Title Page

Protocol Title:

A Phase 3, Randomized, Multi-center, Open-label Study of DB-1303 Versus Investigator's Choice Chemotherapy in Human Epidermal Growth Factor Receptor 2 (HER2)-low, Hormone Receptor Positive (HR+) Metastatic Breast Cancer Patients whose Disease has Progressed on Endocrine Therapy (ET) (DYNASTY-Breast02)

Brief Title:

A Phase 3 Study of DB-1303 vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer

Acronym: DYNASTY-Breast02

Protocol Number: DB-1303-O-3002

Amendment Number: Protocol Amendment 2

Drug Development Phase: Phase 3

Investigational Product: DB-1303

Study Treatments: DB-1303, capecitabine, paclitaxel and nab-paclitaxel.

Indication: HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer

Sponsor Name: DUALITYBIO INC. **(Duality)**

Sponsor Address: 3524 Silverside Road Suite 35B, Wilmington, DE, 19810-4929, U.S.A.

IND Number(s): 158143

EU Trial No: 2023-507333-17

Approval Date: 14 Sep 2023

Sponsor Signatory:

Xiusong Qiu	DocuSigned by: Xiusong Qiu BC54767227BC4E0...	2023/9/15

Confidentiality Statement

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Investigator Protocol Agreement Page

I have read the Clinical Study Protocol (Protocol Number: DB-1303-O-3002, Version 3.0, Version Date: 14 Sep 2023).

I confirm agreement to conduct the study in compliance with the protocol. I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise this study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Affiliate: _____

Affiliate Telephone Number: _____

Principal Investigator Name (print): _____

Principal Investigator Name (signature): _____

Principal Investigator Title: _____

Date: _____

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1.1 Synopsis

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Phase 3</td><td>Therapeutic Area/Indication under Investigation:
Oncology, HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer</td></tr>
<tr><td>Trial Design:
Randomized, multi-center, open-label.</td><td>Sample Size Planned:
Approximately 532 subjects will be enrolled.</td></tr>
<tr><td colspan="2">Study implementation</td></tr>
<tr><td>Study Centers and Location:
Approximately 230 centers, including but not limited to, China, United States, Germany, Hungary, United Kingdom, Australia, South Korea, and Turkey.</td><td>Estimated Study Duration:
Enrolment is planned to occur over approximately 20 months. For each subject there will be a 35-day (+7 days) follow-up visit after the last study treatment administration, followed by long-term/survival follow-up visits every 3 months (±14 days) until death, withdrawal of consent, or study closure, whichever occurs first.</td></tr>
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<tr><td colspan="2">Primary Objectives:
To assess the efficacy of DB-1303 compared with investigator’s choice chemotherapy in terms of a hazard ratio (HR) for progression-free survival (PFS) assessed by blinded independent central review (BICR) in the HR+, HER2-low (IHC 2+/ISH- and IHC 1+) population. The intercurrent event of initiation of subsequent anti-cancer therapy will follow a hypothetical</td></tr>
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strategy, and discontinuation of study treatment will follow a treatment policy strategy.

Key Secondary Objectives:

- To assess the efficacy of DB-1303 followed by any other subsequent anti-cancer therapy compared with investigator's choice chemotherapy followed by any other subsequent anti-cancer therapy in terms of a HR for overall survival (OS) in the HR+, HER2-low (IHC 2+/ISH- and IHC 1+) population. Handling of intercurrent events will follow a treatment policy strategy. .

Other Secondary Objectives:

- To further assess the efficacy of DB-1303 compared with investigator's choice chemotherapy in terms of PFS by Investigator assessment, objective response rate (ORR), and duration of response (DoR) by BICR and Investigator assessment in the HR+, HER2-low population.
- To assess the safety and tolerability profile of DB-1303 compared with investigator's choice chemotherapy.
- To assess symptoms, functioning and health-related quality of life (HRQoL) in subjects treated with DB-1303 compared with investigator's choice single agent chemotherapy.
- To assess the impact of treatment and disease state on health utility using the EQ-5D-5L.

