001 administered as a single agent and in combination with pertuzumab in subjects with human epidermal growth factor receptor 2-positive (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 8.2).

Subjects will receive study treatment (ie, BDC-1001 or BDC-1001 in combination with pertuzumab) as described in Section 5.2. To ensure subject safety, dosing of the first 3 subjects enrolled in the combination treatment arm will receive study treatment staggered by a minimum of 48 hours, and these subjects will be observed for at least 6 hours following the first dose of study treatment. Any subject with acute changes in vital signs will be observed until the events have resolved or are stabilized.

All subjects in both treatment arms will be monitored for adverse events (AEs) and serious adverse events (SAEs) (Section 8.4.5.1). Study data will be provided to the Safety Review Committee (SRC) for ongoing safety monitoring and detection of potential safety concerns (Section 3.1.1).

Subjects will return to the site for study assessments at the visits listed in the Schedule of Assessments. In the event of study treatment discontinuation, subjects will be asked to complete an End of Treatment (EOT; Section 6.25.1) visit 14 days (± 7 days) after the date of the last study treatment, and then return for a Safety Follow-Up (SFU; Section 6.25.2) visit 28 days (+7 days) after the last study treatment. Subjects who discontinue treatment will have long-term follow-up (LTFU; Section 6.25.3) every 12 weeks (± 14 days) for up to 2 years after the last study treatment.

As of Protocol Version 3.0 (01 Aug 2024), any subject(s) still receiving study treatment (BDC-1001) will transition to the Maintenance Phase.

**DURATION OF STUDY:**

The planned overall study duration is approximately 4 years.

**DURATION OF SUBJECT PARTICIPATION:**

Screening: Up to 28 days before Cycle 1 Day 1 (C1D1)

Treatment duration: After C1D1 for a median duration of approximately 12 months. All subjects will be treated until disease progression, unacceptable toxicity, or withdrawal for any reason.

As of protocol Version 3.0 (01 Aug 2024), any subject(s) still receiving study treatment (BDC-1001) will transition to the Maintenance Phase.

**Eligibility Criteria:**

**Inclusion Criteria (Section 4.1):**

A subject must meet all of the following to be included in this study:

1. Be able to understand and sign the informed consent form
2. Be age 18 years or older at the time of informed consent
3. All subjects must agree to have a biopsy prior to enrollment. If, in the judgement of the Investigator, a biopsy is not safely accessible or clinically feasible an archival tumor tissue must be submitted in lieu of a freshly collected specimen
4. Histologically confirmed adenocarcinoma of the breast that is HER2+ (per 2018 ASCO/CAP HER2 testing guidelines) by Clinical Laboratory Improvement Amendments (CLIA) certified laboratory assessment
5. Have received 2 or more prior lines of anti-human epidermal growth factor receptor 2 (HER2)-directed therapies, at least 1 of them is in the metastatic setting and 1 of the prior therapies needs to be trastuzumab deruxtecan (ENHERTU®). Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 12 months of completion of therapy will be considered a line of treatment for metastatic disease
6. Have experienced disease progression on or been otherwise unsuitable for (eg, did not tolerate) the most recent therapy
7. Have measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria
8. Have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
9. Have expected life expectancy of greater than 12 weeks per the Investigator
10. Adequate organ function defined as follows:
    a. Hematology:
        i. Absolute neutrophil count ≥ 1500 cells/$mm^3$
        ii. Platelet count ≥ 75,000 cells/$mm^3$
        iii. Hemoglobin ≥ 9 g/dL (and without transfusion within 7 days)
    b. Renal:
        i. Creatinine clearance ≥ 30 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
        $\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$
    c. Coagulation:
        i. International normalized ratio (INR) and prothrombin time (PT) ≤ 1.5 × upper limit of normal (ULN) unless receiving anticoagulation therapy
        ii. Activated partial thromboplastin time (aPTT) only needs to be assessed if evaluated per standard of care. If evaluated, aPTT ≤ 1.5 × ULN, unless undergoing anticoagulation therapy
    d. Hepatic:
        i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN (or ≤ 5 × ULN in subjects with known hepatic metastases)
        ii. Total bilirubin ≤ 1.5 × ULN (isolated value > 1.5 × ULN is acceptable if direct bilirubin is <35%)
11. Women of childbearing potential should agree not to donate eggs and must use a highly effective contraceptive measure (a method that can achieve a failure rate of less than 1% per year) during treatment and until 7 months

after the end treatment. Highly effective, alternative non-hormonal contraceptive measures are preferred, include the following:

a. Intrauterine device
b. Vasectomized partner
c. Sexual abstinence
d. Bilateral tubal occlusion

12. Potent men that are partners of women of childbearing potential must be willing to use condoms in combination with a second highly effective method of female contraception (as above) during the study and agree not to donate sperm from Screening through 7 months after completion of study. A male partner will be considered as potent unless surgically sterilized (with documentation of sterility).

**Exclusion Criteria (Section 4.2):**

A subject must not meet any of the following criteria to be eligible for this study:

1. Central nervous system metastases with the exception of disease that is asymptomatic, clinically stable (without evidence of progression for at least 4 weeks confirmed by imaging during study Screening), and has not required steroids for at least 28 days before starting study treatment
2. Cardiac disease including the following:
   a. Congestive heart failure (New York Heart Association classes II–IV)
   b. Left ventricular ejection fraction (LVEF) < 50% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
   c. QT corrected - Fridericia's correction formula (QTcF) prolongation of > 480 milliseconds (ms) based on a 12-lead electrocardiogram (ECG)
   d. Serious or uncontrolled cardiac arrhythmia within 6 months before starting study treatment
   e. Myocardial infarction, unstable angina pectoris, or coronary angioplasty, stenting, or surgery within 6 months before starting study treatment
   f. Serious or uncontrolled hypertension (≥ 180 mmHg systolic or ≥ 120 mmHg diastolic) within 6 months before starting study treatment
   g. Pericarditis or pericardial effusion that is symptomatic within 6 months before starting study treatment
3. Pulmonary disease including idiopathic pulmonary fibrosis, interstitial lung disease, pneumonitis requiring steroids, or symptomatic pleural effusion within 6 months before starting study treatment OR ongoing requirement for supplemental oxygen
4. Hepatic disease resulting in symptomatic ascites, encephalopathy, coagulopathy, esophageal/gastric varices, or persistent jaundice
5. Arterial thrombotic event, stroke, or transient ischemia attack within 6 months before starting study treatment
6. Bleeding diathesis or uncontrolled bleeding within 7 days before starting study treatment
7. Bone marrow transplant or solid organ transplant
8. Infection including the following:
   a. Infection requiring systemic therapy within 7 days before starting study treatment
   b. Active human immunodeficiency virus (HIV) as defined by the protocol (Section 6.14.3)
   c. Positive hepatitis B surface antigen test at Screening or within 3 months of starting study treatment, a subject whose hepatitis B surface antigen (HBsAg) is negative and hepatitis B core antibody (HBcAb) is positive may be enrolled if a hepatitis B virus (HBV) DNA test is negative and either the subject is treated with potent antiviral therapy or is retested for HBsAg and HBV DNA every month
   d. Positive hepatitis C antibody test and confirmatory ribonucleic acid (RNA) test at Screening or within 3 months of starting study treatment. Exceptions include subjects that (1) have hepatitis C virus (HCV) viral load below the assay limit-of-quantitation and (2) completed curative antiviral therapy or are compliant with ongoing antiviral therapy
9. Autoimmune disease requiring systemic disease-modifying or immunosuppressive therapy within 2 years before starting study treatment. Exceptions include disease managed with only replacement therapies (eg, thyroxine, etc.)
10. Malignancy within 2 years before starting study treatment other than the disease under study. Exceptions include indolent or definitively treated disease not expected to require treatment during the study, affect the safety of subjects, or affect the endpoints of the trial

11. Any medical condition requiring corticosteroids (> 10 mg daily oral prednisone or equivalent) or other systemic immunosuppressive therapy within 28 days before starting study treatment. Exceptions include inhaled or topical steroids
12. Residual toxicity from previous treatment including the following:
    a. Toxicity related to prior treatment not resolved to Grade ≤ 1
    Exceptions to the above criteria include toxicities that do not pose a risk to vital organ systems (eg, alopecia, etc.) or toxicities that are stable as managed by replacement therapies (eg, hypothyroidism, etc.)
13. Prior anticancer therapies including:
    a. Small molecule toll-like receptor (TLR)7/8 agonist or TLR7/8 agonist that has been conjugated to tumor-targeting antibody such as immune stimulating antibody conjugates (ISAC) within 12 months before starting study treatment
    b. An investigational agent or anticancer therapy within 28 days before starting study treatment or within 5 estimated elimination half-lives, whichever is shorter. Gonadotropin-releasing hormone agonists for ovarian suppression in premenopausal women are permitted
14. History of severe hypersensitivity to any ingredient of BDC-1001 or pertuzumab
15. Received live/attenuated virus vaccine within 28 days before starting study treatment
16. Major surgery within 28 days of starting study treatment
17. Radiation therapy within 2 weeks of C1D1
18. Actively enrolled in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up component of an interventional study
19. Subject is a lactating mother or pregnant as confirmed by pregnancy tests within 48 hours prior to start of study treatment
20. Subject is unwilling or unable to follow protocol requirements
21. Recurrent ascites requiring routine intervention >Q3 months
22. Any condition that, in the opinion of the Investigator, would interfere with evaluation of BDC-1001 and pertuzumab or interpretation of the subject's safety or study results

**TREATMENT PROCEDURES:**

**Investigational Product:**

BDC-1001:

The BDC-1001 dosage form is a sterile lyophilized cake/powder provided in a sterile glass vial (25 mg/mL, 10 mL fill, 250 mg/vial). The lyophilized powder will be reconstituted with sterile water for injection.

Pertuzumab:

The pertuzumab dosage form is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous (IV) infusion. Each single-dose vial contains 420 mg of pertuzumab (14.0 mL/vial) at a concentration of 30 mg/mL in 20 mM L-histidine acetate, 120 mM sucrose, and 0.02% polysorbate 20 at pH 6.0.

**Mode of Administration and Dosing:**

Premedication:

All subjects should be premedicated prior to administration of BDC-1001 for potential infusion-related reactions (IRRs) with paracetamol and diphenhydramine (eg, 1000 mg paracetamol, 50 mg diphenhydramine) or according to institutional standards.

On dosing days when pertuzumab is administered without BDC-1001, premedication for pertuzumab is only required if a subject experiences IRR during the previous dose.

Corticosteroids and other immunomodulators remain excluded for study treatment infusions.

BDC-1001 Administration:

BDC-1001 will be administered every 2 weeks (q2w) at a dose of 20 mg/kg as an intravenous (IV) infusion over 60 minutes (± 15 minutes). BDC-1001 will be administered before pertuzumab on days that both BDC-1001 and pertuzumab are administered.

Pertuzumab Administration:

Pertuzumab will be administered as an IV infusion according to the package insert (ie, initial dose of 840 mg over 60 minutes followed every 3 weeks by a dose of 420 mg over 30 to 60 minutes). On days that both BDC-1001 and pertuzumab are administered, pertuzumab will be administered 30 to 60 minutes after the end of BDC-1001 infusion.

**Duration of Treatment:**

All subjects will be treated until disease progression, unacceptable toxicity, or withdrawal for any reason.

Following progressive disease (PD) according to RECIST v1.1, treatment beyond disease progression will be allowed with the approval of the Sponsor, provided the subject is clinically stable. Clinically stable is defined as follows:

1. Subject is without worsening symptoms attributable to disease progression,
2. Subject maintains ECOG status, and
3. Subject tolerates study treatment (ie, no related SAE or Grade ≥ 3 AE that requires study drug discontinuation) per Investigator clinical judgement.

Subject with confirmed PD (using the scan at first PD as the new baseline) will be discontinued from study treatment.

**Maintenance Phase:**

As of this protocol Version 3.0 (01 Aug 2024), any subjects still receiving study treatment (BDC-1001) will transition to the Maintenance Phase and are to be followed as described in 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). 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.

**STUDY ASSESSMENTS:**

Study assessments will be conducted as outlined in the Schedule of Assessments.

**STATISTICAL ANALYSIS:**

**Analysis Sets:**

The analysis sets are defined as follows:

Safety Analysis Set is defined as enrolled subjects who receive at least 1 dose of BDC-1001 with or without pertuzumab. The Safety Analysis Set will be used primarily for the analysis of safety data.

Full Analysis Set (FAS) will be used primarily for the analysis of tumor response and other anti-tumor activity-related data. The FAS will include subjects who meet the following criteria:

- Receive at least 1 dose of BDC-1001 with or without pertuzumab
- Have 1 or more measurable lesion(s) at baseline and at least 1 postbaseline evaluable scan as assessed using RECIST v1.1 criteria.

Pharmacokinetic Analysis Set (PKAS) will include subjects who meet the following criteria:

- Receive any dose of BDC-1001 with or without pertuzumab
- Have 1 or more post-infusion PK datapoint

Pharmacodynamic Analysis Set (PDAS) will include subjects who meet the following criteria:

- Receive any dose of BDC-1001 with or without pertuzumab
- Have 1 or more sets of biomarker data

**Sample Size:**

Approximately 66 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 objective response rate (ORR). It is assumed under the null hypothesis, that objective response rate (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 evaluable subjects will be enrolled into the first stage. If at least 5 objective responses are observed in an arm, the study will continue to enroll 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 evaluable subjects in an arm.

**Methodology:**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan.

**Safety Analysis:**

Safety will be assessed through summaries of AEs, SAEs, changes in laboratory test results, changes in vital signs and ECGs, and exposure to BDC-1001 and pertuzumab. All safety analyses will be conducted for the Safety Analysis Set.

**Pharmacokinetic Analysis:**

Individual and mean serum BDC-1001 exposure (eg, peak serum concentrations ($C_{max}$) and trough serum concentrations [$C_{min}$]) will be tabulated and plotted by arm and compared to those in the Phase 1 study using a population PK analysis approach. Intersubject variability and drug accumulation will be evaluated.

PK data from this study may also be used for separate pharmacokinetic/pharmacodynamic analyses; the results will be reported separately, if conducted.

Exploratory pharmacodynamic analyses will include assessments of pharmacodynamic biomarkers in both tumor tissue and blood.

The relationship between BDC-1001 concentration and selected efficacy and safety outcomes may be explored. The correlation between biomarkers and clinical outcomes may be analyzed.

**Anti-Tumor Activity Analysis:**

The following anti-tumor activity endpoints will be analyzed and summarized for the subjects in FAS, with at least one evaluable post-baseline tumor assessment per RECIST v1.1: ORR, duration of response, disease control rate. Progression-free survival and overall survival will be analyzed and summarized for subjects in the Safety Population. Additional details will be provided in the statistical analysis plan.

The ORR is defined as the proportion of subjects with best overall response of confirmed complete response (CR) or partial response (PR) as determined by the treating Investigator using RECIST v1.1. Confirmed CR or PR is defined as a repeat tumor assessment performed no less than 4 weeks after the criteria for response is first met.

**Biomarker Analysis:**

Exploratory biomarker analyses may include assessments of pharmacodynamic biomarkers in both tumor tissue and blood, when appropriate for data collected. Biomarkers that may correlate with anti-tumor activity or immunomodulatory effects of BDC-1001 will be explored, as appropriate.

BDC-1001 biological activity will be assessed by exploring pharmacodynamic or predictive biomarkers that may correlate with activity or help to identify subjects likely to respond to BDC-1001 and/or BDC-1001 plus pertuzumab combination treatment, when appropriate for data collected. The correlation between biomarkers and clinical outcomes may be analyzed.

**Immunogenicity Analysis:**

Incidence, titer, and time-course of anti-BDC-1001 antibody (ADA) response will be reported by arm. The potential correlation of immunogenicity with PK, pharmacodynamic, and safety parameters may be assessed.

## SCHEDULE OF ASSESSMENTS

### Table 1: Overview of Schedule of Assessments

| Event | Screening [a] | Cycle 1 | | | | | | | | | | Cycle 2 and Beyond | | EOT Visit [b] | SFU [b] | LTFU [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Day [c]** | | **Day 1** | | **D2** | **D8** | **Day 15** | | **D22** | **Day 29** | | **D36** | **Day 1 unless otherwise indicated** | | **14 d-(±7d) after last Tx.** | **28d (+7d) After last Tx** | **q12 wks (±14d) After last Tx** |
| **Visit Windows** | | | | | **±1d** | **±2d** | | **±2d** | **±2d** | | **±2d** | **±2d for Cycle 2 and Beyond[d]** | | | | |
| **Timing** | | **BI** | **EOI** | | | **BI** | **EOI** | | **BI** | **EOI** | | **BI** | **EOI** | | | |
| Informed consent [e] | ● | | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria [f] | ● | ● | | | | | | | | | | | | | | |
| Administration of BDC-1001 q2w [g] | | ● | | | | ● | | | ● | | | Days 1, 15, 29 | | | | |
| Administration of pertuzumab q3w [h] | | ● | | | | | | ● | | | | Days 1 and 22 | | | | |
| Medical history [i] | ● | | | | | | | | | | | | | | | |
| Demographics [j] | ● | | | | | | | | | | | | | | | |
| Height [k] | ● | | | | | | | | | | | | | | | |
| Physical examination [l] | ● | ● | | ● | | ● | | ● | ● | | | BI[m] on Days 1, 15, 22, 29 | | ● | ● | |
| Weight, ECOG PS [m] | ● | ● | | | | ● | | ● | ● | | | BI[m] on Days 1, 15, 22, 29 | | ● | ● | |
| Vital signs [n] | ● | ● | BI (- 2 h) on Days 1, 15, 22, 29 and EOI (+ 5 min). Vital signs are not required EOI unless infusion reactions occur and after Cycle 2 unless clinically indicated. | | | | | | | | | | | ● | ● | |
| 12-lead ECG [o] | ● | ● | BI (- 2 h) on Days 1, 15, 22, 29 and EOI (+ 5 min). ECGs are not required EOI unless infusion reactions occur and after Cycle 2 unless clinically indicated. | | | | | | | | | | | ● | | |
| ECHO or MUGA [p] | ● | | First assessment will be 6 weeks after the first study treatment then every 3 months during treatment, and start monitoring immediately in the presence of symptoms | | | | | | | | | | | ● | | |
| $SpO_2$ [q] | ● | ● | | ● | | | ● | | ● | ● | | BI on Days 1, 15, 22, 29 | | ● | | |

| Event | Screening [a] | Cycle 1 | | | | | | | | | | Cycle 2 and Beyond | | EOT Visit [b] | SFU [b] | LTFU [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Day [c] | | Day 1 | | D2 | D8 | Day 15 | | D22 | Day 29 | | D36 | Day 1 unless otherwise indicated | | 14 d-(±7d) after last Tx. | 28d (+7d) After last Tx | q12 wks (±14d) After last Tx |
| Visit Windows | | | | | ±1d | ±2d | | ±2d | ±2d | | ±2d | ±2d for Cycle 2 and Beyond[d] | | | | |
| Timing | | BI | EOI | | | BI | EOI | | BI | EOI | | BI | EOI | | | |
| Prior and concomitant medications | ● | ● | | ● | ● | ● | ● | ● | ● | ● | ● | Days 1, 15, 22, 29 | | ● | ● | |
| AEs | ● | ● | | ● | ● | ● | ● | ● | ● | ● | ● | Days 1, 15, 22, 29 | | ● | ● | |
| HIV, HBV, HCV [r] | ● | | | | | | | | | | | | | | | |
| Pregnancy test [s] | ● | ● | Every 4 weeks (±3 days) after Cycle 1 Day 1 and at the EOT | | | | | | | | | | | | | |
| Chemistry and hematology [t] | ● | ● | | | | ●[t] | | ●[t] | ● | | | BI on Days 1, 15, 29 | | ● | ● | |
| Thyroid Panel [u] | ● | | | | | | | | | | | | | ● | | |
| Serum tumor markers [v] | ● | ● | | | | | | | | | | | | | | |
| Coagulation [w] | ● | | | | | | | | | | | | | ● | | |
| Urinalysis [x] | ● | ● | | | | | | | | | | If clinically indicated | | ● | | |
| PK [y] | | ● | ● | | | | | | ● | ● | | ●[y] | ●[y] | ● | | |
| ADA [z] | | ● | | | | | | | ● | | | ●[z] | | ● | | |
| Serum biomarkers [aa] | | ● | ●[aa] | | | ● | ●[aa] | | ● | ●[aa] | | ● | ●[aa] | | | |
| Plasma biomarkers [bb] | | ● | | | | | | | | | | | | ● | | |
| Whole blood biomarkers (PBMC) [cc] | | ● | | | | | | | | | ● | C2 Day 29 | | ● | | |
| Whole blood (RNA) [dd] | | ● | ● | | | | | | | | ● | | | | | |
| Fresh tumor biopsy [ee] | ● | | | | | | | | | | ● | | | | | |
| Archival tissue [ff] | ● | | | | | | | | | | | | | | | |
| Tumor assessment[gg] | ● | Every 6 weeks (± 7 days) during first 24 weeks after Day 1 of Cycle 1, and then every 12 weeks (± 7 days) | | | | | | | | | | | | | | |
| Survival information[hh] | | ● | | | | | | | | | | | | | | |