Exploratory Objectives:

- To assess the pharmacokinetics (PK) of DB-1303 (DB-1303 antibody-drug conjugate [ADC] and free payload P1003).
- To investigate the immunogenicity of DB-1303.
- To compare the effect of DB-1303 with investigator's choice chemotherapy in terms of disease control rate (DCR), and time to response (TTR) by BICR and Investigator assessment, time to second progression or death (PFS2) according to Investigator assessment, time to first subsequent treatment or death (TFST) and time to second subsequent treatment or death (TSST) in the HR+, HER2-low population.
- To define biological responses to DB-1303 and to investigate predictive markers of response, acquired resistance and other markers that may correlate with likelihood of clinical benefit or tolerability.
- To assess patient-reported treatment tolerability.
- To explore the population PK of DB-1303.
- To explore the efficacy and safety Exposure- Response (ER) correlation.

Study Endpoint

Primary Endpoint:

- PFS by BICR according to response evaluation criteria in solid tumors (RECIST) 1.1 in the HR+, HER2-low population.

Key Secondary Endpoints:

- OS in the HR+, HER2-low population.

Other Secondary Endpoints:

- ORR and DoR by BICR and Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population
- PFS by Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population
- TEAEs and SAEs per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, physical examinations, changes from baseline in laboratory findings, electrocardiograms (ECGs), ECHO/MUGA and vital signs.
- The patient reported outcomes (PROs) include: change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores, time to deterioration in EORTC QLQ-C30 scores
- EQ-5D-5L health state utility index

Exploratory Endpoints:

- PK parameters (peak observed concentration [C_{max}], time to C_{max} [T_{max}], etc.) of DB-1303 ADC and free payload P1003.
- ADA prevalence: the proportion of subjects who are ADA positive at any point in time (at baseline and post-baseline). ADA incidence: the proportion of subjects having treatment-emergent ADA.
- DCR, TTR, PFS2, TFST, TSST in the HR+, HER2-low population
- Biomarkers of DB-1303 sensitivity/resistance
    - Protein expression (IHC analysis HER2)
    - Blood analysis for ctDNA at pre-treatment and EOT
- Patient-reported treatment tolerability (PRO-CTCAE)
- To explore the population PK of DB-1303 ADC and released payload.
- To explore the efficacy and safety exposure- response (ER) correlation with DB-1303 ADC and released payload.

Study Design:

The study is an open-label, multi-center, randomized study in HR+, HER2-low breast cancer subjects whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6 inhibitor in the metastatic setting. The primary purpose of the study is to determine the efficacy and safety of DB-1303 compared with investigator's choice single agent chemotherapy in the target population.

Approximately 532 subjects with HER2-low (IHC 2+/ISH and IHC 1+) expression will be randomized 1:1 across approximately 230 centers globally to receive either DB-1303 or

investigator's choice single agent chemotherapy (capecitabine, paclitaxel or nab-paclitaxel) until RECIST 1.1 defined disease progression (PD), unless there is unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. The details of study treatment and their schedules are provided below.

Study Treatments and Duration

Compound	Dose	Route	Schedule
DB-1303	8 mg/kg	IV	Every 3 weeks
Capecitabine	1000 or 1250 mg/m^2	Oral	Twice daily orally for 2 weeks followed by a 1-week rest period in 3-week cycles
Paclitaxel	80 mg/m^2	IV	Every week (QW) in 3-week cycles
Nab-paclitaxel [a]	100 mg/m^2	IV	Every week (QW) for 3 weeks followed by a one-week rest period in 4-week cycles

IV = intravenous; QW = every week

[a] Although nab-paclitaxel is given in 4-week cycles, the schedule of activities(SoA) must be followed; e.g., tumor assessment scans every 6 weeks [Q6W ± 1 week]).

Tumor evaluation scans will be performed at screening (as baseline) with follow ups every 6 weeks (Q6W ± 1 week) from the date of randomization for 48 weeks, and then every 9 weeks (Q9W ± 1 week, starting at Week 48) thereafter until objective (RECIST 1.1 defined) disease progression.

The study will compare PFS, OS and other measures of efficacy between the study treatment groups and further characterize the safety and tolerability profile of DB-1303.

Duration of Treatment:

Unless specific treatment discontinuation criteria are met or the subject withdraws consent, all subjects will continue receiving treatment until RECIST 1.1 defined disease progression. For subjects randomized to the investigator's choice single agent chemotherapy arm, crossover to DB-1303 will not be permitted.

Follow-up of Subjects post Discontinuation of Study Treatment:

After discontinuation of study treatment, all subjects will have post treatment follow up scheduled at 35 days (+7 days) after their last dose of study treatment. Subjects who have discontinued treatment for reasons other than progressive disease will also be followed up with tumor assessments until radiological progression (or death). All subjects will be followed up for PFS2 and survival status, unless consent was withdrawn.

Survival:

All subjects randomized should be followed up for survival unless consent was withdrawn. Long-term/survival follow-up visits will be performed every 3 months (±14 days) from the date of the 35-day (+7 days) follow-up visit until death, withdrawal of consent, or study

closure, whichever occurs first.

Data Monitoring Committees:

The safety of all Duality Biologics clinical studies is closely monitored on an ongoing basis by Duality Biologics Safety. An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 subjects have been randomized, whichever occurs later. The IDMC will review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter, or more frequently if indicated or requested by the Medical Monitor based on available safety data, and at each meeting make recommendations to continue, amend, or stop the study based on safety findings. In addition, the IDMC will be asked to review efficacy data at pre-specified timepoints. An interstitial lung disease (ILD) Adjudication Committee will review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the clinical database and other sources, including imaging data, may be provided to the adjudication committee to fully characterize medical history (e.g., smoking, radiation, and pulmonary history), diagnostic evaluation, treatment, and outcome of the event. Further details can be found in the ILD Adjudication Charter.

Study Completion

The end of the study hypothesis-testing period is defined as the date when approximately 337 OS events have been observed. The study closure is defined as the date when the last subject discontinues study treatment and applicable follow-up occurs, or the study is ended by the Sponsor.

Study Population:

Subjects must meet all of the eligibility criteria to be enrolled in the study.

Inclusion Criteria

1. Male or female adults (defined as ≥ 18 years of age or acceptable age according to local regulations at the time of voluntarily signing of informed consent).
2. Pathologically documented breast cancer that:
   1) Is advanced or metastatic
   2) Has HER2low expression (IHC 1+ or IHC 2+/ISH-) as determined- by the central laboratory result from the most recently collected pre-randomization tumor sample (see inclusion criterion 3).
   3) Was never previously reported as HER2-positive (IHC 3+ or ISH+) as per ASCO/CAP guidelines.
   4) Is documented as HR+ (either ER and/or PgR positive [ER or PgR ≥1%]) per ASCO/CAP guidelines (Allison et al 2020). If a subject has had multiple ER/PgR results after metastatic disease, the most recent test result will be used to confirm

eligibility.

3. Must have an adequate tumor tissue sample available for assessment of HER2 by central laboratory, preferably in formalin fixation and paraffin embedding (FFPE) blocks based on a mandatory FFPE tumor sample obtained at the time of metastatic disease or later; the most recently collected pre-randomization tumor sample that meets the tissue requirements specified in protocol Section 8.6 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. (See Section 8.6 and the laboratory manual for additional details).
4. ECOG performance status of 0 or 1
5. Must have had either:
   1) Disease progression on endocrine therapy + CDK4/6 inhibitor within 6 months of starting first line treatment for metastatic disease and considered appropriate for chemotherapy as the next treatment by the investigator, OR
   2) Disease progression on at least 2 previous lines of ET with or without a targeted therapy (such as CDK4/6, mTOR or PI3-K inhibitors) administered for the treatment of metastatic disease.