Abbreviations: ADA = anti-BDC-1001 antibody; AE = adverse event; aPTT = activated partial thromboplastin time; BI = before infusion; CA=cancer antigen; C1 = Cycle 1; d or D = day; Disc = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOI = end of infusion, EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LTFU = long-term follow-up; MUGA = multi-gated acquisition scan; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PT = prothrombin time; q2w = every 2 weeks; q3w = every 3 weeks; q12 wks = every 12 weeks; RNA = ribonucleic acid; SFU = Safety Follow-Up; $SpO_2$ = peripheral capillary oxygen saturation; T4 = thyroxine; TSH = thyroid-stimulating hormone; Tx = treatment.

a Assessments performed in the Screening Period must be done within 28 days prior to Cycle 1 Day 1, beginning with the day informed consent is obtained, with the following exceptions: concomitant medications, vital signs, physical exam, and ECOG PS assessment must be done within 14 days prior to Cycle 1 Day 1.

b The subject should attend the EOT visit 14 days (± 7 days) after the last study treatment. SFU, and LTFU are calculated from the date of the last administered study drug (BDC-1001 or pertuzumab).

c All calculations of visit date should be based on Day 1, the first day a dose of study treatment is administered for each cycle.

d Visit window is ± 2 days for study treatment administration.

e Informed consent must be dated and signed before any study-specific procedure is performed (Section 6.2).

f On Day 1 before the initial study drug treatment, recheck all Inclusion and Exclusion Criteria to meet protocol eligibility requirements. Refer to Section 4.1 and Section 4.2.

g BDC-1001 will be administered q2w as described in Section 5.2.2 (i.e., on Days 1, 15, and 29 of each cycle). Study treatment must be administered on Day 1. All subsequent doses may be administered within ± 2 days.

h For subjects assigned to receive the combination of BDC-1001 and pertuzumab, pertuzumab will be administered q3w as described in Section 5.2.3; (i.e., on Days 1 and 22 of each cycle). Study treatment must be administered on Day 1.The dose on Day 22 may be administered ±2 d .

i Medical history and tumor history should be completed as described in Section 6.6.

j Demographic data will include age, gender, and self-reported race/ethnicity (Section 6.6).

k Additional details regarding height are provided in Section 6.4.

l A full physical examination is required at Screening. All other physical examinations can be symptom directed. Additional information is provided in Section 6.4.

m After completing 6 months of treatment, the Investigator and Sponsor may agree that the frequency of physical examinations and ECOG PS may be reduced to occur on an every-even-cycle basis unless more frequent assessments are clinically indicated. Additional details are provided in Section 6.7.

n Vital signs assessments are described in Section 6.8. Vital signs are not required after cycle 2 for EOI unless infusion reactions occur or unless clinically indicated. The timing of collection pre- and post-infusion is presented in Table 8.

o ECG is to be performed in accordance with Section 6.9. ECGs are not required after cycle 2 for EOI unless infusion reactions occur or unless clinically indicated. The timing of collection pre-and post-infusion is presented in Table 8.

p ECHO/MUGA is to be performed at Screening, 6 weeks after the first study treatment, then every 3 months during treatment and start monitoring immediately in the presence of symptoms. Additional details are provided in Section 6.10.

q Pulse oximetry will be performed as described in Section 6.11.

r Additional information is provided in Section 6.14.

s Pregnancy testing of female subjects of child-bearing potential will consist of a serum pregnancy test performed at Screening, and pregnancy testing on Cycle 1 Day 1 BI, every 4 weeks (±3 days) during treatment, and at EOT. Positive urine pregnancy test will be confirmed with a serum pregnancy test. May be determined up to -48 hours before administration of study treatment. Additional information is provided in Section 6.15.

t Chemistry and hematology laboratory tests may be determined up to -48 hours before each dose and should be collected as described in Section 6.16.1 (chemistry) and Section 6.16.2 (hematology). For subjects receiving BDC-1001 as a single agent, chemistry and hematology labs are only collected on Day 1, 15, and 29 of each Cycle. For subjects receiving BDC-1001 in combination with pertuzumab, chemistry and hematology labs are collected on Days 1, 15, 22, and 29 for C1 and Days 1, 15, and 29 for all subsequent cycles.

u TSH and free T4 will be performed as described in Section 6.17. May be determined up to -48 hours before the dose.

v Serum tumor markers (ie, CA 27.29 and CA 15-3, etc.), will be performed by local laboratory per standard of care (refer to Section 6.18).

w Coagulation laboratory tests, PT (or INR) and/or aPTT as described in Section 6.16.3.

x Urinalysis or urine dipstick as described in Section 6.16.4. May be determined up to -48 hours before each dose.

y Serum PK will be collected before BDC-1001 infusion and up to 15 minutes after the end of BDC-1001 infusion, on Days 1 and 29 of Cycles 1, 2, 3, and 4; Day 1 of every other odd cycle after every 12 week tumor assessment (ie, Cycle 5, 7, 9, etc); Day 29 of every other even cycle (ie, Cycle 6, 8, 10, etc) before every 12 week tumor assessment; and at EOT (Section 6.19).

z Serum ADA will be collected before BDC-1001 infusion on Days 1 and 29 of Cycles 1, 2, 3, and 4; before BDC-1001 infusion on Day 1 of every other odd cycle after every 12 week tumor assessment (ie, Cycle 5, 7, 9, etc); before BDC-1001 infusion on Day 29 of every other even cycle (ie, Cycle 6, 8, 10, etc) before every 12 week tumor assessment; and at EOT (Section 6.20).

aa Serum biomarkers will be collected on Cycle 1 Day 1 (before BDC-1001 infusion and 4 hrs±1 hr post-EOI), Cycle 1 Day 15 (before BDC-1001 infusion and 4 hrs±1 hr post-EOI), Cycle 1 Day 29 (before BDC-1001 infusion and 4 hrs ±1 hr post-EOI), Cycle 4 Day 1 (before BDC-1001 infusion and 4 hrs±1 hr post-EOI), and Cycle 5 (before BDC-1001 infusion and 4 hrs±1 hr post-EOI), (Section 6.21).

bb Plasma biomarkers will be collected before BDC-1001 infusion on Cycle 1 Day 1 and EOT (Section 6.21).

cc Whole blood biomarkers for PBMC will be collected before BDC-1001 infusion on Cycle 1 Day 1, Cycle 1 Day 36 (during on treatment biopsy, if conducted), before BDC-1001 infusion on Cycle 2 Day 29, and EOT (Section 6.21).

dd Whole blood for RNA will be collected before BDC-1001 infusion on Cycle 1 Day 1 and 4 hrs±1 hr post-EOI, and Cycle 1 Day 36 (during on treatment biopsy, if conducted) (Section 6.21).

ee Screening fresh tumor tissue biopsy is required for all subjects (Section 6.22.1). On-treatment biopsy at Cycle 1 Day 36 may be collected if safely accessible and clinically feasible, at the discretion of the Investigator. An optional additional biopsy may be collected preferably at time of progression, response, or at any time during the study.

ff Archival tumor tissue must be submitted if a fresh biopsy is not collected (Section 6.22.2).

gg Tumor assessments should be done during the Screening Period within 28 days before Cycle 1 Day 1, every 6 weeks (± 7 days) during first 24 weeks after Day 1 of Cycle 1, and then every 12 weeks (± 7 days). Brain scans are required only for subjects with known brain metastases. Tumor measurement will be conducted while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow up. Subjects who experience an objective response (ie, tumor reduction) should have a confirmatory assessment performed 4 weeks (+7 days) after initial response. Additional details are provided in Section 6.23.

hh Survival information should be collected as described in Section 6.24.

**Table 2: Overview of Schedule of Assessments – Maintenance Phase - Q2W Dosing**

| Event | Treatment Cycle Days |
|---|---|
| Consent to Maintenance Phase | Prior to performing any assessments or procedures in the Maintenance Phase |
| Administration BDC-1001 | Days 1, 15, and 29 |
| Physical examination | Per local SOC/investigator discretion |
| Weight, ECOG PS | Per local SOC/investigator discretion |
| Vital signs | Per local SOC/investigator discretion |
| 12-lead ECG | Per local SOC/investigator discretion |
| AEs/SAEs | Per local SOC/investigator discretion<br>(Only SAEs and other reportable events such as pregnancy will be collected and reported to Sponsor for subjects during the Maintenance Phase.) |
| ECHO or MUGA | Per local SOC/investigator discretion |
| $SpO_2$ | Per local SOC/investigator discretion |
| Serum Pregnancy (if applicable) | Monthly |
| Chemistry | Per local SOC/investigator discretion |
| Hematology | Per local SOC/investigator discretion |
| Thyroid Panel/TSH | Per local SOC/investigator discretion |
| Coagulation | Per local SOC/investigator discretion |
| Urinalysis | Per local SOC/investigator discretion |
| Tumor Assessment | Per local SOC/investigator discretion |
| Post Treatment Safety Evaluation | Per local SOC/investigator discretion |

Abbreviations: AE = adverse event; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MUGA = Multigated Acquisition Scan; SAE = serious adverse event; SOC = standard of care; $SpO_2$ = peripheral capillary oxygen saturation; TSH = thyroid -stimulating hormone

For the Maintenance Phase, no data will be entered into electronic case report forms. Lab results will not be submitted to the Sponsor and radiographic images will not be submitted to the study central imaging vendor. Subjects should undergo a post treatment safety evaluation per local standard of care and as clinically directed in the opinion of the Investigator.

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| 1L, 2L, 3L | first-line, second-line, third-line |
| ASCO | American Society of Clinical Oncology |
| ADA | anti-BDC-1001 antibody |
| ADCC | antibody-dependent cell-mediated cytotoxicity |
| AE | adverse event |
| ALT | alanine aminotransferase |
| APC | antigen presenting cells |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| ATC | anatomical therapeutic classification |
| AUC | area under the concentration-time curve |
| BI | before infusion |
| BUN | blood urea nitrogen |
| CA27.29 or CA15-3 | cancer antigen 27.29 or 15-3 |
| CAP | College of American Pathologists |
| C1D1 | Cycle 1 Day 1 |
| CI | confidence interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| $C_{max}$ | peak serum concentration |
| $C_{min}$ | trough serum concentration |
| CQA | Clinical Quality Assurance |
| CR | complete response |
| CRS | cytokine release syndrome |
| CT | computed tomography |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOI | end of infusion |
| EOT | end of treatment |
| ERBB2 | erb-b2 receptor tyrosine kinase 2 |
| FAS | Full Analysis Set |
| FIH | first-in-human |

| Abbreviation | Definition |
|---|---|
| GCP | Good Clinical Practice |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HER2 | human epidermal growth factor receptor 2 |
| HER2+ | human epidermal growth factor receptor 2-positive |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| iCPD | immune confirmed progressive disease |
| IEC | Independent Ethics Committee |
| IFNγ | interferon gamma |
| IL | interleukin |
| INR | international normalized ratio |
| IP | inducible protein |
| IRB | Institutional Review Board |
| iRECIST | Immunotherapy Response Evaluation Criteria in Solid Tumors |
| IRR | infusion-related reaction |
| ISAC | immune stimulating antibody conjugate |
| iUPD | immune unconfirmed progressive disease |
| IV | intravenous |
| LTFU | long-term follow-up |
| LVEF | left ventricular ejection fraction |
| mAb | monoclonal antibody |
| MBC | metastatic breast cancer |
| MCP | monocyte chemoattractant protein |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIP | macrophage inflammatory protein |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| MUGA | multi-gated acquisition scan |
| NCI CTCAE v5.0 | National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 |

| Abbreviation | Definition |
|---|---|
| ORR | objective response rate |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PD | progressive disease |
| PDAS | Pharmacodynamic Analysis Set |
| PFS | progression-free survival |
| PK | pharmacokinetic |
| PKAS | Pharmacokinetic Analysis Set |
| PR | partial response |
| PS | performance status |
| PT | prothrombin time |
| q1w, q2w, q3w | Weekly, every 2 weeks, every 3 weeks |
| QTcF | QT corrected - Fridericia's correction formula |
| RECIST v1.1 | Response Evaluation Criteria in Solid Tumors version 1.1 |
| RNA | ribonucleic acid |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SAR | serious adverse reaction |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SD | stable disease |
| SFU | Safety Follow-Up |
| SI | International System of Units |
| SJS | Stevens-Johnson syndrome |
| SOC | standard of care |
| SOP | standard operating procedure |
| SRC | Safety Review Committee |
| SVT | supraventricular tachycardia |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TEAE | treatment-emergent adverse event |
| TEN | toxic epidermal necrolysis |
| TLR | toll-like receptor |
| TNFα | tumor necrosis factor alpha |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |

| Abbreviation | Definition |
|---|---|
| WHO | World Health Organization |

## DEFINITION OF TERMS

| Term | Definition |
|---|---|
| Applicable regulatory requirements | Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products. |
| Baseline | The last assessment before first study treatment administration. |
| End of Study | When the last subject has completed their Safety Follow-Up (SFU). |
| End of Treatment (EOT) | The date of the last study drug administration. |
| Enrolled | A subject is considered enrolled once the Principal Investigator or designee completes assessment of subject eligibility and confirms that the subject meets all inclusion and no exclusion criteria for the trial. |
| Follow-up Phase | Starts 1 day after discontinuation of study treatment and ends on the subject's last follow-up visit. |
| Maximum Tolerated Dose (MTD) | The highest dose that will produce the desired effect without resulting in unacceptable side effects. |
| Screening Period | Begins on the day the first Screening assessment is performed according to the Schedule of Assessments and ends on the day before subject's first study treatment administration. The Screening Period is a maximum of 28 days. |
| Study treatment | Study treatment refers to medicinal products under investigation in this study, and whose use is required by this study. This includes BDC-1001 and pertuzumab. |

# 1. INTRODUCTION

## 1.1. Disease Background

Breast cancer is the second most common cancer in women after skin cancer. In 2020, 2.3 million women were diagnosed with breast cancer and 685,000 deaths attributed to breast cancer were reported worldwide (World Health Organization 2021). About 20% of breast cancers have high expression of human epidermal growth factor receptor 2 (HER2), also known as erb-b2 receptor tyrosine kinase 2 (ERBB2). HER2 is a proto-oncogene that encodes a transmembrane protein involved in signal transduction pathways that promote cell growth and differentiation.

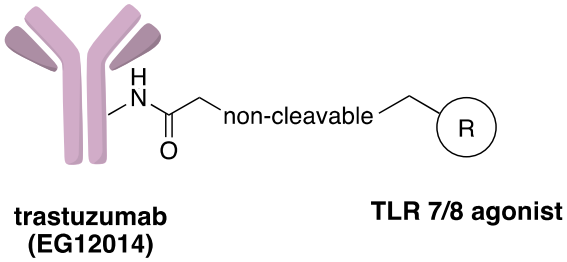
Treatments approved for human epidermal growth factor receptor 2-positive (HER2+) breast cancer include monoclonal antibodies, trastuzumab, pertuzumab, and margetuximab; small molecule tyrosine kinase inhibitors, lapatinib, neratinib, tucatinib, pyrotinib, and antibody-drug conjugates, ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd). These therapies are moderately to highly effective and are most recently associated with objective response rates (ORR) of 25-82.7% and Investigator-assessed median progression-free survival (PFS) of 10-25.1 months in second-line (2L) HER2+ metastatic breast cancer (MBC; ENHERTU®), and an objective response rate (ORR) of 82.7% and Investigator-assessed median PFS of 25.1 months (ENHERTU® USPI 2022, DESTINY-Breast03 trial) in third-line (3L) HER2+ MBC (Hurvitz et al 2023). However, patients with MBC eventually develop tumor relapse, and currently the 5-year survival rate for women with MBC is only about 29%, while the 5-year survival rate for men with MBC is 19%. Clinical resistance, the development of local recurrence or metastasis, and significant morbidity remain prominent issues associated with the management of HER2+ breast cancer. Clinically significant toxicities of HER2-directed therapies include gastrointestinal and hematological toxicities, infection, interstitial lung disease, and left ventricular dysfunction. Thus, an unmet need persists for novel therapies for HER2+ MBC following the use of trastuzumab deruxtecan, and for therapies that may improve the safety and efficacy of HER2-directed interventions in earlier lines of therapy.

## 1.2. Study Treatment Background

### 1.2.1. BDC-1001 Background

BDC-1001 is an immune-stimulating antibody conjugate (ISAC) designed to be delivered systemically and act locally by targeting HER2-expressing tumors and related metastatic disease for destruction by the innate and adaptive immune systems. BDC-1001 consists of an investigational biosimilar of the humanized monoclonal antibody (mAb) trastuzumab (EG12014) that is chemically conjugated to a toll-like receptor (TLR)7/8 agonist (payload) with an intervening non-cleavable linker (Figure 1). Additional information is provided in the current BDC-1001 Investigator's Brochure.

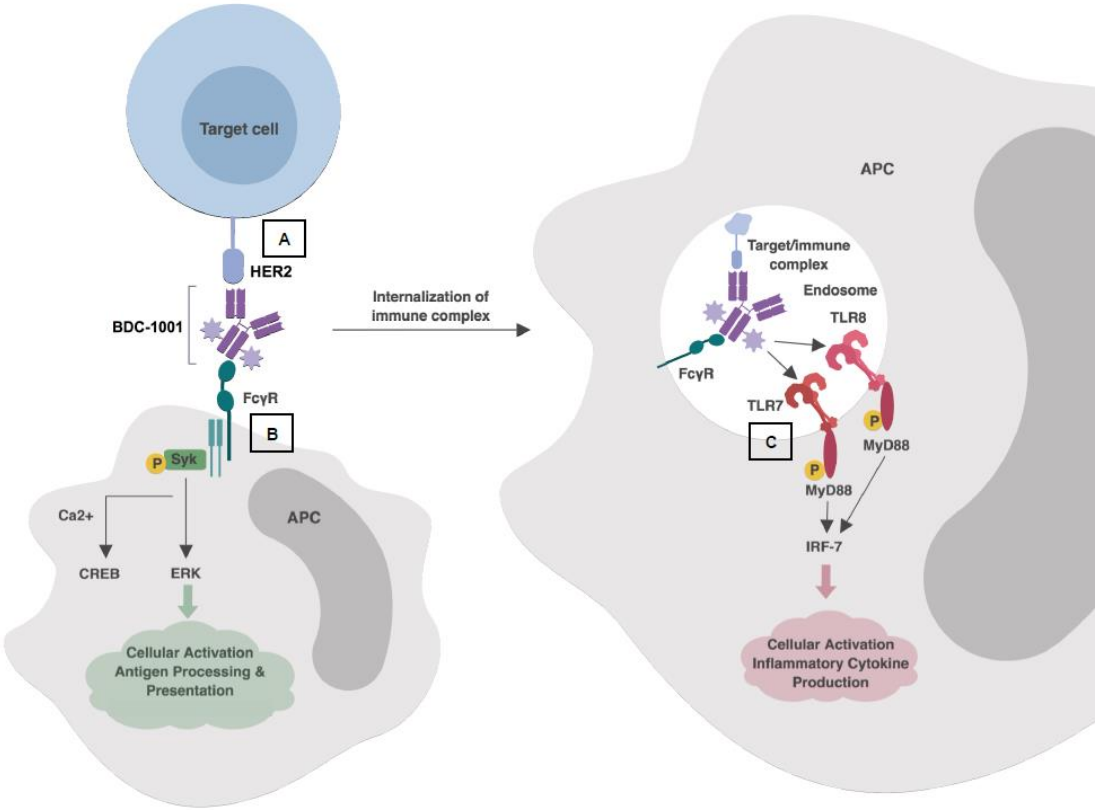
**Figure 1: Schematic Representation of BDC-1001**




The immunosuppressive tumor microenvironment often prohibits dendritic cells and other antigen presenting cells (APCs) from effectively stimulating tumor reactive T cells. The presence of TLR7/8 agonist molecules allows BDC-1001 to combine the anti-tumor effects of trastuzumab with localized stimulation of the immune system (Carmi et al. 2015; Singh et al. 2014; Sagiv-Barfi et al. 2018). The proposed mechanism of action depicted in Figure 2 is tripartite with BDC-1001 binding to HER2 expressing tumor cells via the antibody variable region leading to tumor cell killing and phagocytosis. The immune-stimulating TLR7/8 agonist attached to BDC-1001 activates myeloid APCs such as macrophages and dendritic cells and is expected to lead to increased cytotoxicity, processing and presentation of tumor neoantigens that subsequently stimulate T cell-mediated immunity (Engblom, Pfirschke, and Pittet 2016; Schon and Schon 2008; Marabelle et al. 2017). Importantly, BDC-1001 was designed to mitigate the risk of non-specific immune activation associated with TLR7/8 activation as the linker-payload is not active until it is internalized by immune cells that express the requisite Fc gamma receptors and TLR7/8.

In pre-clinical models, treatment with BDC-1001 surrogates led to complete and durable regression in multiple human tumor cell lines (including human breast cancer cell lines) with variable levels of HER2 expression that were refractory to treatment with the naked anti-HER2 antibody, trastuzumab. Mechanistic studies indicate T cells and phagocytes are required for anti-tumor activity.

**Figure 2: Proposed Mechanism of Action for BDC-1001**



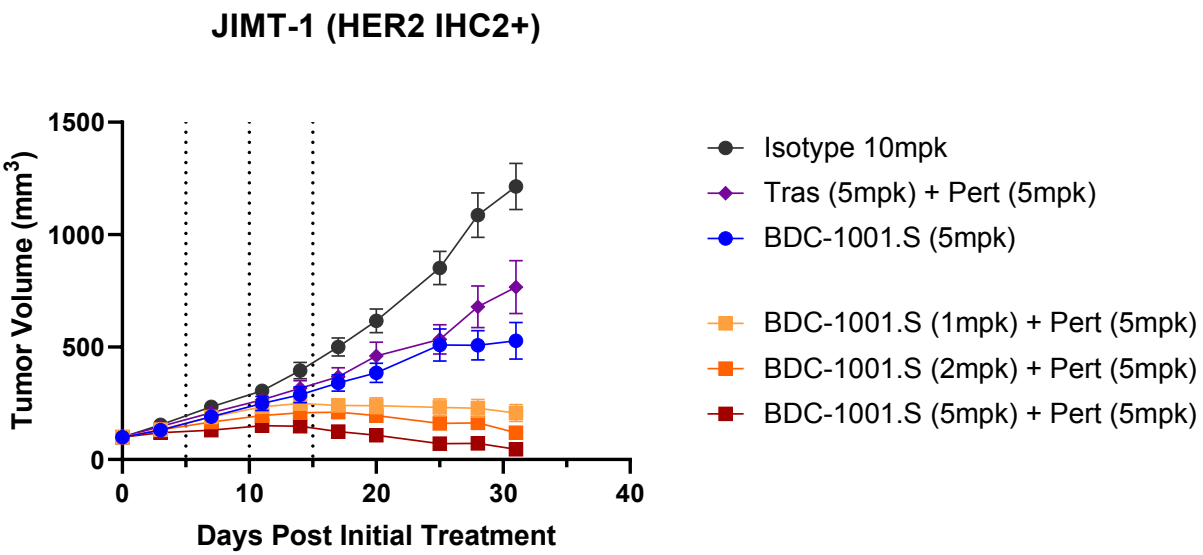

The proposed mechanism of action is tripartite, involving the antibody variable domain, the antibody Fc region and the TLR7/8 binding domain. (A) Fv portion of antibody recognizes HER2 expressing cancer cells; (B) APCs recognize antibody bound to HER2 expressing cancer cells via their Fc gamma receptors (FcγRs) and internalize tumor-immune complex following FcR clustering; (C) Once internalized, the TLR7/8 agonist attached to BDC-1001 gains access to the phagolysosome and mediates downstream events associated with TLR activation. Note that the number of HER2 molecules and bound BDC-1001 have been reduced to 1 each for schematic purpose.

### 1.2.1.1. Nonclinical Studies

The pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology of BDC-1001 have been examined in nonclinical studies. Details of these experiments are described in the current BDC-1001 Investigator's Brochure. An overview of relevant study data is provided below.

Preclinical studies demonstrate that BDC-1001 murine surrogates (BB087) can elicit better anti-tumor activity compared with trastuzumab (see BDC-1001 Investigator's Brochure), and the anti-tumor activity can be enhanced when administered in combination with pertuzumab in HER2-expressing breast tumor models (JIMT-1 cell line derived from trastuzumab-resistant breast cancer) where BDC-1001 monotherapy did not elicit complete regression. The combination of BDC-1001 surrogate and pertuzumab also elicits superior anti-tumor activity as compared to the combination of trastuzumab and pertuzumab (Figure 3).

**Figure 3: BDC-1001.S + Pertuzumab Augment Anti-Tumor Efficacy in JIMT-1 Model**




SCID/beige mice with JIMT-1 HER2 IHC2+ tumors (n=6 per group) were treated systemically with the indicated test article(s) Q5Dx4 (dashed lines). The BDC-1001 surrogate (BB087) was administered at the indicated dose. % TGI is calculated on Day 20 relative to trastuzumab and pertuzumab combination: ((Average$_{Control}$-Average$_{Treated}$)/Average$_{Control}$)*100.

### 1.2.1.2. Clinical Studies

As of March 2024, Bolt Biotherapeutics is conducting 2 clinical studies of BDC-1001. Study BBI-20201001, is a first-in-human (FIH) Phase 1/2 clinical study investigating BDC-1001 as monotherapy and in combination with nivolumab in advanced or metastatic HER2-positive colorectal, gastroesophageal, endometrial, and breast cancer. Study BBI-20231001 is a Phase 2 study investigating BDC-1001 as monotherapy and in combination with pertuzumab in patients with metastatic HER2-positive breast cancer. No final efficacy or safety data are available and interim safety results from both studies are summarized below.

As of the data cutoff date of 23 January 2024, 167 patients received at least 1 dose of BDC-1001 either in monotherapy or in combination with nivolumab (BBI-20201001 n=164 and BBI-20231001 n = 3). The most common treatment-emergent adverse events (TEAEs) occurring in greater than 10% of patients were infusion related reaction (27.5%), fatigue (25.1%), nausea (25.1%), abdominal pain (20.3%), anemia (17.4%), vomiting (16.8%), diarrhea (15.0%), constipation (13.8%), decreased appetite (12.6%), dyspnea (12.0%), and pyrexia (10.2%). Most of these events were mild or moderate in severity.

Infusion-related reactions (IRRs) are the most frequently occurring TEAE in subjects treated with BDC-1001. All reported events were mild to moderate (grade 1 or grade 2 per CTCAE), and all but 1 were assessed as not serious. The single serious grade 2 IRR event was considered resolved with treatment with diphenhydramine, and the BDC-1001 dose was not changed.

In the 2 ongoing clinical studies with BDC-1001, 53 subjects (32.3%) experienced at least 1 serious adverse event (SAE) in the BDC-1001 treated population. The most common SAEs

occurring in ≥ 2 patients in the BDC-1001 treated population included abdominal pain (3.6%), acute kidney injury, anemia, dyspnea, and urinary tract infection (each 1.8% respectively), and disease progression, gastric hemorrhage, large intestinal obstruction, pneumonia, small intestinal obstruction, and urinary tract obstruction (each 1.2% respectively). Of the reported SAEs, 9 SAEs were considered related to BDC-1001. Seven SAEs were grade 2 or 3 in severity with 1 event of pulmonary hemorrhage assessed as grade 4 and 1 event of death assessed as grade 5.

Cumulatively, 67 deaths occurred in the BDC-1001 program. Of these deaths, 52 were attributed to progressive disease, 2 to adverse events (AEs), 1 to a car accident, and 12 were assessed as "unknown" or the cause of death was "blank". All unknown or blank causes of death were attributed to progressive disease.

Of the 2 deaths attributed to AEs, 1 was reported as a head injury with no relationship to BDC-1001, and 1 was reported as death. The death event was unwitnessed at home as noted by the investigator which was likely caused by underlying disease. As the investigator could not definitively rule out a potential contribution by BDC-1001, the case is conservatively being assessed as related to BDC-1001 pending further clarifying information.

Eight subjects experienced 9 AEs leading to discontinuation of BDC-1001: 4 events were related SAEs, grade 3 ejection fraction decreased and supraventricular tachycardia, grade 4 pulmonary hemorrhage, and grade 5 death.

Based on the cumulative data to date, no important identified risks were assessed as of the data cutoff date. However, 1 important potential risk of decreased left ventricular ejection fraction was identified based on class effect, mechanism of action, AE reports, and ejection fraction readings. Treatment management of decreased left ventricular ejection fraction should be managed as per protocol.

For more details, refer to the current BDC-1001 Investigator's Brochure.

### 1.2.2. Pertuzumab Background

Pertuzumab is a mAb that targets HER2 and prevents dimerization of HER2 with other members of the HER family (HER1, HER3, and HER4), thereby blocking ligand-activated downstream signaling. Pertuzumab is also capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) in cell-based assays. Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing. These molecules have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination.

Pertuzumab is approved in combination with trastuzumab and chemotherapy for the treatment of subjects with early stage and metastatic HER2+ breast cancers (PERJETA® USPI 2021). While it is not approved for use in the absence of trastuzumab, or in later lines of therapy, the addition of pertuzumab to trastuzumab, and docetaxel in the pivotal, placebo-controlled, first-line (1L) MBC study, CLEOPATRA resulted in a 6.1 month improvement in PFS (12.4 months vs 18.5 months; hazard ratio [HR]=0.62, p<0.0001; 95% confidence interval [CI]=0.51, 0.75). At the time of the final overall survival (OS) analysis, the pertuzumab-containing arm demonstrated

a statistically significant OS advantage over the placebo arm (HR=0.68, p=0.0002; 95% CI=0.56, 0.84), as well, with an increase in median OS to 56.5 months in the pertuzumab-treated group from 40.8 months in the placebo-treated group. Similar benefit has been seen with the addition of pertuzumab to trastuzumab plus chemotherapy in the neoadjuvant (NEOSPERE) pathological complete response (CR=39.3% vs. 21.5%; p=0.0063), and adjuvant (APHINITY HR=0.82; 95% CI=0.68, 0.99 with no statistical difference in OS) settings.

Safety signals (> 5% increase) associated with the addition of pertuzumab to trastuzumab plus chemotherapy in the metastatic setting (PERJETA® USPI 2021, CLEOPATRA trial) include increases in the following: mucosal inflammation (28 vs. 20%), rash (34 vs. 24%), diarrhea (67 vs. 46%), febrile neutropenia (14 vs. 8%). Safety signals in the neoadjuvant settings (NEOSPHERE) were similar, with mucosal inflammation (26 vs. 21%), pyrexia (17 vs. 10%), rash (26 vs. 21%), diarrhea (46 vs. 34%), stomatitis (18 vs. 7%), and dysgeusia (15 vs. 10%) being increased in the pertuzumab/trastuzumab/chemotherapy arms relative to the trastuzumab/chemotherapy/placebo arm. It is noteworthy that, when pertuzumab was added to trastuzumab without chemotherapy in the neoadjuvant setting, rates of these toxicities were not increased in the pertuzumab plus trastuzumab group relative to the trastuzumab plus chemotherapy group: mucosal inflammation (3 vs. 21%), pyrexia (8 vs. 10%), (11 vs. 21%), diarrhea (28 vs. 34%), stomatitis (7 vs. 5%), and dysgeusia (10 vs. 5%). This suggests that these toxicities, primarily associated with the chemotherapeutic agents, may be exacerbated by the addition of trastuzumab or trastuzumab plus pertuzumab, but that they are not related to trastuzumab, pertuzumab, or the combination of trastuzumab and pertuzumab in the absence of chemotherapy.

Left ventricular dysfunction, a known risk associated with HER2 inhibition, was not increased in pertuzumab-treated subjects in the pivotal pertuzumab trial in 1L MBC; however, in neoadjuvant trials, the rate of left ventricular dysfunction $\geq$ 10% and to < 50% was increased as high as 8% among subjects receiving pertuzumab/trastuzumab/chemotherapy regimen relative to 1-3% in trastuzumab/chemotherapy-treated subjects (PERJETA® USPI 2021). In the adjuvant APHINITY trial (PERJETA® USPI 2021), LVEF declines of > 10% and to < 50% were seen in an equal percentage of subjects treated with pertuzumab/trastuzumab/chemotherapy and those receiving trastuzumab/chemotherapy without pertuzumab (3%). Taken in totality, these data suggest that pertuzumab may mildly increase the cardiac dysfunction associated with trastuzumab.

All of these risks associated with the addition of pertuzumab to trastuzumab plus chemotherapy have been assessed to be acceptable for a highly effective treatment regimen.

Since BDC-1001 consists of a biosimilar of trastuzumab, BDC-1001, the combination of BDC-1001 with pertuzumab has the potential for a favorable safety and efficacy profile in subjects with advanced HER2+ breast cancer. Further details on the safety and efficacy of pertuzumab are provided in the current pertuzumab Investigator's Brochure.

### 1.3. Study Rationale

Current therapies are moderately to highly effective against HER2+ breast cancer, with combination therapy of trastuzumab, pertuzumab, and a taxane providing median PFS of

18.7 months, and median OS of 56.5 months in 1L treatment of MBC (PERJETA® USPI 2021, CLEOPATRA trial). More recently, fam trastuzumab-deruxtecan-nxki (ENHERTU®) provided an Investigator-assessed median PFS of 25.1 months (ENHERTU® USPI 2022 in subjects with 2L treatment for MBC, DESTINY-Breast03 trial), and a median PFS of 18.8 and 19.4 months, with a median OS of 29.1 and 39.2 months in subjects with 3L MBC (DESTINY-Breast01 and 02 trials, respectively) (Hurvitz et al, 2023; Modi et al, 2020; André et al, 2023). While trastuzumab deruxtecan (ENHERTU) has changed the breast cancer treatment landscape, no effective treatments are available for subjects with HER2+ MBC whose tumors are refractory to or relapsed after receiving trastuzumab deruxtecan.

In addition, cytopenias, cardiac dysfunction, gastrointestinal toxicity, and pneumonitis are significant toxicities associated with current MBC therapies. Thus, there is an unmet medical need for safe effective therapies for subjects with HER2+ MBC, who are refractory to or have relapsed following trastuzumab deruxtecan treatment.