   Of note with regards to the ≥2 lines of previous ET requirement:

   - Single agent anti-CDK4/6 therapy for the treatment of metastatic disease is considered a line of therapy
   - Disease progression on adjuvant ET or progression within 12 months of stopping ET can be treated as one prior line ET; these subjects will only require 1 additional line of ET in the metastatic setting
   - Any progression >12 months after discontinuing adjuvant ET or completing a course of adjuvant ET will not be considered a line of therapy
   - Single agent PARP inhibitor therapy is not considered a line of ET
   - Changes in dosing schedules, or discontinuations/re-starting of the same drugs or the addition of a targeted therapy to an ET without progression (e.g., adding a CDK4/6 to a current aromatase inhibitor regimen) will not be considered separate lines of therapy.
6. No prior chemotherapy for advanced or metastatic breast cancer. Subjects who have received chemotherapy in the neo-adjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval (defined as completion of systemic chemotherapy to diagnosis of advanced or metastatic disease) of >12 months.
7. Life expectancy ≥12 weeks at screening.
8. Subjects must have at least one measurable lesion as defined per RECIST v1.1 or have non-measurable, bone-only disease that can be assessed by CT or MRI or X-Ray. Lytic or mixed lytic bone lesions that can be assessed by CT or MRI or X-Ray in the absence of measurable disease as defined above is acceptable; subjects with sclerotic/osteoblastic

bone lesions only in the absence of measurable disease are not eligible.

9. Has LVEF ≥ 50% by either echocardiography (ECHO) or multiple-gated acquisition (MUGA) within 28 days before randomization.
10. Adequate organ and bone marrow function within 14 days before randomization. For all parameters listed below, the most recent results available must be used to meet the inclusion criteria:

Item	Laboratory value
Hematology (without receiving erythropoietin [EPO], granulocyte colony-stimulating factor [G-CSF], or granulocyte-macrophage colony stimulating factor [GM-CSF] within 14 days and blood, red blood cell (RBC), platelet transfusion within 7 days prior to the sampling)	
Platelet count	≥ 100,000/mm^3
Hemoglobin (Hb)	≥ 9.0 g/dL
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Chemistry	
Creatinine	Creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault equation, see Section 11.6.2)
AST and ALT	≤ 3 × ULN (if liver metastases are present, < 5 × ULN)
Total bilirubin	≤1.5 × ULN if no liver metastases or <3 × ULN in the presence of Gilbert's syndrome or liver metastases at baseline
Serum albumin	≥ 2.5 g/dL
Coagulation	
INR/PT and either partial thromboplastin or activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

11. Has adequate treatment washout period before randomization, defined as table below.

Previous treatment	Washout period
Hormonal therapy	≥ 3 weeks
Immunotherapy (non-antibody-based therapy)	≥ 3 weeks
Small molecule targeted agents	≥ 2 weeks or 5 half-lives, whichever is longer
Antibody-based anti-cancer therapy	≥ 4 weeks with the exception of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g., denosumab for the treatment of complications resulting from bone metastases)
Chloroquine/Hydroxychloroquine	≥ 3 months

Traditional Chinese Medicine with anti-tumor activity	≥ 2 weeks
Major surgery	≥ 4 weeks (or 2 weeks for low-invasive cases [e.g., colostomy]), excluding operations or surgeries that can be recovered within 14 days prior to randomization, and have been recovered by the investigator's assessment, e.g., tumor biopsy, puncture, palliative operation, rectal/gastrostomy, etc.
Radiation therapy	≥ 4 weeks (radiation therapy including palliative radiation therapy to chest). ≥2 weeks (palliative radiation therapy to other areas).
CAR-T	≥2 weeks

12. Evidence of post-menopausal status (Section 11.4.1) or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner. For women of childbearing potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine beta-human chorionic gonadotropin (β-HCG) pregnancy test prior to each administration of study treatment.