BDC-1001 is a novel ISAC, covalently linking a TLR7/8 agonist to a trastuzumab biosimilar. In cellular proliferation assays, performed in the absence of immune cells, BDC-1001 and trastuzumab elicit similar levels of in vitro ADCC, antibody-dependent cellular phagocytosis, and inhibition of cancer cell proliferation in HER2-expressing cell lines. In vitro modeling in the presence of freshly harvested antibody presenting cells (APCs) demonstrate that this novel ISAC activates primary human myeloid APCs in an FcγR and TLR-dependent manor. In vivo, BDC-1001 murine surrogates (BB087) can elicit better anti-tumor activity compared with trastuzumab (see BDC-1001 Investigator's Brochure). Comparison of local delivery of trastuzumab combined with the TLR agonist to systemic delivery of the surrogate ISAC (T785-ISAC) in a murine model demonstrated that only the ISAC was successful in reducing tumor burden (Ackerman et al. 2021). The anti-tumor activity of the ISAC can be further enhanced when administered in combination with pertuzumab in HER2-expressing, trastuzumab-resistant breast tumor models (JIMT-1, CALU-3, NCI-N87). The combination of the BDC-1001 surrogate and pertuzumab also elicits superior anti-tumor activity as compared to the combination of trastuzumab and pertuzumab (Figure 3) (see BDC-1001 Investigator's Brochure).

The study population consists of subjects with HER2+ MBC who have received 2 or more prior therapies targeting HER2, with trastuzumab deruxtecan (ENHERTU®) as 1 of the prior therapies. These subjects represent an unmet medical need with high benefit:risk potential for clinical trial exploration.

BDC-1001 is also being evaluated in the ongoing dose escalation and expansion study (BBI-20201001) in subjects with advanced HER2-expressing solid tumors (see Section 1.2.1.2). The clinical experience has demonstrated acceptable safety and promising early clinical activity in a heavily pre-treated subject population. As of 11 August 2023, 131 subjects received BDC-1001 (94 as monotherapy [Part 1] and 37 in combination with nivolumab [Part 2]). Six patients had a response (1 complete response and 5 partial responses). Fourteen patients had stable disease lasting at least 24 weeks. The median (minimum, maximum) durations of treatment for this efficacy data cut were 3.79 weeks (0.1, 83.4) in the BDC-1001 monotherapy and 5.29 weeks (0.1, 46.4) for subjects receiving BDC-1001 in combination with nivolumab (Li, et al, 2023a).

Because BDC-1001 consists of a biosimilar of trastuzumab, and the addition of pertuzumab has been demonstrated to significantly enhance the pre-clinical and clinical activity of trastuzumab, as well as the pre-clinical activity of BDC-1001, and because the safety profile of the trastuzumab + pertuzumab combination, in the absence of chemotherapy and of BDC-1001 are favorable, BDC-1001 as a single agent and in combination with pertuzumab has the potential for tolerable safety as well as significant efficacy in subjects with advanced HER2+ breast cancer. BDC-1001 may provide particular benefit to subjects whose tumors demonstrate resistance to or have experienced relapse following trastuzumab deruxtecan, and who have no other treatment options.

Rationales for the study design and dose are provided in Section 3.2.

### 1.4. Risk/Benefit Assessment

In this study, BDC-1001, a novel ISAC that retains the functionality of trastuzumab while adding the immune-activating functionality of APCs via TLR7/8 engagement, is studied alone and in combination with pertuzumab in subjects with relapsed/refractory advanced HER2+ breast cancer, following trastuzumab deruxtecan therapy. There are currently no approved treatment options for this subject population. Both pre-clinical and clinical data support the favorable benefit:risk assessment for this combination.

In vitro, BDC-1001 and trastuzumab elicit similar levels of in vitro ADCC, antibody-dependent cellular phagocytosis, and inhibition of cancer cell proliferation in HER2-expressing cell lines. However, in vivo, BDC-1001 murine surrogates elicit better anti-tumor activity compared with trastuzumab (see BDC-1001 Investigator's Brochure). Preclinical data not only demonstrate enhanced activity when pertuzumab is added to trastuzumab, the addition of pertuzumab to the BDC-1001 surrogate in murine models also significantly increased tumor growth inhibition relative to that of the trastuzumab plus pertuzumab combination.

Clinically, pertuzumab in combination with trastuzumab and chemotherapy enhances the efficacy of trastuzumab in 1L metastatic HER2+ MBC (PFS HR=0.62, p<0.0001; OS HR=0.68, 95% CI, p=0.0002), as well as early breast cancer (HR= 0.82 [0.68, 0.99], and has been approved in both settings. It is noteworthy that the addition of pertuzumab to trastuzumab plus docetaxel adds little to the rate of overall AEs of the combination. Mild increases were seen in the rates of mucosal inflammation (28 vs. 20%), rash (34 vs. 24%), diarrhea (67 vs. 46%), and febrile neutropenia (14 vs. 8%). In the neoadjuvant setting, these same toxicities, which are associated with the trastuzumab, pertuzumab, plus docetaxel combination, were not increased when trastuzumab and pertuzumab were given in combination, in the absence of chemotherapy. Left ventricular dysfunction, a known risk associated with HER2 inhibition, has been shown to be somewhat increased (7-8% vs. 2-3% decrease in LVEF of > 10%, to < 50%) by the addition of pertuzumab to trastuzumab-based regimens in some but not all early stage breast cancer studies (see Section 1.2.2; PERJETA® USPI 2021). These toxicities have all been deemed by clinicians, and regulatory bodies as well within acceptable range for highly effective treatment.

BDC-1001 as a single agent has also shown promising efficacy among subjects with relapsed/refractory HER2+ malignancies. At the dose for this trial (20 mg/kg q2w dose), BDC-1001 monotherapy had an ORR of 67% (4/6) in subjects with documented

HER2+ advanced solid tumors. At the time of the data cutoff, no subjects with breast cancer were enrolled in the 20 mg/kg q2w cohort; however, 1 subject with HER2+ breast cancer, who was enrolled after the data cutoff date, is currently receiving BDC-1001 at the recommended phase 2 dose (RP2D) and has SD (12% tumor shrinkage) at Week 6 (date of tumor assessment: 13 March 2023), indicating anti-tumor activity in HER2+ breast cancer.

To date, the ongoing trials for BDC-1001, BBI-20201001 and BBI-20231001, demonstrate acceptable safety and promising clinical activity for this novel ISAC. BDC-1001 has been well tolerated and interim safety data are presented in Section 1.2.1.2. No IRRs were identified. While left ventricular ejection fraction decreased has been assessed as an important potential risk for BDC-1001, as of the data cutoff date of January 2024, no occurrences have been observed in Study BBI-20231001. Treatment of this event should be managed per the protocol. Overall, based on the totality of safety information collected to 23 January 2024, it is the opinion of the sponsor that the benefit-risk assessment of BDC-1001 in the populations under study remains acceptable and warrants continued investigation in clinical trials.

The 20 mg/kg q2w dose, chosen for this study, is 50% of a dose that was well tolerated, and on which no dose-limiting toxicities were observed in the FIH study. For this reason, a 3 subject run-in is not felt to be required in this study. All enrolled subjects will be monitored closely for safety.

Given the mechanism of action of BDC-1001, its trastuzumab backbone, the enhanced pre-clinical and clinical activity conferred by pertuzumab when added to trastuzumab, pre-clinical evidence of enhanced clinical activity when pertuzumab is added to BDC-1001, and data available on the safety and efficacy of BDC-1001, the benefit/risk ratio remains positive for continued evaluation of BDC-1001 as a single agent and for evaluation of BDC-1001 in combination with pertuzumab in subjects with HER2+ MBC whose tumors are refractory to or have relapsed after trastuzumab deruxtecan.

For more details, refer to the current BDC-1001 Investigator's Brochure.

# 2. STUDY OBJECTIVES

## 2.1. Objectives and Endpoints

The objectives and endpoints to be evaluated in the study are outlined in Table 3.

**Table 3: 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<br>• 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 | • Evaluation of BDC-1001 activity in the context of additional exploratory predictive and/or prognostic biomarkers related to tumor and immune biology by such methods as gene expression profiling, mutational, protein and tissue image analysis |
| • 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 | • Changes in TLR7/8 pathway activation, myeloid and T cell content, and activation status by such methods as gene expression profiling, protein, and tissue image analysis.<br>• Evaluation of changes in additional exploratory biomarkers in tumor tissue and blood related to tumor and immune biology by such methods as gene expression profiling, mutational, protein and tissue image analysis |

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

# 3. INVESTIGATIONAL PLAN

## 3.1. 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+ 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 8.2).

Subjects will receive study treatment (ie, BDC-1001 or BDC-1001 in combination with pertuzumab) as described in Section 5.2. To ensure subject safety, dosing of the first 3 subjects enrolled in the combination treatment arm will receive study treatment staggered by a minimum of 48 hours, and these subjects will be observed for at least 6 hours following the first dose of study treatment. Any subject with acute changes in vital signs will be observed until the events have resolved or are stabilized.

All subjects in both treatment arms will be monitored for AEs and SAEs (Section 8.4.5.1). Study data will be provided to the Safety Review Committee (SRC) for ongoing safety monitoring and detection of potential safety concerns (Section 3.1.1).

Subjects will return to the site for study assessments at the visits listed in the Schedule of Assessments. In the event of study treatment discontinuation, subjects will be asked to complete an End of Treatment (EOT) visit (Section 6.25.1), 14 days (± 7 days) after the last dose of study treatment (EOT), and then return for a Safety Follow-Up visit (SFU; Section 6.25.2), 28 days (+ 7 days) after last treatment. Subjects who discontinue treatment will have long-term follow-up (LTFU; Section 6.25.3) every 12 weeks (± 14 days) after last treatment.

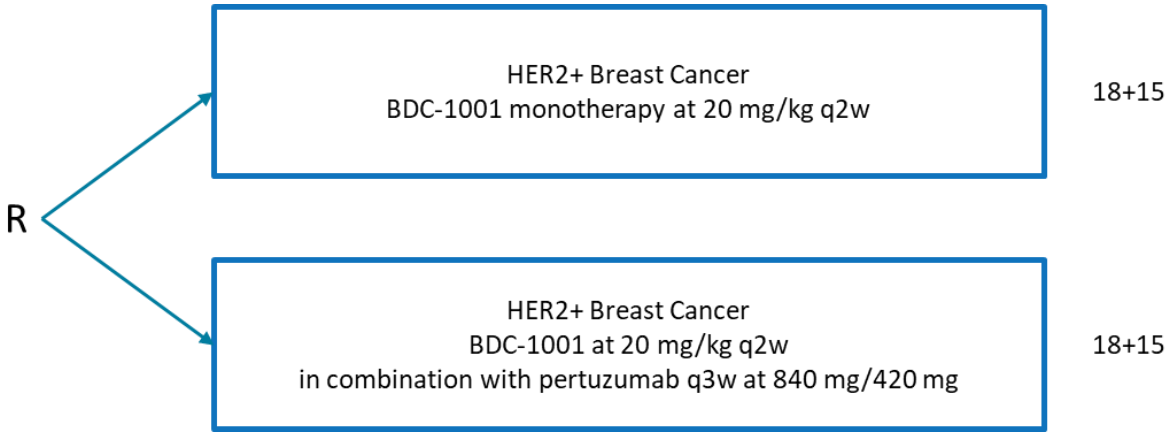
**Maintenance Phase:**

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 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). 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.

An overview of the study is displayed in Figure 4.

**Figure 4: Study Schema**




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

### 3.1.1. 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 8.4.5.1).

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. Additional meetings may be conducted ad hoc 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.

### 3.1.2. Number of Subjects

Approximately 66 evaluable subjects may be enrolled into this study.

### 3.1.3. Duration of Treatment

All subjects will be treated for a median duration of approximately 12 months, until disease progression according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1 and iRECIST), unacceptable toxicity, or withdrawal for any reason. Subjects with confirmed PD (using the scan at first PD as the new baseline) will be discontinued from study treatment; although if a subject is experiencing clinical benefit (is clinically stable), they may remain in the study after consultation with the medical monitor. Clinically stable is defined as follows:

1. Subject is without worsening symptoms attributable to disease progression,
2. Subject maintains Eastern Cooperative Oncology Group (ECOG) performance status (PS), and
3. Subject tolerates study treatment (ie, no related SAE or Grade ≥ 3 AE that requires study drug discontinuation) per Investigator clinical judgement.

**Maintenance Phase:**

As of this protocol Version 3.0 (01 Aug 2024), any subject still receiving study treatment (BDC-1001) will transition to the Maintenance Phase and are to be followed as described in 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). 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.

### 3.1.4. Duration of Study

The planned overall study duration is approximately 4 years.

The definition of the end of the study is when the last subject has completed their SFU. The Sponsor or regulatory authorities may terminate the study at any time at their discretion.

## 3.2. Rationale for Study Design, Dose Selection, and Study Population

### 3.2.1. Rationale for Study Design

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

The target dose and regimen of BDC-1001 for this study is 20 mg/kg q2w. This target dose and regimen are well tolerated as a single agent (see Section 1.2.1.2 for details).

Pertuzumab will be given at the approved dose (840 mg on Week 1, followed by 420 mg q3w thereafter).

Bayesian toxicity monitoring will be used to monitor treatment related SAE rates to ensure subject safety (Section 8.4.5.1).

### 3.2.2. Rationale for Selection of BDC-1001 Recommended Dose

The dose and regimen of BDC-1001 for this study will be the RP2D of BDC-1001 of 20 mg/kg q2w, as determined in the ongoing FIH study BBI-20201001 [NCT04278144]. BDC-1001 will be administered in combination with the approved dose of pertuzumab (described above).

This starting dose for BDC-1001 is based on the dose escalation phase of Study BBI-20201001, which enrolled subjects with a wide range of HER2-expressing solid tumor types, including tumor types to be evaluated in the dose expansion phase. The evaluated dosing levels and dosing frequencies ranged from 0.15 mg/kg up to 20 mg/kg and q1w, q2w, and q3w, respectively, to assess safety, tolerability, and clinical activity to determine the RP2D.

As of 23 January 2024, no clinically meaningful differences in the safety profile of BDC-1001 monotherapy were observed across the different dosing levels and dosing frequencies tested regarding the percentage of subjects requiring dose interruptions, dose reductions, and drug discontinuations for AEs, as well as the percentage of subjects with SAEs (Section 1.2.1.2). BDC-1001 monotherapy is well tolerated and no safety signals or trends could be observed. Therefore, from a safety and tolerability perspective, these doses and regimens are considered acceptable for further evaluation.

The most clinically meaningful efficacy was observed at a dose of BDC-1001 20 mg/kg q2w. Among 7 subjects treated with BDC-1001 20 mg/kg q2w monotherapy, 1 CR (14%), 1 PR (14%) and 3 SDs (43%) were observed (Li et al, 2023b).

Population PK results confirmed linear PK characteristics of BDC-1001 at 5 mg/kg q3w and above, with population mean clearance of 1.6 L/day and median terminal half-life of 4.3 days (range: 1.2-12). The population mean volume of central distributional compartment was estimated to be 4.3 liters, which is close to the physiological volume of serum/plasma in humans (~3.5 liters); the volume of peripheral distributional compartment was estimated to be 2.6 liters; together, these estimates suggest BDC-1001 distribution in humans is consistent with the conventional knowledge that mAb therapeutics distribute primarily within the vascular space, with modest extravasation into the peripheral tissues. At 20 mg/kg q2w monotherapy, where most clinically meaningful efficacy was observed, the median steady-state trough serum concentration ($C_{min}$) of BDC-1001 has reached or exceeded 10 µg/mL, which was the $C_{min}$ level in the preclinical xenograft model where significant regression of tumors was observed.

Exposure-response of BDC-1001 demonstrated a positive association between anti-tumor activity and $C_{min}$, peak serum concentration ($C_{max}$), and area under the concentration-time curve

(AUC) in the BDC-1001 q2w treated subjects. However, this positive association was not observed for subjects treated with BDC-1001 q3w and was weaker in q1w subjects. At 20 mg/kg q2w, where most clinically meaningful efficacy was observed, the median steady-state $C_{min}$ of BDC-1001 has reached or exceeded 10 µg/mL, which was the $C_{min}$ level in the preclinical xenograft model where significant regression of tumors was observed.

The results from the dose escalation phase of Study BBI-20201001 support BDC-1001 20 mg/kg q2w as a dose for further evaluation.

# 4. SELECTION OF STUDY POPULATION

Potential subjects must sign an informed consent form (ICF) before any study specific screening tests may be conducted.

Screening tests are described in Section 6.1.

## 4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment in the study:

1. Be able to understand and sign the informed consent form
2. Be age 18 years or older at the time of informed consent
3. All subjects must agree to have a biopsy prior to enrollment. If, in the judgement of the Investigator, a biopsy is not safely accessible or clinically feasible an archival tumor tissue sample must be submitted in lieu of a freshly collected specimen
4. Histologically confirmed adenocarcinoma of the breast that is HER2+ (per 2018 ASCO/CAP HER2 testing guidelines) by Clinical Laboratory Improvement Amendments (CLIA) certified laboratory assessment
5. Have received 2 or more prior lines of anti-HER2-directed therapies, at least 1 of them is in the metastatic setting and 1 of the prior therapies needs to be trastuzumab deruxtecan (ENHERTU®). Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 12 months of completion of therapy will be considered a line of treatment for metastatic disease
6. Have experienced disease progression on or been otherwise unsuitable for (eg, did not tolerate) the most recent therapy
7. Have measurable disease according to RECIST v1.1 criteria
8. Have ECOG PS of 0 or 1
9. Have life expectancy of greater than 12 weeks per the Investigator
10. Adequate organ function defined as follows:
    a. Hematology:
        i. Absolute neutrophil count ≥ 1500 cells/$mm^3$
        ii. Platelet count ≥ 75,000 cells/$mm^3$
        iii. Hemoglobin ≥ 9 g/dL (and without transfusion within 7 days)
    b. Renal:
        i. Creatinine clearance ≥ 30 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
        [(140-age) × (weight in kg) × (0.85 if female)] / [72 × (serum creatinine in mg/dL)]
    c. Coagulation:
        i. International normalized ratio (INR) and prothrombin time (PT) ≤ 1.5 × ULN unless receiving anticoagulation therapy
        ii. Activated partial thromboplastin time (aPTT) only needs to be assessed if evaluated per standard of care. If evaluated, aPTT ≤ 1.5 × upper limit of normal (ULN), unless undergoing anticoagulation therapy

d. Hepatic:

i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN (or ≤ 5 × ULN in subjects with known hepatic metastases)
ii. Total bilirubin ≤ 1.5 × ULN (isolated value > 1.5 × ULN is acceptable if direct bilirubin is <35%)

11. Women of childbearing potential should agree to not donate eggs and must use a highly effective contraceptive measure (a method that can achieve a failure rate of less than 1% per year) during treatment and until 7 months after the end treatment. Highly effective, alternative non-hormonal contraceptive measures are preferred, include the following:

a. Intrauterine device
b. Vasectomized partner
c. Sexual abstinence
d. Bilateral tubal occlusion

12. Potent men that are partners of women of childbearing potential must be willing to use condoms in combination with a second highly effective method of female contraception (as above) during the study and agree not to donate sperm from Screening through 7 months after completion of study. A male partner will be considered as potent unless surgically sterilized (with documentation of sterility).