    Women of childbearing potential are defined as those who are not surgically sterile (i.e., underwent bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

13. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Section 11.4.2) from the time of screening and must agree to continue using such precautions for 7 months after the last dose of study treatment. Not all methods of contraception are highly effective. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject for the duration of the study treatment and the drug washout period (7 months). Periodic abstinence (e.g., calendar ovulation, symptothermal, post ovulation methods), the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects must not donate ova, or retrieve for their own use, from the time of screening and throughout the study treatment period, and for at least 7 months after the last dose of study treatment. They should refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to randomization in this study.
14. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening and throughout the duration of the study treatment and the washout period (4 months after the last dose of DB-1303, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine). Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject for the duration of the study treatment and

the drug washout period. Periodic abstinence (e.g., calendar ovulation, symptothermal, post ovulation methods), the rhythm method, and the withdrawal method are not acceptable methods of contraception. It is strongly recommended for the female partners of a male subject also use at least one highly effective method of contraception throughout this period, as described Section 11.4.2. In addition, male subjects should refrain from fathering a child or donating sperm throughout the duration of the study and the washout period (4 months after the last dose of DB-1303, 6 months after the last dose of paclitaxel or nab paclitaxel, and 3 months after the last dose of capecitabine). Preservation of sperm should be considered prior to randomization in this study.

Exclusion Criteria

1. Ineligible for all options in the investigator's choice chemotherapy arm. Subjects with contraindications to capecitabine, paclitaxel, and nab-paclitaxel treatment, per local prescribing information, cannot be enrolled to the study.
2. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, uncontrolled or significant cardiovascular disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to give written informed consent.
3. Clinically uncontrolled pleural effusion, ascites or pericardial effusion requiring drainage, peritoneal shunt or cell-free concentrated ascites reinfusion therapy within 2 weeks prior to the randomization.
4. Uncontrolled or significant cardiovascular disease includes any of the following:
    1) Subjects with a medical history of myocardial infarction within 6 months before randomization or symptomatic CHF (NYHA Class II to IV). Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any myocardial infarction related symptoms, should have a cardiologic consultation before randomization to rule out myocardial infarction.
    2) Uncontrolled hypertension (defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg)
    3) Uncontrolled and/or clinically important cardiac arrhythmias
    4) Corrected QT interval by Fredericia's method (QTcF) prolongation to >470 ms (both females and males) based on average of screening triplicate 12-lead electrocardiogram (ECG)
5. Has as a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
6. Subjects with prior use of immunosuppressive medication within 14 days prior to first study dose, except for intranasal and inhaled corticosteroids or systemic corticosteroids at

doses less than 10 mg/day of prednisone or equivalent.

7. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within three months prior to study randomization, severe asthma, severe chronic obstructive pulmonary disorder [COPD], restrictive lung disease, significant pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e., rheumatoid arthritis, Sjogren's syndrome, sarcoidosis etc.), and/or prior pneumonectomy (complete).
8. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals
9. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study randomization.
10. Active primary immunodeficiency, known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjects should be tested for HIV prior to randomization if required by local regulations or by the institutional review board (IRB)/independent ethics committee (IEC).

    Notes:

    1) Inactive hepatitis B surface antigen (HBsAg) carriers, treated and with stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Subjects with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Subjects receiving antivirals at screening should have been treated for > 2 weeks before randomization.
    2) Subjects with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for subjects testing positive for HCV antibody. Subjects receiving antivirals at screening should have been treated for > 2 weeks before randomization.
11. Receipt of live, attenuated vaccine (mRNA and replication-deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first dose of study treatment. Note: Subjects, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of study treatment.
12. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline.

    Note: Subjects may be enrolled with chronic, stable Grade 2 toxicities (defined as no

worsening to ≥Grade 2 for at least 3 months prior to randomization and managed with standard of care treatment) that the investigator deems related to previous anticancer therapy, such as:

1) Chemotherapy-induced neuropathy
2) Fatigue
3) Residual toxicities from prior immune-oncology treatment: Grade 1 or Grade 2 endocrinopathies which may include:

- Hypothyroidism/hyperthyroidism
- Type 1 diabetes
- Hyperglycemia
- Adrenal insufficiency
- Adrenalitis
- Skin hypopigmentation (vitiligo)

13. Pregnant or breastfeeding female subjects, or subjects who are planning to become pregnant.
14. Subjects with a known hypersensitivity to either the drug substances, inactive ingredients in the drug product or to other monoclonal antibodies
15. History of another primary malignancy within 3 years, except adequately resected non melanoma skin cancer, curatively treated in situ disease, other solid tumors curatively treated, or contralateral breast cancer.
16. Previous treatment with anti-HER2 therapy.
17. Prior treatment with antibody-drug conjugate that comprised an exatecan derivative that is a topoisomerase I inhibitor.
18. Prior randomization or treatment in a previous DB-1303 study regardless of treatment assignment.
19. Participation in another clinical study with a study treatment administered in the last 30 days or if the washout period is less than five half-lives prior to first dose of study treatment or concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow up period of an interventional study. Of note, tissue screening for this study while a subject is on treatment in another clinical study is acceptable.
20. Has substance abuse or any other medical conditions such as psychological conditions, that may, in the opinion of the Investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.

Route of Administration, Dosage Form and Doses:

DB-1303 is given as intravenous infusion at 8 mg/kg under a 21-day treatment cycle.

On Day 1 of Cycle 1, subjects will receive DB-1303 no less than 90-minute IV infusion. If the first infusion is well tolerated, the following infusion may be administered at least 30 minutes. The subject's weight at screening will be used to calculate the initial dose. If, during the course of treatment, the subject's weight has changed by ≥ ± 10%, the subject's dose will be recalculated based on the subject's updated weight. However, sites can modify the dosage if the weight changes after screening and if the site's local practice is more conservative than the 10% threshold for dose adjustment (e.g., dose adjustment if 5% variance in the subject's weight).

For the administration of paclitaxel, nab-paclitaxel, and capecitabine, see Table 5 and the respective local prescribing information.

Analysis and Statistic Considerations:

Sample Size Determination:

The study provides adequate power to show a statistically significant between-treatment difference in PFS. Based on a 2-sided significance level of 5%, a total of 262 PFS events will provide approximately 90% power to detect a hazard ratio of 0.67 (increase in median PFS from 6 to 9 months), assuming an exponential distribution for both treatment groups.

If PFS is significant, the study also provides sufficient power to demonstrate a statistically significant difference in OS. Based on a 2-sided alpha of 5% and taking into account two interim OS analyses, a total of 337 OS events will be required to achieve 80% power to detect a hazard ratio of 0.72 (increase in median OS from 20 to 27.8 months), assuming an exponential distribution for both treatment groups.

Assuming dropout rate of 20% for PFS and 10% for OS, an enrollment duration of 20 months, and the final analysis of PFS and OS occur at approximately 22 and 51 months, respectively, approximately 532 subjects will need to be randomized.

Efficacy Analyses:

The primary endpoint of the study is PFS by BICR according to RECIST 1.1. PFS is defined as the time from the date of randomization until the date of disease progression, as defined by RECIST 1.1, or death (by any cause in the absence of progression), whichever comes first. The key secondary efficacy endpoint is OS. The null hypothesis for the primary and key secondary efficacy endpoints (PFS and OS) is that there is no difference in PFS/OS distribution between DB-1303 and the investigator's choice chemotherapy. Other secondary efficacy endpoints include PFS by Investigator assessment according to RECIST 1.1 and ORR and DoR by BICR and Investigator assessment according to RECIST 1.1.

The ITT population comprises all subjects randomized. The ITT population will be used for all efficacy endpoints and will be analyzed according to randomized treatment regardless of the treatment received (ITT principle).

PFS will be tested once, when PFS reaches approximately 262events in the ITT population. This is estimated to occur approximately 22 months after the first subject is randomized (2

months after randomization is completed) assuming a non-uniform accrual of subjects with a duration of 20 months including 6 months of ramp up period.

OS will be tested at two interim and one final analyses as described below:

1. The first interim OS analysis will be performed at the time of the final PFS analysis. It is expected that 135OS events (40% information fraction) will have been observed.
2. The second interim OS analysis will occur when approximately 226 OS events have been observed (67% information fraction). This is anticipated to occur approximately 32 months after the first subject is randomized.
3. The final OS analysis will be performed when approximately 337 OS events have been observed, which is expected to occur approximately 51 months after the first subject is randomized.

To strongly control the family wise error rate at 5% (2-sided) in terms of the primary and key secondary endpoints, a multiple testing procedure (MTP) with the following gatekeeping strategy will be employed:

Step 1: Test PFS at a 5% alpha level. If significance is achieved, go to Step 2.