## 4.2. Exclusion Criteria

A subject must not meet any of the following criteria to be eligible for this study:

1. Central nervous system metastases with the exception of disease that is asymptomatic, clinically stable (without evidence of progression for at least 4 weeks confirmed by imaging during study Screening), and has not required steroids for at least 28 days before starting study treatment
2. Cardiac disease including the following:
   a. Congestive heart failure (New York Heart Association classes II–IV)
   b. Left ventricular ejection fraction (LVEF) < 50% by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
   c. QT corrected - Fridericia's correction formula (QTcF) prolongation of > 480 milliseconds (ms) based on a 12-lead electrocardiogram (ECG)
   d. Serious or uncontrolled cardiac arrhythmia within 6 months before starting study treatment
   e. Myocardial infarction, unstable angina pectoris, or coronary angioplasty, stenting, or surgery within 6 months before starting study treatment
   f. Serious or uncontrolled hypertension (≥ 180 mmHg systolic or ≥ 120 mmHg diastolic) within 6 months before starting study treatment
   g. Pericarditis or pericardial effusion that is symptomatic within 6 months before starting study treatment

3. Pulmonary disease including idiopathic pulmonary fibrosis, interstitial lung disease, pneumonitis requiring steroids, or symptomatic pleural effusion within 6 months before starting study treatment OR ongoing requirement for supplemental oxygen
4. Hepatic disease resulting in symptomatic ascites, encephalopathy, coagulopathy, esophageal/gastric varices, or persistent jaundice
5. Arterial thrombotic event, stroke, or transient ischemia attack within 6 months before starting study treatment
6. Bleeding diathesis or uncontrolled bleeding within 7 days before starting study treatment
7. Bone marrow transplant or solid organ transplant
8. Infection including the following:

    a. Infection requiring systemic therapy within 7 days before starting study treatment
    b. Active human immunodeficiency virus (HIV) as defined by the protocol (Section 6.14.3)
    c. Positive hepatitis B surface antigen test at Screening or within 3 months of starting study treatment, a subject whose hepatitis B surface antigen (HBsAg) is negative and hepatitis B core antibody (HBcAb) is positive may be enrolled if a hepatitis B virus (HBV) DNA test is negative and either the subject is treated with potent antiviral therapy or is retested for HBsAg and HBV DNA every month
    d. Positive hepatitis C antibody test and confirmatory ribonucleic acid (RNA) test at Screening or within 3 months of starting study treatment. Exceptions include subjects that (1) have hepatitis C virus (HCV) viral load below the assay limit-of-quantitation and (2) completed curative antiviral therapy or are compliant with ongoing antiviral therapy

9. Autoimmune disease requiring systemic disease-modifying or immunosuppressive therapy within 2 years before starting study treatment. Exceptions include disease managed with only replacement therapies (eg, thyroxine, etc.)
10. Malignancy within 2 years before starting study treatment other than the disease under study. Exceptions include indolent or definitively treated disease not expected to require treatment during the study, affect the safety of subjects, or affect the endpoints of the trial
11. Any medical condition requiring corticosteroids (> 10 mg daily oral prednisone or equivalent) or other systemic immunosuppressive therapy within 28 days before starting study treatment. Exceptions include inhaled or topical steroids
12. Residual toxicity from previous treatment including the following:

    a. Toxicity related to prior treatment not resolved to Grade ≤ 1
    Exceptions to the above criterion include toxicities that do not pose a risk to vital organ systems (eg, alopecia, etc.) or toxicities that are stable as managed by replacement therapies (eg, hypothyroidism, etc.)

13. Prior anticancer therapies including:

    a. Small molecule TLR7/8 agonist or TLR7/8 agonist that has been conjugated to tumor-targeting antibody such as ISACs within 12 months before starting study treatment

b. An investigational agent or anticancer therapy within 28 days before starting study treatment or within 5 estimated elimination half-lives, whichever is shorter. Gonadotropin-releasing hormone agonists for ovarian suppression in premenopausal women are permitted

14. History of severe hypersensitivity to any ingredient of BDC-1001 or pertuzumab
15. Received live/attenuated virus vaccine within 28 days before starting study treatment
16. Major surgery within 28 days of starting study treatment
17. Radiation therapy within 2 weeks of C1D1
18. Actively enrolled in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up component of an interventional study
19. Subject is a lactating mother or pregnant as confirmed by pregnancy tests within 48 hours prior to start of study treatment
20. Subject is unwilling or unable to follow protocol requirements
21. Recurrent ascites requiring routine intervention >Q3 months
22. Any condition that, in the opinion of the Investigator, would interfere with evaluation of BDC-1001 and pertuzumab or interpretation of the subject's safety or study results

## 4.3. Subject Discontinuation

Subjects may withdraw from study treatment or from the study at any time, for any reason. Subjects who withdraw from treatment should be encouraged to complete the SFU visit (see Schedule of Assessments – Maintenance Phase [Table 2]).

If a subject withdraws consent from participation, the Investigator should make reasonable efforts to document the reason(s) for withdrawal of consent, while fully respecting the subject's rights.

If a subject is discontinued from the study for any other reason, the primary reason for discontinuation must be recorded in the subject's source documents.

### 4.3.1. Removal of Subjects from the Treatment or Study

Subjects may be removed from study treatment at any time without the subject's consent if the Investigator or Sponsor determines that it is not in the best interest of the subject to continue participation.

A subject will be discontinued from the study for any of the following reasons:

- A female subject has a pregnancy that is confirmed
- Sponsor or regulatory authorities close the study

A subject may be discontinued from the study, after discussion between the Investigator, Sponsor, and the Medical Monitor for any of the following reasons:

- A subject develops a life-threatening SAE that puts them at significant risk.
- A subject has a prolonged interruption of study treatment (> 6 weeks from planned dose) or holding of BDC-1001 for > 12 weeks if due to a treatment-related AE, unless continued treatment is approved by the Medical Monitor. Note: subjects will be

withdrawn from study treatment if an immune-related toxicity does not resolve to Grade 1 or baseline within 12 weeks of study drug interruption.
- A subject is noncompliant with study requirements.

If a subject is discontinued due to an AE or pregnancy, the Sponsor must also be notified within 24 hours, as appropriate.

If a subject discontinues due to an AE or other medical reason, the subject must continue to be followed at regular intervals until the AE normalizes, is determined to be chronic by the Investigator, or returns to the subject's baseline condition. Additional follow-up schedule for these subjects will be made on an individual basis by the Sponsor and the Investigator together.

The visit schedule for follow-up after discontinuation is described in the Schedule of Assessments.

#### 4.3.2. Lost to Follow-Up

Subjects will be considered as lost to follow-up if they miss 3 consecutive study contacts (telephone calls and/or clinic visits).

#### 4.3.3. Replacement of Subjects

Subjects that discontinue study treatment before their first radiographic tumor assessment (minimum of 4 weeks after C1D1) will be replaced.

### 4.4. Method of Assigning Subjects

This is an open-label study that will be randomized as described in Section 4.5.

Subjects will be considered enrolled once the Investigator or designee completes assessment of subject eligibility and confirms that the subject meets all inclusion and exclusion criteria for the trial.

### 4.5. Randomization Procedures

Eligible subjects will be randomly assigned to treatment according to **Interactive Response Technology**, in a 1:1 ratio to receive BDC-1001 as a single agent or in combination with pertuzumab.

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.

#### 4.5.1. Blinding

There will be no blinding used in this study.

# 5. ENROLLMENT PROCEDURES

## 5.1. Method of Assigning Subjects

This is an open-label study that will be randomized as described in Section 4.5.

Subjects will be considered enrolled once the Investigator or designee completes assessment of subject eligibility and confirms that the subject meets all inclusion and exclusion criteria for the trial.

### 5.1.1. Description of BDC-1001

[redacted]

### 5.1.2. Description of Pertuzumab

The pertuzumab dosage form is a sterile, clear to slightly opalescent, colorless to pale brown liquid for intravenous (IV) infusion. Each single-dose vial contains 420 mg of pertuzumab (14.0 mL/vial) at a concentration of 30 mg/mL in 20 mM L-histidine acetate, 120 mM sucrose and 0.02% polysorbate 20 at pH 6.0.

### 5.1.3. Preparation/Handling/Storage/Accountability

Refer to the current Pharmacy Manual.

#### 5.1.3.1. Labelling and Packaging

Refer to the current Pharmacy Manual.

#### 5.1.3.2. Storage and Stability

BDC-1001 drug product should be stored in accordance with the current Pharmacy Manual.

Pertuzumab should be stored in accordance with the current pertuzumab Investigator's Brochure and the current Pharmacy Manual.

#### 5.1.3.3. Acquisition and Accountability

Refer to the current Pharmacy Manual.

#### 5.1.3.4. Return of BDC-1001 and Pertuzumab

Refer to the current Pharmacy Manual.

## 5.2. Dosing and Administration

BDC-1001 will be administered either as a single agent or in combination with pertuzumab. In the combination arm, treatment for the first 3 subjects will be staggered by a minimum of 48 hours. The 3 subjects will be observed for at least 6 hours after the first dose of study treatment. Subjects with acute changes in vital signs will be observed until the events have resolved or stabilized. Please note that no observation period is required after administration of study drugs except in the first dose for the first 3 subjects in the combination arm.

### 5.2.1. Premedication

All subjects should be premedicated prior to administration of BDC-1001 for potential IRRs with paracetamol and diphenhydramine (eg, 1000 mg paracetamol, 50 mg diphenhydramine) or according to institutional standards.

On dosing days when pertuzumab is administered without BDC-1001, premedication for pertuzumab is only required if a subject experiences IRR during the previous dose.

Corticosteroids and other immunomodulators remain excluded for study treatment infusions.

### 5.2.2. BDC-1001 Administration

BDC-1001 will be administered q2w at a dose of 20 mg/kg IV by infusion pump over 60 minutes (± 15 minutes). BDC-1001 will be administered before pertuzumab on days that both BDC-1001 and pertuzumab are administered.

Vital signs must be assessed prior to administration of BDC-1001. Subjects that have any persistent low-grade IRR may prolong the infusion time to 90-120 minutes (including flushing time).

Refer to the current Pharmacy Manual for specific instructions for the storage and preparation and administration of BDC-1001.

### 5.2.3. Pertuzumab Administration

Pertuzumab will be administered as an IV infusion according to the package insert (ie, initial dose of 840 mg over 60 minutes followed every 3 weeks by a dose of 420 mg over 30 to 60 minutes). On days that both BDC-1001 and pertuzumab are administered, pertuzumab will be administered 30 to 60 minutes after the end of BDC-1001 infusion.

Refer to the current Pharmacy Manual for specific instructions for the storage and preparation and administration of pertuzumab.

### 5.2.4. Dose Modifications

#### 5.2.4.1. Dose Interruptions

BDC-1001 and/or pertuzumab may be interrupted at the discretion of the Investigator for up to 1 cycle (6 weeks for reasons other than a treatment-related AE) from the planned date of administration. Treatment may be held for up to 12 weeks after a treatment-related AE, unless continued treatment is approved by the Medical Monitor. In the combination arm, pertuzumab must be administered in combination with BDC-1001, not as a single agent. Thus, both BDC-1001 and pertuzumab treatment must be interrupted in a subject who receives combination treatment when BDC-1001 treatment interruption is warranted.

If a subject is assessed as requiring a dose delay longer than 6 weeks, the subject may be withdrawn from study treatment (Section 4.3.1). After a 6-week interruption, study treatment may be resumed if the Investigator and Sponsor agree that it is in the best interest of the subject. Pertuzumab may be restarted according to the package insert (ie, initial dose of 840 mg over 60 minutes followed every 3 weeks by a dose of 420 mg over 30 to 60 minutes). BDC-1001 and/or pertuzumab may be held for up to 12 weeks if due to a treatment-related AE, unless continued treatment is approved by the Medical Monitor. The Investigator may consider dose interruptions or discontinuation of BDC-1001 based on other events not listed in Table 4 according to clinical judgement, in consultation with the Medical Monitor.

**Table 4: BDC-1001 Dose Interruption and Resumption Parameters**

| Toxicities | Dose Interruption Criteria (within 3 days before administration) | Dose Resumption Rules |
|---|---|---|
| Infusion-Related Reactions | Refer to Section 5.3 and Appendix A | |
| Immune-Related Events | Refer to Section 5.3.2 | |
| Cardiac Toxicity | Refer to Section 5.3.3 | |
| All other non-hematological toxicities | • NCI-CTCAE v5.0 Grade ≥ 3<br>• Grade ≥ 3 fatigue lasting ≥ 48 hours<br>• Grade 3 electrolyte abnormality with clinical symptoms or lasting ≥ 48 hours<br>• Grade 3 nausea/vomiting or diarrhea lasting ≥ 48 hours with adequate antiemetic and other supportive | Resolved to Grade 1 or baseline values |
| Hematological laboratory abnormalities | • Febrile neutropenia<br>• Grade 4 thrombocytopenia, Grade 3 with bleeding<br>• NCI-CTCAE v5.0 Grade ≥ 3; the treatment interruption with BDC-1001 will be at the discretion of the Investigator. | Treatment with BDC-1001 will be resumed at the discretion of the Investigator |

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; NCI = National Cancer Institute

#### 5.2.4.2. BDC-1001 Dose Reductions

No intrasubject dose escalations or reductions are permitted for BDC-1001.

#### 5.2.4.3. Pertuzumab Dose Reductions

No intrasubject dose escalations or reductions are permitted for pertuzumab.

### 5.3. Management of Specific Safety Concerns

#### 5.3.1. Infusion-Related Reactions

All subjects should be premedicated for potential IRRs as described in Section 5.2.1.

If an IRR is observed during BDC-1001 administration, the infusion rate should be reduced (infusion duration may increase to 120 minutes) or the infusion should be interrupted or discontinued based on the symptoms. The management of IRR is summarized in Appendix A. Any medications used to treat Grade 1 or 2 IRR may be continued for subsequent infusions per institutional protocol.

Corticosteroids and other immunomodulators remain excluded as prophylactic medication. Additional details on allowable concomitant medications are provided in Section 5.4.

Prophylactic or supportive treatment of study treatment-induced AEs will be otherwise as per Investigator's discretion and institutional guidelines.

Refer to the pertuzumab Investigator's Brochure for safety management recommendations of pertuzumab-related IRRs.

#### 5.3.2. Immune-Related Events

For guideline on diagnosis, monitoring, and management of immune-related toxicity, please refer the following additional assessments and National Comprehensive Cancer Network Guidelines-Management of Immunotherapy-Related Toxicities (Thompson et al, 2023):

- Observation of immune-related clinical signs and symptoms
- Thyroid-stimulating hormone (TSH)/ triiodothyronine (T3)/ thyroxine (T4)
- Pulse oximetry at every cycle

Dosing adjustments will be made for BDC-1001 as described in Table 5. Subjects may continue pertuzumab treatment pending approval from the Medical Monitor.

**Table 5: Dose Modifications Guidelines for BDC-1001 and Pertuzumab**

| Immune-Related Adverse Reactions | Severity | Treatment Modification |
|---|---|---|
| **Pneumonitis** | Grade 2 | Withhold until adverse reactions recover to Grade 1 or baseline [a] |
| | Grade 3 or 4, or recurrent Grade 2 | Permanently discontinue |
| **Colitis** | Grade 2 or 3 | Withhold until adverse reactions recover to Grade 1 or baseline [a] |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue |
| **Nephritis** | Grade 2 with creatinine > 1.5 to ≤ 3 times ULN | Withhold until adverse reactions recover to Grade 1 or baseline [a] |
| | Grade ≥ 3 with creatinine > 3 times ULN | Permanently discontinue |
| **Endocrinopathies** | • Symptomatic hypophysitis, Type 1 diabetes associated with Grade ≥ 3 hyperglycemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis<br>• Hyperthyroidism Grade ≥ 3 | • Withhold until adverse reactions recover to Grade 1 or baseline [a]<br>• For subjects with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated. Otherwise, treatment should be discontinued.<br>• Hypothyroidism may be managed with replacement therapy without treatment interruption. |
| **Hepatitis** | Grade 2 with AST or ALT > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN | Withhold until adverse reactions recover to Grade 1 or baseline [a] |
| | Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN | Permanently discontinue |
| | In subjects with liver metastasis and elevated LFTs, Grade 2 AST or ALT > 3 to 5 times baseline, or total bilirubin > 1.5 to 3 times baseline | Permanently discontinue |
| **Skin reactions** | Grade 3 or suspected SJS or TEN | Withhold until adverse reactions recover to Grade 1 or baseline [a] |
| | Grade 4 or confirmed SJS or TEN | Permanently discontinue |
| **Other immune-related adverse reactions** | • Based on severity and type of reaction (Grade 2 or Grade 3) | Withhold until adverse reactions recover to Grade 1 or baseline [a] |
| | • Grade 3 or 4 myocarditis<br>• Grade 3 or 4 encephalitis<br>• Grade 3 or 4 Guillain-Barré syndrome<br>• Grade 4 or recurrent Grade 3 | Permanently discontinue |
| **Infusion-related reactions** | Grade 3 or 4 | Permanently discontinue |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFTs=liver function transferases; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal
Note: Toxicity grades follow the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0).

a If treatment-related toxicity does not resolve to Grade 1 or baseline within 12 weeks after last dose, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, all therapies should be permanently discontinued.

All therapies should be permanently discontinued for Grade 4 or ≥ 1 recurrence of Grade 3 immune-related adverse reactions, unless otherwise specified in Table 5.

### 5.3.3. Cardiac Toxicity

Decreases in LVEF have been reported with drugs that block HER2 activity, and subjects who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of a LVEF decrease. Changes in LVEF should be managed with the actions outlined in Table 6.

To monitor for potential anti-HER2 related toxicities the following additional assessments will be performed at baseline and regularly throughout the study in accordance with the Schedule of Assessments:

- ECG
- ECHO or MUGA tests. These assessments will be performed at screening, 6 weeks after the first study treatment, then every 3 months thereafter during treatment if no abnormal findings are noted. In the presence of symptoms, monitoring should begin immediately.