Step 2: Test OS at the 5% alpha level.

For the OS hypothesis, the alpha allocated will be distributed between the two interim and final analyses using the Lan DeMets spending function that approximates the O'Brien Fleming alpha-spending approach (Lan and DeMets 1983). Under this procedure, the adjusted significance levels at the interim and final analyses are determined by the information fraction available at the time of analysis (i.e., actual number of events observed at interim / planned number of OS events at the final analysis) and the correlation computed from the actual number of events from each analysis, giving greater weight to analyses performed at the end of the study than those performed earlier. If the study continues to final analysis, all remaining alpha will be spent at the final analysis, and the nominal significance level will be adjusted by the actual number of events.

For the primary endpoint, PFS distribution will be compared between DB-1303 and investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-), and prior taxane use in the non-metastatic setting (yes vs no). The stratification variables in the statistical modelling will be based on the values entered in interactive response technology (IRT). If there are insufficient events per stratum, the strata will be pooled following a pooling strategy that will be prespecified in the statistical analysis plan (SAP). The hazard ratio and its confidence interval (CI) will be estimated from a stratified Cox Proportional Hazards model with strata being the same as the stratification variables from IRT.

Safety Analyses:

Safety summaries will be provided using the safety analysis set (SAS). The SAS will include all subjects who received at least 1 dose of study treatment. Safety data will be presented using

descriptive statistics unless otherwise specified. Safety data will be summarized according to the treatment received. Data from all cycles of treatment will be combined in the presentation of safety data. AEs including serious adverse events (SAEs), AEs leading to death, AEs leading to discontinuation, AEs leading to dose reductions, and adverse events of special interest (AESIs) will be listed individually by subject using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and NCI-CTCAE v5.0. The number of subjects experiencing each AE will be summarized by treatment arm and CTCAE Grade. Other safety summaries will be outlined in the SAP.

Pharmacokinetics Analyses:

The PK analyses will be performed on the PK Analysis Set using actual sample times and noncompartmental analysis method. Blood concentration-time data for DB-1303 ADC and free payload P1003 will be listed and summarized using descriptive statistics by study cycle at each nominal collection time. Applicable plots will illustrate the appropriate data. PK parameters will be estimated. The PK parameters of DB-1303 ADC, and free payload P1003 (including C_{max} and T_{max}) will be listed and summarized using descriptive statistics. Descriptive statistics will be provided for the PK parameters for each analyte as appropriate.

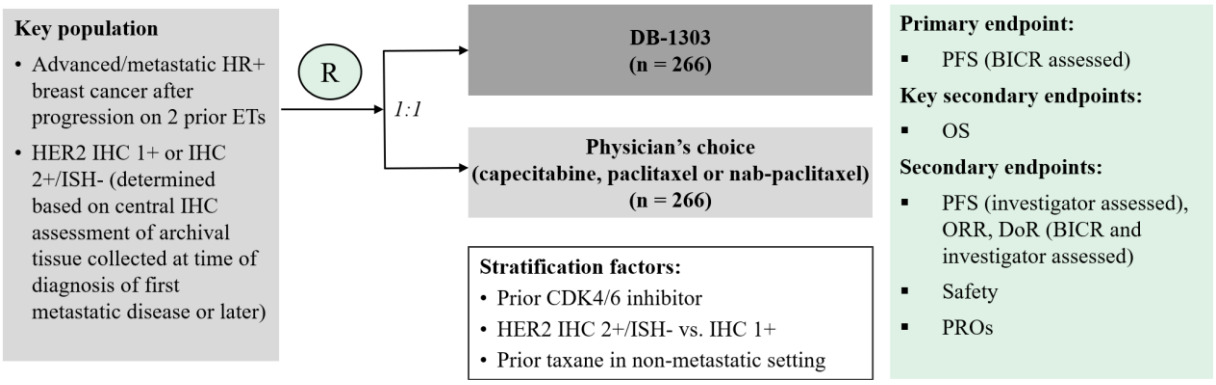
Anti-Drug Antibody Analyses:

The ADA prevalence and incidence will be summarized by frequency and percentage of subjects.