**Table 6: Management of LVEF Changes (Based on Absolute Changes)**

| Symptomatic CHF | LVEF < 45% | LVEF 45% to 49% and Decrease is ≥ 10% From Baseline | LVEF > 49% or > 45% and Decrease is < 10% from Baseline |
|---|---|---|---|
| Discontinue study treatment | Interrupt study treatment dosing.<br>Repeat LVEF assessment within 3 weeks. | Interrupt study treatment dosing.<br>Repeat LVEF assessment within 3 weeks. | Continue study treatment. |

Abbreviations: CHF = congestive heart failure; LVEF = left ventricular ejection fraction
Note: LVEF decreases are all in absolute percentages.

Study treatment may be resumed if the LVEF has recovered to greater than 49%, or to 45% to 49% associated with less than a 10% absolute decrease below pretreatment values.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, study treatment should be discontinued, unless the Investigator deems that the benefits for the individual subject outweigh the risks and with the approval from Medical Monitor.

### 5.3.4. Cytokine Release Syndrome

Although cytokine release syndrome (CRS) has not been observed to date in preclinical studies, 3 subjects had Grade 1 CRS that was related to treatment in the ongoing study BBI-20201001. One subject received 12 mg/kg BDC-1001 in the monotherapy arm and 2 subjects received 20 mg/kg in the expansion arm. Data from experimental clinical studies of other

immune-modulating agents have demonstrated potential CRS events. Therefore, guidelines for the grading and management of CRS have been provided in Appendix B.

## 5.4. Prior and Concomitant Medications

### 5.4.1. Recording of Use of Concomitant Medications

The Investigator or qualified designee will review prior medication use and will record them in the electronic case report form (eCRF). Concomitant medications will be recorded in accordance with the Schedule of Assessments.

### 5.4.2. Prohibited Concomitant Therapy

Prohibited prior and concomitant medications are excluded in accordance with the eligibility criteria (Section 4) except as necessary to manage AEs. Subjects are not allowed to receive concomitant therapies as described in Sections 5.4.2.1 and 5.4.2.2.

#### 5.4.2.1. Anti-Cancer Therapy

The following anticancer medications and treatments are prohibited during the study:

- Any concurrent, systemic anti-neoplastic therapy (ie, chemotherapy, immunotherapy, or standard or investigational agents for treatment of advanced HER2-expressing solid tumors) other than BDC-1001 and pertuzumab as specified in this protocol.
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted for non-target lesions. During irradiation, study treatment will be interrupted and resumption will be discussed with the medical monitor.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study.

#### 5.4.2.2. Immunomodulatory Therapy

Subjects should not be using immunomodulating agents, including, but not limited to, steroids, TNFα inhibitors, cyclophosphamide, methotrexate, azathioprine, and thalidomide.

Systemic corticosteroids, IL-6, and TNFα inhibitors may be administered in the treatment of AEs at the judgement of the Investigator after consultation with the Medical Monitor.

Low-dose glucocorticoids up to 10 mg per day prednisone or equivalent are allowed. The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone) for subjects with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the subject is enrolled in the study.

## 5.5. Study Treatment Compliance

All study treatment will be administered at the study site.

At each study visit, the subject should be reminded of the significance of returning to the study site for the next scheduled visit. Attendance and assessments will be recorded in the eCRF.

### 5.5.1. Concomitant Medications

All subjects should be premedicated for potential IRRs as described in Section 5.2.1. Subjects should not be premedicated with corticosteroids or immunomodulators.

Subjects who experience infusion-associated symptoms may be treated symptomatically with ibuprofen, diphenhydramine, acetaminophen, and/or cimetidine or other H2 receptor antagonists, as per standard practice. Serious infusion-associated events should be managed with supportive therapies as clinically indicated (such as supplemental oxygen and E2 adrenergic agonists).

Systemic corticosteroids may be administered at the discretion of the Investigator for the management of AEs.

Gonadotropin-releasing hormone agonists for ovarian suppression in premenopausal women are permitted.

Approved COVID-19 vaccines are allowed but should be administered at least 72 hours prior to any BDC-1001 treatment and not on the day of treatment. All other inactivated vaccines are allowed at any time, except on the day of treatment. Live/attenuated vaccines are not allowed at any time during treatment.

## 5.6. Discontinuation of Study Treatment / Withdrawal from Study

Subjects will be advised that they are free to discontinue study treatment or withdraw from the study at any time. Treatment beyond disease progression will be allowed with the approval of the Sponsor, provided the subject is clinically stable (Section 3.1.3). Discontinuation of study treatment allows further study assessments to be collected. Withdrawal from the study results in no further collection of assessments.

An individual subject may discontinue from study treatment or withdraw from the study for any of the following reasons:

- Completed dosing as specified in the protocol
- Radiological progression per RECIST v 1.1
- Clinical progression
- AE
- Physician decision
- Lost to follow-up
- Study terminated by sponsor
- Death
- Protocol deviation

- Pregnancy
- Withdrawal of consent
- Patient decision

## 6. STUDY ASSESSMENTS AND PROCEDURES

Descriptions of assessments and related guidance/instructions are provided in the sections below.

All assessments and procedures should be conducted in accordance with the Schedule of Assessments.

Additional guidance for study assessments and procedures is provided in the following appendices and the current pertuzumab Investigator's Brochure:

- Appendix A - Infusion Reaction Guideline
- Appendix B - Management of Cytokine Release Syndrome
- Appendix C - RECIST v1.1 Criteria for Tumor Response
-

- Appendix D - iRECIST Criteria for Tumor Response
- Appendix E- Statistical Consideration for Defining Date of iRECIST PD

In the Maintenance Phase, study assessments and procedures will be performed per local standard of care. See Table 2 for schedule and procedures.

### 6.1. Screening Period and Enrollment Description

A signed and dated ICF must be obtained before any study-related procedures or assessments are conducted.

All subjects will be screened for eligibility to participate in the study. Screening assessments are outlined in the Schedule of Assessments. The Screening Period is up to 28 days prior to C1D1, beginning with the day informed consent is obtained. If subjects need to be rescreened, a limited set of Screening tests may be used by the Investigator in consultation with the Medical Monitor.

If Screening assessments are performed on Study Day 1, they can be considered to be Day 1 data and there is no need to repeat them.

### 6.2. Informed Consent

The subject's written informed consent must be obtained prior to his/her participation in the study and should be documented in the subject's medical records. Additional guidance and information regarding informed consent is provided in Section 9.1.2.

### 6.3. Eligibility Criteria Review

Eligibility criteria (inclusion criteria [Section 4.1] and exclusion criteria [Section 4.2]), will be checked during the Screening Period and will be confirmed on Day 1 before the initial study drug treatment. Assessments will include laboratory results, ECGs, and other assessments to meet protocol eligibility requirements.

### 6.4. Physical Examination, Weight, and Height

A physical examination will be assessed in accordance with the Schedule of Assessments. A full physical examination is required at Screening. All other physical examinations can be symptom-directed. Physical examinations, including ECOG PS, will include evaluation of the body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; neck, thyroid, pulmonary; cardiovascular; abdominal; gastrointestinal, genitourinary (optional); lymphatic; extremities; musculoskeletal/extremities; neurological and psychiatric.

Weight and height will also be recorded in kilograms and centimeters, respectively.

### 6.5. Study Treatment Administration

Study treatment should be administered as directed in Section 5.2, and at the days and times outlined in the Schedule of Assessments.

## 6.6. Medical History and Demographics

The subject's medical history and demographic information will be obtained by the Investigator or qualified designee during the Screening Period.

Demographic information includes age, gender, and self-reported race/ethnicity.

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures, as well as classification by origin, tissue type, grade, stage, markers, and mutations if available), reproductive status, medications (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken within 14 days prior to planned first dose administration must be recorded in the eCRF, and all active conditions or any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Substance use will also be recorded.

Tumor history, including, but not limited to, results of tumor mutational burden, programmed death ligand 1 (by immunohistochemistry), actional genomic mutations such as HER2 amplification/mutation, PIK3CA mutation, etc., and microsatellite stability/instability testing should be recorded, if known.

## 6.7. ECOG Performance Status

ECOG PS will be assessed in accordance with the Schedule of Assessments and will be assessed using the grading scale shown in Table 7.

**Table 7: ECOG Performance Status**

| ECOG Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 5 | Dead |

Abbreviations: ECOG = Eastern Cooperative Oncology Group
Source: (Oken et al. 1982)

## 6.8. Vital Signs

Vital signs will be measured in accordance with the Schedule of Assessments. These assessments include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressure while the subject is in a supine or seated position.

The timing of pre- and post-infusion vital sign and ECG collections is presented in Table 8. For subjects with clinically normal ECGs, measurements are not required after Cycle 2 for EOI

unless infusion reactions occur or unless clinically indicated. Moreover, ECGs at EOI are not required unless infusion reactions occur.

**Table 8: Timing of Vital Signs and ECG Collections**

| | |
|---|---|
| **BDC-1001 or Pertuzumab dose only days** | |
| Before infusion | Maximum 2 hours |
| End of infusion | + 5 minutes |
| **Combination dose days** | |
| Before BDC-1001 infusion | Maximum 2 hours |
| End BDC-1001 infusion | + 5 minutes |
| End of Pertuzumab infusion | + 5 minutes |

Before infusion, assessment of blood pressure and pulse rate will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, mobile phone). Vital signs and ECGs are not required after Cycle 2 for EOI unless infusion reactions occur or unless clinically indicated.

## 6.9. Electrocardiograms

Standard supine or semi-recumbent 12-lead ECGs will be performed at the time points outlined in the Schedule of Assessments. All ECG measurements should be performed from a supine/semi-recumbent position. Standard ECG parameters will be measured, including RR, PR, QRS, QT, and QTcF (to be specified in the eCRF). All ECG measurements must be evaluated by the Investigator or delegated physician for the presence of abnormalities and clinical significance. ECGs are not required after Cycle 2 for EOI unless infusion reactions occur or unless clinically indicated.

The timing of pre- and post-infusion ECG collections is presented in Table 8.

## 6.10. Echocardiograms or Multi-gated Acquisition Scans

Standard ECHOs or MUGAs will be performed. These assessments will be performed at screening, 6 weeks after the first study treatment, then every 3 months thereafter during treatment if no abnormal findings are noted. In the presence of symptoms, monitoring should begin immediately (Schedule of Assessments). Left ventricular ejection fraction will be measured by either ECHO or MUGA. All ECHOs or MUGAs must be evaluated by the Investigator or delegated physician for the presence of abnormalities and clinical significance.

## 6.11. Pulse Oximetry

Pulse oximetry is a general method for measuring subject oxygenation in the clinic. Peripheral capillary oxygen saturation will be monitored by pulse oximetry at the time points outlined in the Schedule of Assessments. By detecting signs of early hypoxemia, pulse oximetry may lead to a more rapid treatment of serious hypoxemia (from possible pneumonitis, for example) and prevention of serious complications.

## 6.12. Prior and Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the subject during the trial. Concomitant medications will be recorded at the time points outlined in the Schedule of Assessments. Refer to Section 5.4 for detailed information regarding allowed and prohibited concomitant medications.

## 6.13. Adverse Events

AEs will be managed as described in Section 7 and in accordance with Schedule of Assessments. Investigators will assess the severity of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0), unless otherwise specified.

## 6.14. Viral Screening

### 6.14.1. Hepatitis B Screening

Subjects with active HBV infection are defined as having a positive HBsAg. A subject whose HBsAg is negative and HBcAb is positive may be enrolled if an HBV DNA test is negative and either the subject is treated with potent antiviral therapy or is retested for HBsAg and HBV DNA every month. The test will be performed by local laboratory.

### 6.14.2. Hepatitis C Screening

Subjects with active HCV infection are defined as having a positive HCV antibody test followed by a positive HCV RNA test at Screening. The HCV RNA test will be performed only for subjects who have a positive HCV antibody test. Subjects who are positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. The test will be performed by local laboratory.

### 6.14.3. HIV Screening

Subjects with active HIV infection are defined as those as having a positive HIV antibody test. The test will be performed by local laboratory.

## 6.15. Pregnancy Testing

### 6.15.1. Pregnancy Testing

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering pregnancy during the study and for at least 7 months following the last dose of BDC-1001 or pertuzumab administered during the study. Pregnancy tests should be performed for any woman of childbearing potential. Pregnancy tests are not required for postmenopausal subjects (12 months since last menstruation) or subjects who have no possibility of pregnancy due to sterilization surgery, etc. Serum ß-human chorionic gonadotropin (evaluated by local laboratory) will be evaluated at Screening. Pregnancy testing will be performed at C1D1 before infusion, every 4 weeks during treatment, and at the EOT visit. Positive urine pregnancy test will be

confirmed with a serum pregnancy test. Testing may be determined 48 hours before administration of study treatment.

In the Maintenance Phase, subjects are to be followed as described in Table 2.

### 6.15.2. Pregnancy On-Study

In the event of suspected pregnancy, a confirmatory serum pregnancy test should be performed. Subjects who become pregnant during the study must discontinue study treatment.

The Investigator or designee must report any pregnancy that occurs during the study within 24 hours of awareness using the same procedure as described for reporting SAEs (Section 7.2.4).

The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date.

## 6.16. Clinical Laboratory Safety Assessments

Clinical laboratory tests will be conducted in accordance with the Schedule of Assessments. Laboratory values will be assigned toxicity grades, when available, using the NCI CTCAE v5.0 scale. Laboratory tests may be determined up to 48 hours before each dose during treatment. Comparable analytes may be collected according to local standards (eg. blood urea nitrogen [BUN] vs. urea, etc.) following notification of the Sponsor.

The Investigator must review laboratory reports before treatment, document this review, and record any clinically significant changes occurring during the study as an AE (see Section 7.1). All laboratory reports must be filed in the source documents.

In the Maintenance Phase, safety assessments will be performed per local standard of care. See Table 2 for schedule and procedures.

### 6.16.1. Chemistry

Chemistry tests will be performed by a local laboratory and will include the following:

- BUN, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bicarbonate (total $CO_2$), sodium, potassium, chloride, magnesium, calcium, phosphate, creatinine, amylase, total protein, and albumin.

### 6.16.2. Hematology

Hematology tests will be performed by a local laboratory and will include the following at all timepoints:

- Red blood cell count, hemoglobin, hematocrit, and indices per local standards (eg, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell distribution width).

- White blood cell count with differential (eg, absolute and percent neutrophils, lymphocytes, monocytes, eosinophils, basophils).
- Platelet count.

### 6.16.3. Coagulation

Coagulation laboratory tests will be performed by local laboratory.

Coagulation laboratory tests include: PT (or INR) and aPTT reported according to local standards.

### 6.16.4. Urinalysis

Urinalysis or urine dipstick should be conducted as outlined in the Schedule of Assessments. Urine tests will be performed by local laboratory include tests for pH, specific gravity, glucose, ketones, protein, leukocytes, nitrite, and bilirubin.

## 6.17. Thyroid Function Testing

TSH and free T4 will be conducted in accordance with the Schedule of Assessments. TSH and free T4 may be determined up to -48 hours before the dose. The tests will be performed by local laboratory.

## 6.18. Serum Tumor Markers

Serum tumor markers (eg, cancer antigen [CA27.29 and CA15-3, etc.]), will be tested by local laboratory per standard of care according to the Schedule of Assessments.

Tumor markers may be used for exploratory determination of anti-tumor activity.

## 6.19. Pharmacokinetics

Serum will be collected from all subjects enrolled in the study for assessment of BDC-1001 PK. PK sampling should be conducted in accordance with the Schedule of Assessments.

The actual time of study treatment administration and the exact time of blood sampling must be recorded in source document.

Refer to the current version of the Laboratory Manual for detailed information.

## 6.20. Immunogenicity (Anti-BDC-1001 Antibodies)

Serum will be collected from all subjects enrolled in the study for assessment of anti-BDC-1001 antibodies (ADAs). ADA sampling will be conducted in accordance with the Schedule of Assessments.

Refer to the current version of the Laboratory Manual for detailed information.

## 6.21. Exploratory Biomarker Assessments

Exploratory biomarker analysis will be performed as part of this study to allow exploration of the mode of action, pharmacodynamic biomarker characterization of BDC-1001, and to potentially identify subjects most likely to benefit from treatment with BDC-1001 in the future.

Blood will be collected for biomarker evaluation (including, but not limited to, immune cell activation, changes in blood based-biomarkers, and other biomarkers that are related to BDC-1001 mechanism of action and tumor immune biology) according to the Schedule of Assessments. Samples will be processed to obtain their derivatives and may be evaluated for immune-related, tumor type-related, and other exploratory biomarkers.

Any remaining samples collected for PK, biomarker assays, and immunogenicity assessment may be used for exploratory biomarker profiling, identification, and pharmacodynamic assay development purposes as appropriate if subject consents to future research.

Refer to the current version of the Laboratory Manual for detailed information.

## 6.22. Tumor Specimens

### 6.22.1. Fresh Tissue Biopsy

Screening fresh tumor tissue biopsy is required for all subjects.

An on-treatment biopsy may be collected if safely accessible and clinically feasible, at the discretion of the Investigator. An optional additional biopsy may be collected preferably at time of progression, response or at any time during the study.

For freshly collected biopsy specimens, acceptable samples include those outlined below, provided there are tissue architecture regardless of needle gauge or retrieval method:

- Core needle biopsy sample collection for deep tumor tissue; at least 3 cores
- Excisional, incisional, punch, or forceps biopsy sample collection for cutaneous, subcutaneous, or mucosal lesions
- Tumor tissue resections

The following specimens are not acceptable: fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or cell smears), brushing, cell pellets from pleural effusion, and lavage samples as well as tumor tissue that have been decalcified.

Any remaining tumor samples may be used for future research including exploratory biomarker profiling, identification, and pharmacodynamic assay development purposes as appropriate if subject consents to future research.

Refer to the current version of the Laboratory Manual for detailed information.

### 6.22.2. Archival Tissue

Archival tumor tissue sample will be submitted if a fresh biopsy is not collected at Screening.

Representative tumor specimens in paraffin blocks are preferred. If an archival block is unavailable, unstained serial sections on slides must be submitted.

The following specimen types are acceptable: resections, core needle biopsies, excisional, incisional, punch, or forceps biopsies. For core needle biopsy specimens, preferably, at least 3 cores embedded in a single paraffin block should be submitted for evaluation. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or cell smears), brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. Tumor tissue that has been decalcified is not acceptable.

The submitted tumor tissue should be of good quality based on total and viable tumor content. An archival tumor specimen should be submitted if available.

## 6.23. Tumor Assessments

Tumor response will be assessed in accordance with the Schedule of Assessments. All subjects will be evaluated for response of tumor lesions (CR, PR, SD, PD) by RECIST v1.1 criteria (Eisenhauer et al. 2009). Subjects with a response of PD will also be evaluated by Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST) criteria (Seymour et al. 2017), and both results will be entered in the eCRF. The iRECIST criteria are required to confirm PD.

Subjects who experience an objective response (ie, CR or PR) should have a confirmatory assessment performed at least 4 weeks (+ 7 days) after the initial response.

Subjects who have radiographic progression and have continued on study per iRECIST should have scans performed 4 to 6 weeks following immune unconfirmed progressive disease (iUPD) to immune confirmed progressive disease (iCPD). The date of disease progression will be defined according to Appendix E (see Section 8.4.7, as well).

Tumor imaging modality will be CT or magnetic resonance imaging (MRI). The same imaging modality should be used for tumor assessments at Screening and those that will be performed every 6 weeks (± 7 days) during the first 24 weeks after C1D1 and after that every 12 weeks (± 7 days) regardless of any delays in dosing. The assessment will be conducted before Day 1 of each cycle if possible. CT or MRI scans of the chest, abdomen and pelvis are mandatory. However, if there is no brain metastasis at the time of Screening, brain CT or MRI should only be done when symptoms associated with brain metastasis occur. If there are central nervous system metastases (eg, spinal cord, brain) and a CT or MRI is performed at Screening, then these lesions must be evaluated according to the schedule of assessment.

CT and MRI scans will be performed using institutional standard operating procedures (SOPs). The same scan modality and machine should be used throughout the study for each subject, if possible. Scans will be read by institutional radiologists and reported. The reports will be filed in source documents and the results entered into the eCRF.

Tumor measurement will be conducted while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow-up.

Tumor assessment images will be collected and may be reviewed at the Sponsor's discretion.

During the Maintenance Phase, tumor assessments will be performed per local standard of care and will not be captured in the study database or submitted for central review.

## 6.24. Survival Information

The survival status of each subject will be monitored during study treatment and after discontinuation of study treatment for any reason (not applicable for subjects who have withdrawn from the study).

During the study, the Medical Monitor may request that a survival report be conducted to obtain an accurate number of deaths across the study. The Medical Monitor will provide instructions on these survival reports immediately before they commence as well as a timeline for contacting subjects.

The cause of death will be recorded for subjects who die, if available.

## 6.25. Procedures at End of Treatment and Follow-Up

### 6.25.1. End of Treatment

The date of EOT is defined as the date of the last dose of study drug administration.

The EOT assessments, outlined in Schedule of Assessments, will be performed 14 days (± 7 days) after the last day of study drug administration. If the required assessments at EOT have been performed during the treatment period, they do not need to be replicated.

The same imaging tumor modality used at the time of Screening by CT or MRI scans should be performed. CT or MRI scans of the chest, abdomen, and pelvis are mandatory. However, if there is no brain metastasis at the time of Screening, brain CT or MRI should only be done when symptoms associated with brain metastasis occur (Section 6.23).

The reason for treatment discontinuation should be recorded.

For women deemed of childbearing potential, a pregnancy test should be conducted (Section 6.15.1).

### 6.25.2. Safety Follow-Up

The SFU visit assessments, outlined in the Schedule of Assessments, should occur 28 days (+7 days) after the last study treatment. 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 AEs, the Investigator will follow the AEs until the event has resolved or the condition has stabilized. Every attempt will be made to

follow AEs through resolution. If assessments at EOT or treatment period are performed within this period, they can be considered to be the SFU data and there is no need to repeat them.

### 6.25.3. Long-Term Follow-Up / End of Study

All subjects who discontinue study treatment will be followed for:

- Assessment of treatment-related AEs/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 EOT, until any of the following occur: the subject has radiographic progression, 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. Completion of LTFU (up to 2 years) is not required for a subject to be considered as having completed the clinical study.

### 6.25.4. Treatment after the End of Study

Upon completion of the study, the Sponsor will follow local regulatory/International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for any follow-up treatment provided to subjects. Each Investigator is responsible for ensuring that appropriate post-study care is provided for each subject's medical condition.

# 7. ADVERSE EVENTS

Adverse events should be collected/recorded in accordance with the Schedule of Assessments.

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.

## 7.1. Adverse Event Definitions

### 7.1.1. Adverse Event

An AE is any unfavorable and unintended medical occurrence (including an abnormal laboratory finding) temporally associated with the use of an investigational product or protocol-imposed intervention whether or not considered related to the investigational product.

The following are AEs:

- Abnormal medical occurrence (eg, symptom, sign, laboratory test result, ECG, radiological scan, etc.) that emerges during the protocol-specified AE reporting period and is considered clinically significant by the Investigator
- Worsening of a chronic or pre-existing medical condition in frequency or severity that is considered clinically significant by the Investigator
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)

The following are NOT AEs:

- Signs/symptoms, laboratory abnormalities related to the natural disease course (ie, disease progression). Signs/symptoms of clinical sequelae resulting from disease progression will be reported as AEs/SAEs if they fulfill the AE/SAE definition.
- Hospitalization or death due to disease progression
- Planned or elective admissions to a hospital

### 7.1.2. Serious Adverse Event

An SAE is any AE that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or,
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which

hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

## 7.2. Detecting and Reporting Adverse Events and Serious Adverse Events

AE information that should be reported to the Sponsor includes, but is not limited to, the following:

- Change in the event's outcome, including recovery
- New signs or symptoms or a change in the diagnosis
- Change in causality based on new information
- Significant new diagnostic test results
- Additional narrative information on the clinical course of the event

Adverse events (including AEs, SAEs) will be elicited by asking the subject a non-leading question. A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted.

All AEs occurring after the first dose of study drug and up to the SFU visit-will be recorded on the AE eCRF. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to the first dose of study drug will be recorded as part of medical history.

At each visit, the Investigator should determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject, or elicited by questioning the subject. Subjects should be questioned in a general way, without asking about the occurrence of any particular symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 7.1. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. All laboratory values must be evaluated by the Investigator as to clinical significance, consistent with institutional policies. All abnormal laboratory values considered clinically significant by the Investigator and without a corresponding diagnosis must be recorded as an AE on the eCRF. Abnormal laboratory findings attributed to the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe or frequent than expected for the subject's condition.

Always report diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until a diagnosis becomes available.

If the signs and symptoms are distinct and do not lead to a common diagnosis, they should be reported as individual entries of AE or SAE. For serious events due to hospitalization, the reason for hospitalization must be reported as the SAE. A pre-planned procedure or treatment requiring hospitalization for preexisting conditions which does not worsen in severity should not be reported as SAEs (refer to Section 7.1 for definitions).

Any other serious, untoward event that occurs subsequent to the reporting period that the Investigator assesses as related to either study drug should be reported and managed as an SAE.

Investigator should follow subjects with AEs until the target event has resolved, to baseline or the condition has stabilized. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they are no longer clinically relevant.

24-hour medical and safety coverage is available at [redacted] in United States, at [redacted] in France, at [redacted] in Italy, and at [redacted] in Spain.

**Maintenance Phase:**

To continue to collect important safety information on subject(s) in the Maintenance Phase, reporting of SAEs and other reportable events (pregnancy and overdose) will continue per protocol (see Table 2).

Further, the following AEs, whether serious or not, will be reported using the same process as for reporting SAEs as described in Section 7.2.4 (though SAE reporting timeline requirements do not apply to non-serious events reported in these categories):

- Adverse events, whether serious or not, leading to study treatment discontinuation
- Adverse events, whether serious or not, leading to study treatment to be interrupted or delayed.

Other non-serious AEs will not be collected by the Sponsor as they are unlikely to meaningfully change the safety profile established in the earlier phases of this study.

### 7.2.1. Grading and Intensity

All AEs will be graded according to the NCI CTCAE v5.0 and general guidelines outlined in Table 9.

**Table 9: NCI CTCAE v5.0 Definitions of Severity for Adverse Reactions**

| Toxicity | Grade / Details |
|---|---|
| **Grade 1** | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no interventions required<br>(an AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities) |
| **Grade 2** | Moderate; minimal, local or noninvasive intervention indicated; some limitation of activities<br>(an AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed) |
| **Grade 3** | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization required; disabling; limitation of subject's ability to care for him/herself<br>(an AE that prevents normal everyday activities; treatment or other intervention usually needed) |
| **Grade 4** | Life-threatening consequences; urgent intervention required<br>(an event that puts the subject at immediate or potential risk of death, requires hospitalization, or which drastically impacts a subject's well-being) |
| **Grade 5** | Death related to adverse event (fatal) |

### 7.2.2. Relationship to Study Treatment / Causality

The Investigator should assess causal relationship between an AE and the study treatment on the basis of his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

**Related:**

The AE follows a reasonable temporal sequence from study treatment administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

- The AE follows a reasonable temporal sequence from study treatment administration and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

**Not Related:**

- The AE does not follow a reasonable temporal sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

### 7.2.3. Outcome and Action Taken

The outcome or action taken with respect to study treatment will be recorded on the eCRFs.

### 7.2.4. Serious Adverse Event Reporting Requirements

SAEs must be reported to the Sponsor within 24 hours of knowledge by the Investigator or staff.

During the Maintenance Phase, SAE reporting will be done via the paper Safety Report Form. No data will be entered in the eCRF. The study clinical database will be closed after the last subject remaining on treatment enters the Maintenance Phase.

## 7.3. Follow-up of Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology if available
- New or updated information will be recorded in the originally completed eCRF. For the Maintenance Phase, the information will be recorded using the paper Safety Report Form.

- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information
- All SAEs and non-serious Grade 3 or higher AEs must be followed until the event has resolved to the baseline or Grade 1, stabilized, or until the Investigator assesses it as non-resolvable/persisting or until last contact with the subject. Other AEs still ongoing after discontinuation of the study treatment should be followed at least until last scheduled SFU visit, 28 days (+ 7 days) after the last dose of study drug administration.

## 7.4. Pregnancy Reporting

Pregnancies must be reported to the Sponsor within 24 hours of knowledge by the Investigator or staff. For the Maintenance Phase, pregnancy reporting will be done via paper Pregnancy Report Form.

## 7.5. Overdose Reporting

An overdose in this study is defined as any of the following:

- Any single dose of BDC-1001 that is ≥ 10% more than the assigned dose
- An infusion duration that is < 45 minutes (not including flushing)

For an overdose, the Investigator should contact the Medical Monitor immediately and document the quantity of the excess dose as well as the duration of the overdose in the eCRF. Decisions regarding any treatments, dose interruptions or dose modifications should be made by the Investigator, in consultation with the Medical Monitor.

For the Maintenance Phase, the Investigator should contact the Medical Monitor immediately in the event of an overdose and document the quantity of the excess dose as well as the duration of the overdose in a Safety Report Form.

Overdose will not be reported as an AE/SAE although resulting symptoms should be reported.

# 8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

A full Statistical Analysis Plan (SAP) will provide specific details on the analytical methods and data displays.

## 8.1. Endpoints

Study endpoints are outlined in Table 3.

## 8.2. Determination of Sample Size

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 are observed in an arm, the study will continue to enroll 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.

## 8.3. Analysis Populations

### 8.3.1. Safety Analysis Set

The Safety Analysis Set is defined as enrolled subjects who receive at least 1 dose of BDC-1001 with or without pertuzumab. The Safety Analysis Set will be used primarily for the analysis of safety, PFS, and OS data.

### 8.3.2. Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be used primarily for the analysis of anti-tumor activity-related data. The FAS will include subjects who meet the following criteria:

- Receive at least 1 dose of BDC-1001 with or without pertuzumab
- Have 1 or more measurable lesion(s) at baseline as assessed and at least 1 postbaseline evaluable scan using RECIST v1.1 criteria at least 4 weeks after C1D1.

### 8.3.3. Pharmacokinetic Analysis Set (PKAS)

The Pharmacokinetic Analysis Set (PKAS) will include subjects who meet the following criteria:

- Receive any dose of BDC-1001 with or without pertuzumab
- Have 1 or more post-infusion PK datapoint

### 8.3.4. Pharmacodynamic Analysis Set (PDAS)

The Pharmacodynamic Analysis Set (PDAS) will include subjects who meet the following criteria:

- Receive any dose of BDC-1001 with or without pertuzumab
- Have 1 or more set of biomarker data

## 8.4. Statistical Methods

### 8.4.1. Demographics and Baseline Characteristics

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

### 8.4.2. Prior and Concomitant Medications

Concomitant medications will be coded by the World Health Organization (WHO) Drug Dictionary to Anatomical Therapeutic Classification (ATC) and preferred drug name. Prior and concomitant medications will be summarized by ATC level and preferred drug name and listed.

### 8.4.3. Study Drug Exposure

Descriptive statistics will be used to summarize study drug exposure including duration of treatment, cumulative dose of study drug, and number and percent of subjects with dose modifications (ie, dose interruption and permanent dose discontinuations).

### 8.4.4. General Principles

All individual subject data may be presented in the subject data listings.

Continuous data will be summarized using the following summary statistics: the number of observations (N), mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using counts and percentages. All summaries will be presented by study arm and overall, when appropriate.

### 8.4.5. Safety Analyses

Safety will be assessed through summaries of AEs, SAEs, changes in laboratory test results, changes in vital signs and ECGs, and exposure to BDC-1001 and pertuzumab. All safety analyses will be conducted in the Safety Analysis Set.

Treatment-emergent AEs are defined as AEs that start on or after the first administration of study treatment. The reported AE term will be assigned a standardized preferred term using Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be summarized based on the number and percentage of subjects experiencing the event by MedDRA system organ class and preferred term. The causal relationship between the occurrence of an AE and study treatment will be judged by the Investigator. In the event that a

subject experiences repeated episodes of the same AE, the event with the greatest severity grade and strongest causal relationship to study treatment will be used for purposes of incidence tabulations.

AEs-summaries include:

- All TEAEs
- TEAEs by relationship (yes, no) to study treatment and maximum severity grade (according to NCI CTCAE v5.0)
- TEAE by severity that are defined by NCI CTCAE v5.0
- TEAEs with action of study treatment interrupted
- TEAEs with action of study treatment discontinued
- SAEs by relationship (yes, no) to study treatment
- Immune-related AE

Hematology and serum chemistries will be summarized in a descriptive manner.

Laboratory values will be assigned toxicity grades, when available, using the NCI CTCAE v5.0 scale. Directional shifts in laboratory 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. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

#### 8.4.5.1. Monitoring of Safety Data

Continuous safety monitoring by an SRC will be adopted for each arm based on the rate of SAEs attributable to study treatment. Continuous safety monitoring will be conducted to ensure ongoing evaluation of subject safety.

A Bayesian toxicity monitoring rule will be implemented. Specifically, if the probability (true study treatment related SAE rate > 30%) is > 70% in any given arm, the enrollment to that arm will be halted pending the SRC review. A beta (0.5, 0.5) prior for the true study treatment-related SAE rate is utilized. Table 10 shows the stopping boundaries for this safety monitoring rule in up to 33 subjects per treatment arm.

**Table 10: Bayesian Toxicity Monitoring Safety Stopping Rules**

| Number of Subjects | Early Stop if Number of Subjects with Related SAE |
|---|---|
| 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 |
| | Reach Max N |

Abbreviations: N = number of subjects; SAE = serious adverse event

An ad hoc meeting will be conducted to review accumulated safety data, including SAEs, if a threshold in Table 10 is crossed and the timing doesn't fall in the regular SRC review meeting schedules (as set forth in the SRC Charter). If the SRC considers the safety profile inadequate for BDC-1001 as monotherapy or in combination with pertuzumab, then enrollment to either or both 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 arms that include the implicated study treatment (ie, 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 arms should emerging safety data suggest an unacceptable risk.

Although the decision of whether to close an 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 one or both arms is to be closed.

The SRC will not be providing oversight for the Maintenance Phase.

### 8.4.6. Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum BDC-1001 exposure (eg, $C_{max}$ and $C_{min}$) will be tabulated and plotted by arm and compared to those in the Phase 1 study using a population PK analysis approach. Intersubject variability and drug accumulation will be evaluated.

PK data from this study may also be used for separate pharmacokinetic/pharmacodynamic analyses; the results will be reported separately, if conducted.

Exploratory pharmacodynamic analyses will include assessments of pharmacodynamic biomarkers in both tumor tissue and blood.

The relationship between BDC-1001 concentration and selected efficacy and safety outcomes may be explored. The correlation between biomarkers and clinical outcomes may be analyzed.

PK and PD assessments will no longer be collected for subjects in the Maintenance Phase.

### 8.4.7. Anti-Tumor Activity Analyses

The anti-tumor activity endpoints of ORR, duration of response (DOR) and disease control rate will be analyzed and summarized for the subjects in FAS. The endpoints of PFS and OS will also be analyzed and summarized for subjects in the Safety population. Additional details will be provided in the SAP.

The primary endpoint of ORR is defined as the proportion of subjects with best overall response of confirmed CR or PR as determined by the treating Investigator using RECIST v1.1 criteria (Appendix C RECIST v1.1 Criteria for Tumor Response). 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. The iRECIST criteria are required to confirm PD only and will not be performed at each tumor assessment.

Duration of response (DOR) will be calculated for subjects who achieve confirmed CR or PR. For such subjects, DOR is defined as the duration from the start date of CR or PR (whichever response status is observed first) and subsequently confirmed, to the earliest of documented date of PD per RECIST v 1.1 or death.

Disease control rate is defined as the best overall response rate of confirmed CR, PR, or stable disease lasting 24 or more weeks (≥ 2 tumor assessments) following the initiation of BDC-1001.

Progression-free survival (PFS) is defined as the duration from the date of first study treatment administration (C1D1) to the earliest date of documented PD per RECIST v1.1 or death. A death will be considered a PFS event.

Overall survival (OS) is defined as the duration from the date of first study treatment administration to the date of death, irrespective of cause.

Time-to-event endpoints of DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method with 95% CIs calculated. The right-censored criteria will be described in

SAP, and the progression or censoring date will be determined based on described conventions. Median duration of study follow-up will also be presented.

Subjects will not be followed for OS in the Maintenance Phase.

### 8.4.8. Biomarker Analysis

Exploratory biomarker analyses may include assessments of pharmacodynamic biomarkers in both tumor tissue and blood, when appropriate for data collected. Biomarkers that may correlate with anti-tumor activity or immunomodulatory effects of BDC-1001 will be explored, as appropriate.

BDC-1001 biological activity will be assessed by exploring pharmacodynamic or predictive biomarkers that may correlate with activity or help to identify subjects likely to respond to BDC-1001 and/or BDC-1001 plus pertuzumab combination treatment, when appropriate for data collected. The correlation between biomarkers and clinical outcomes may be analyzed.

### 8.4.9. Immunogenicity Analysis

Incidence, titer, and time-course of ADA response will be reported by arm. The potential correlation of immunogenicity with PK, pharmacodynamic, and safety parameters may be assessed.

The incidence of ADA formation in each dose group will be summarized by frequency counts and percentages. The impact of positive results on PK, safety and biological activity will be assessed when appropriate for data collected.

# 9. STUDY ADMINISTRATION

## 9.1. Ethical Conduct of Study

This study will be conducted under applicable local legal and regulatory requirements, as well as the guiding principles of the World Medical Association Declaration of Helsinki, and will include current Good Clinical Practice (GCP) according to ICH guidelines.

Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an independent ethics committee (IEC); the study will be conducted by scientifically and medically qualified persons; the anticipated benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will provide written informed consent before any protocol-specific tests or evaluations are performed.

### 9.1.1. Approval by Independent Ethics Committee or Institutional Review Board

Before initiating the study, the Investigator must obtain written confirmation from the IEC/institutional review board (IRB) that the IEC/IRB is properly constituted and compliant with all requirements and local regulations. The Investigator will provide the IEC/IRB with all appropriate material, such as the protocol, current BDC-1001 and pertuzumab Investigator's Brochures, site- or country-specific ICF, and other written information provided to the subjects.

IEC/IRB approval of the protocol, informed consent document, and all recruiting materials are obtained in writing by the Investigator and copies are received by the Sponsor. A copy of the IEC/IRB confirmation will be provided to the Sponsor. IEC/IRB approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes. The Investigator will provide appropriate reports on the progress of the study to the IEC/IRB and to the Sponsor or designee in accordance with applicable local regulations.

### 9.1.2. Subject Informed Consent

The subject's written informed consent must be obtained prior to his/her participation in the study and should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion, consistent with local institutional policies. The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date that informed consent was given should be recorded on the eCRF.

The ICF should provide an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific Screening procedures or any study treatments are administered. The written ICF should be prepared in the local language(s) of the potential subject population, consistent with national and local regulations and GCP.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that

have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) is provided in the Sponsor ICF template for the Investigator to prepare the documents to be used at his or her site.

For studies in the United States, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

The consent form should be signed and personally dated by the subject or legally acceptable representative prior to his/her participation in the study.

### 9.1.3. Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is obligated to inform the IRB/IEC of progress of the study and notify the IRB/IEC of study closure. The Investigator must also provide the Sponsor with copies of IRB/IEC correspondence that relate to study approvals, updates, or changes. The Investigator is also responsible for forwarding to the IRB/IEC reports of any SAEs from other studies conducted with the same investigational product that were provided by the Sponsor.

### 9.1.4. Sponsor Safety Reporting to Regulatory Authorities / Investigator Sites

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system and all country Regulatory Authorities where the study is being conducted, according to local applicable regulations. The sponsor or designee shall notify the Investigator sites of serious, related, and unexpected AE(s) per local country requirements.

### 9.1.5. Serious Adverse Event Notification to the Institutional Review Board/ Independent Ethics Committee

Suspected unexpected serious adverse reactions will be reported to the IRB/IEC according to their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

### 9.1.6. Confidentiality

All information concerning BDC-1001 or pertuzumab is considered confidential by the Sponsor.

Subject confidentiality will be maintained per local legal and regulatory requirements and ICH GCP guidelines. To comply with GCP guidelines and requirements, subject records will be reviewed during monitoring visits and audits conducted by the Sponsor, Sponsor's representatives, or health authorities. During these activities, every reasonable effort will be made to keep medical information, including subject identifying information, as confidential as possible as required by law.

## 9.2. Regulatory: Data Quality Control and Quality Assurance

All subject data relating to the study will be recorded in the eCRF unless defined differently with the site. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 9.2.1. Compliance with Laws and Regulations

This study will be conducted in accordance with the ICH E6 Guideline for GCP, and applicable local country laws and guidelines.

### 9.2.2. Study Monitoring and Data Collection

The Sponsor or contract research organization monitor are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other appropriate documents).

The monitor is responsible for visiting clinical site(s) at regular intervals throughout the study to verify adherence to the protocol, accuracy, completeness, consistency of data, and adherence to ICH GCP and local regulations on the conduct of clinical research. In accordance with ICH GCP and the Sponsor’s audit plans, this study may be selected for audit by representatives from Sponsor. Inspection of site facilities and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The monitor is responsible for inspecting eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure actions that are taken to prevent recurrence of the detected deviations are documented.

The Investigator agrees to cooperate with the monitor to ensure that any issues detected during the course of these monitoring visits are addressed, documented, and resolved.

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. Data from the safety database will be summarized or listed separately.

### 9.2.3. Audit and Inspection

The Sponsor or third-party designee (contract or consultant) Clinical Quality Assurance (CQA) auditors, which is independent of and separate monitoring or quality control functions, may audit clinical Investigator sites to evaluate trial conduct and compliance with the protocol, SOPs, GCP and applicable regulatory requirements.

If regulatory authorities request an inspection, the Investigator must inform the Sponsor immediately that such request has been made.

### 9.2.4. Protocol Adherence

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case-by-case basis. Under no circumstances is a site Investigator allowed to collect additional data or conduct any additional procedures for any research-related purpose involving any investigational drugs under the protocol. Investigators ascertain that they will apply diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study, this deviation must be considered as a protocol amendment. Unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

### 9.2.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given favorable opinion by the IRB/IEC.

If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least 1 administration of study treatment, information should be collected for safety purposes.

A deviation to any protocol procedure or waiver to any stated criteria is not allowed in this study except where necessary due to potential hazard(s) to the subject. The Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved procedures in the protocol.

The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

### 9.2.6. Records Retention

The Investigator must retain records and documents, including signed ICF, pertaining to the conduct of this study. ICH Guideline for GCP (refer to Section 4.9 of the guideline) and US FDA regulations (21 CRF 312.62) require that records and documents pertaining to the conduct of this study and the distribution of study treatment, including ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for (i) 2 years after the last marketing application approval in an ICH region, (ii) after at least 2 years have elapsed since formal discontinuation of clinical development of BDC-1001, or (iii) for a longer period as required by national or local law (at least 25 years from study completion in the EU). No records may be destroyed without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 9.2.7. Investigator Reporting Policy

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication. Thereafter, the study site will have the opportunity to publish the results of the study, provided that the Sponsor has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of Sponsor's Legal Affairs and with proper regard to the protection of subjects' identities.

## 9.3. Termination

The Sponsor plans to terminate this study following completion of the study objectives.

However, the Sponsor may terminate the study at any time by sending a written notice of the termination reasons to the Investigator. If an Investigator or the Investigator's IEC/IRB intends to terminate participation in the study, the Investigator must inform the Sponsor immediately and provide the rationale for such termination.

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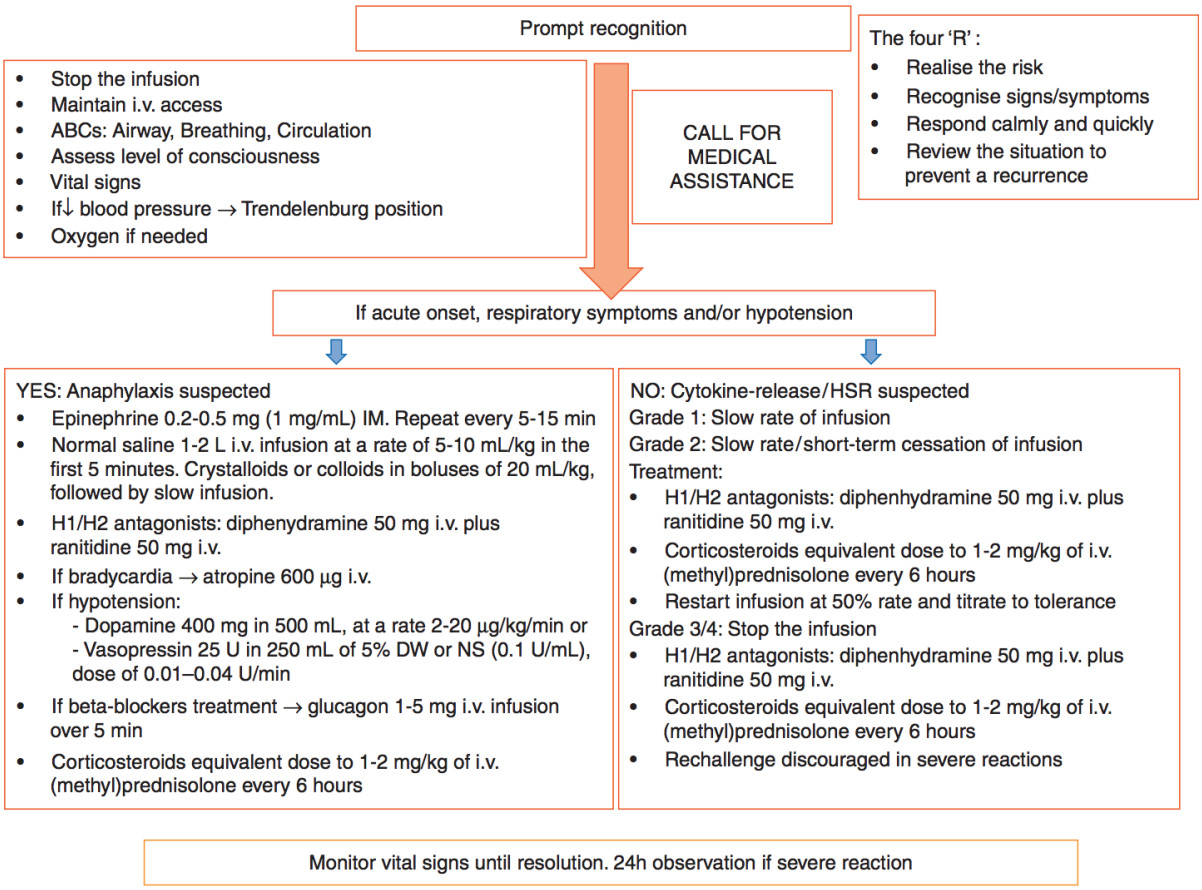
# 11. APPENDICES

## Appendix A: Infusion Reaction Guideline




From Rosello, Blasco et al., Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines, Ann Oncol, 2018 (Rosello et al. 2018)

## Appendix B: Management of Cytokine Release Syndrome

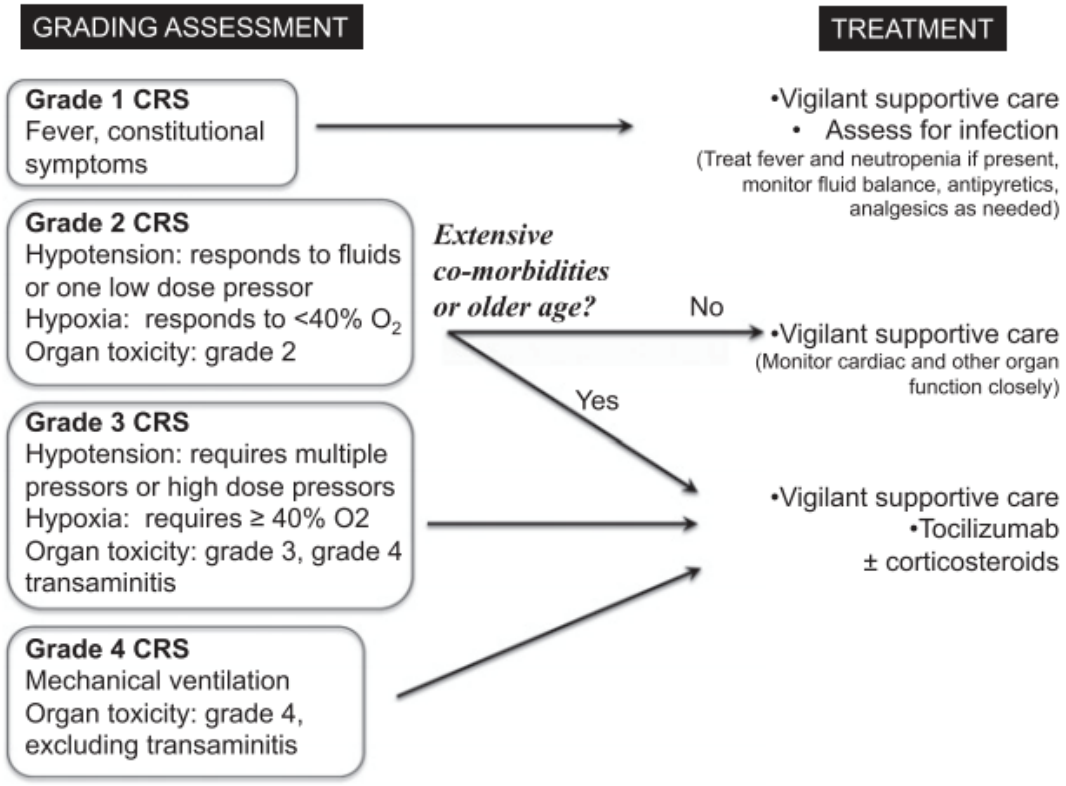



**Table 2**
ASTCT CRS Consensus Grading

| CRS Parameter | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Fever*** | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C | Temperature ≥38°C |
| | | With | | |
| **Hypotension** | None | Not requiring vasopressors | Requiring a vasopressor with or without vasopressin | Requiring multiple vasopressors (excluding vasopressin) |
| | | And/or† | | |
| **Hypoxia** | None | Requiring low-flow nasal cannula‡ or blow-by | Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask | Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation) |

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Source: (Lee et al. 2019)

**Table 3. High-dose vasopressors (all doses are required for ≥3 hours)**

| Pressor | Dose |
|---|---|
| Norepinephrine monotherapy | ≥20 μg/min |
| Dopamine monotherapy | ≥10 μg/kg/min |
| Phenylephrine monotherapy | ≥200 μg/min |
| Epinephrine monotherapy | ≥10 μg/min |
| If on vasopressin | Vasopressin + norepinephrine equivalent of ≥10 μg/min* |
| If on combination vasopressors (not vasopressin) | Norepinephrine equivalent of ≥20 μg/min* |

*VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (μg/min)] + [dopamine (μg/kg/min) ÷ 2] + [epinephrine (μg/min)] + [phenylephrine (μg/min) ÷10].

From ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells (Lee et al. 2019).

# Appendix C: RECIST v1.1 Criteria for Tumor Response

## Table 11: RECIST v1.1 Criteria for Tumor Response

| **Disease Response Criteria for Target and Non-target Lesions** | |
|---|---|
| **Evaluation of Target lesions** | |
| Complete Response (CR): | Disappearance of all target lesions. Pathologic nodes must have a reduction in the short axis to < 10 mm. |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. |
| 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. |
| Progressive Disease (PD): | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study recorded since the treatment started or the appearance of 1 or more new lesions. In addition to 20% increase, the sum must also demonstrate an absolute increase of at least 5 mm. |
| **Evaluation of Non-target Lesions** | |
| Complete Response (CR): | Disappearance of all non-target lesions and normalization of tumor marker level. |
| Incomplete Response/ Stable Disease (SD): | Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits. |
| Progressive Disease (PD): | Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. |

Abbreviations: CR = complete response; LD = longest diameter PD = progressive disease; PR = partial response; SD = stable disease
Source: (Eisenhauer et al. 2009).

**Table 12: 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 et al. 2009).

**Table 13: 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 |

Abbreviations: 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 Disease 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 et al. 2009)

## Appendix D: iRECIST Criteria for Tumor Response

### Table 14: iRECIST Criteria for Tumor Response

| RESPONSE CATEGORY | CRITERIA |
|---|---|
| Complete Response (iCR) | All lesions resolved |
| Partial Response (iPR) | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. |
| Progressive Disease (iPD) | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study recorded since the treatment started or the appearance of 1 or more new lesions. In addition to 20% increase, the sum must also demonstrate an absolute increase of at least 5 mm |
| | Wait up to 12 weeks to confirm PD to account for flare |
| Stable Disease (iSD) | Does not meet other criteria |

Abbreviations: iCR = immune complete response; iPD = immune progressive disease iPR = immune partial response; iSD = immune stable disease
Source: (Seymour et al. 2017)

### Table 15: iRECIST Guidelines for Progression Evaluation

| **Any factor below on the confirmatory scan (after iUPD) indicates iCPD** | |
|---|---|
| Target Lesions | SoD increases ≥ 5 mm from iUPD TL<br>SoD does not have to increase 20% from iUPD |
| Non-Target Lesions | Any further increase in size (qualitative assessment) from an iUPD NTL<br>Does not have to meet "unequivocal" standard |
| New Lesions | There are ANY additional new lesions<br>OR<br>Size of previously detected new lesions increases<br>Target NL: NL iSoD increases ≥ 5 mm<br>NT NL: any significant growth |
| **Any factor below indicates progression (iUPD) after iSD/iPR/iCR** | |
| Target Lesions | SoD crosses PD threshold (1st time, or again)<br>Based on the nadir (ie, smallest value ever) |
| Non-Target Lesions | New unequivocal progression<br>OR<br>If already showed PD, and did not regress, ANY growth |
| New Lesions | New lesions of ANY size appear for the first time, or additional new lesions appear<br>If new lesions had previously appeared, and are still present, ANY growth<br>Target NL: NL iSoD increases ≥ 5 mm<br>NT NL: visible growth<br>Note: track nadir for target NL iSoD and total # of new lesions |

Abbreviations: TL = target lesion; NL = new lesion; NT NL = non-target new lesion; iCPD = immune confirmed progressive disease; iUPD = immune unconfirmed progressive disease; SoD = sum of diameters for all target lesions; iSoD = immune sum of diameters for new lesion target
Source: (Seymour et al. 2017)

## Appendix E: Statistical Consideration for Defining Date of iRECIST PD

- iUPD subsequently confirmed: The date used is the first UPD date.
- iUPD never confirmed:
  - If a subsequent iSD, iPR or iCR is seen, the initial iUPD is ignored
  - Otherwise, iUPD date is used

Abbreviations: iCR = immune confirmed response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; UPD = unconfirmed progressive disease

## Appendix F: Summary of Changes from Version 2.0 to 3.0

The protocol was revised to introduce a Maintenance Phase to allow any subject still receiving study drug to continue to receive BDC-1001. Other administrative changes, clarification, and formatting changes were made throughout the protocol.

| Protocol Version | Summary of Changes |
|---|---|
| 3.0 | Incorporate a Maintenance Phase to allow any subject(s) still receiving study treatment to continue on the study:<br>• Synopsis, Table 2 (Overview of Schedule of Assessments – Maintenance Phase – Q2W Dosing), Sections 3.1, 3.1.3, 4.3, 6, 6.15.1, 6.16, 6.23, 7.2, 7.2.4, 7.3, 7.4, 7.5, 8.4.5.1, 8.4.6, 8.4.7, and 9.2.2 |
| | Update records retention requirements to comply with health authorities:<br>• Section 9.2.6 |
| | Other administrative changes, clarification, and formatting changes were made throughout the protocol. |

Document Approvals
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