ADA prevalence, which is the percentage of subjects who were ADA positive at any time point (baseline or post-baseline), will be summarized. The ADA incidence will also be reported, which is the proportion of subjects having treatment-emergent ADA during the study period. Treatment-emergent ADA includes subjects who were ADA negative at baseline and became ADA positive post-baseline (treatment-induced ADA), subjects who were ADA positive at baseline and post-baseline but had an increase in ADA titer of defined threshold from baseline to post-baseline (treatment -boosted ADA), and subjects who had missing ADA data at baseline and were positive post-baseline.

1.2 Study Schema

The study design is summarized in figure below.



ADA = anti-drug antibody; BICR = blinded independent central review; CDK = cyclin-dependent kinase; DoR = duration of response; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IHC = immunohistochemistry; ISH = in situ hybridization; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PROs = patient reported outcomes; R = randomization.

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities

Study Period	Tissue Screening	SCN	Cycle 1 (21 days)			Cycle 2 and subsequent cycles (21 days per cycle)	EOT Visit	Safety FU [29]	Long Term FU or EOS [30]	For details see CSP Section
Visit Time (Days)		**(Day -28 to -1)**	**C1D1[2]**	**C1D8 ±1 day**	**C1D15 ±1 day**	**CXD1±3 days**	**within 7 days of EOT [28]**	**35 days after last dose +7 days**	**Every 3 months ±14 days**	
Informed Consent										
Tissue screening consent [1]	X									9.1
Main informed consent [2]		X								9.2
Procedures and Assessments										
Eligibility [3]		X								5
Randomization [3]			X							6.3
Demographics and medical history [4]		X								9.2
Full physical examination		X								8.2.2
Targeted physical examination [5]			X			X	X	X		8.2.2
Height		X								8.2.2
Weight [6]		X	X			X	X	X		6.2.1

Study Period	**Tissue Screening**	**SCN**	**Cycle 1 (21 days)**			**Cycle 2 and subsequent cycles (21 days per cycle)**	**EOT Visit**	**Safety FU [29]**	**Long Term FU or EOS [30]**	**For details see CSP Section**
Visit Time (Days)		**(Day -28 to -1)**	**C1D1[2]**	**C1D8 ±1 day**	**C1D15 ±1 day**	**CXD1±3 days**	**within 7 days of EOT [28]**	**35 days after last dose +7 days**	**Every 3 months ±14 days**	
ECOG PS [7]		X	X			X	X	X		8.2.8
Vital sign [8]		X	X	X	X	X	X	X		8.2.3
SpO_2 [9]		X	X			X	X			8.2.6
HRCT chest [10]		X				X				8.2.6, 8.2.10.1
Pulmonary function test [11]		X								8.2.6, 8.2.10.1
ECHO/MUGA (LVEF) [12]		X				X	X			8.2.7
12-lead ECG [13]		X	X			X	X			8.2.4, 11.6.3
Ophthalmologic assessment [14]		X					X			8.2.9
Adverse events [15]	X	X	X	X	X	X	X	X	X	8.3, 11.3
Concomitant medication	X	X	X	X	X	X	X	X		6.5
Survival status									X	8.1.2
PFS2								X	X	8.1.3
Subsequent cancer therapy following EOT								X	X	8.1.2, 8.1.3

Study Period	Tissue Screening	SCN	Cycle 1 (21 days)			Cycle 2 and subsequent cycles (21 days per cycle)	EOT Visit	Safety FU [29]	Long Term FU or EOS [30]	For details see CSP Section
Visit Time (Days)		**(Day -28 to -1)**	**C1D1[2]**	**C1D8 ±1 day**	**C1D15 ±1 day**	**CXD1±3 days**	**within 7 days of EOT [28]**	**35 days after last dose +7 days**	**Every 3 months ±14 days**	
Laboratory Procedures/Assessments										
Tumor sample (for HER2 status) [16]	X									8.6
Viral infection laboratory testing [17]		X								8.2.5, 11.2
Pregnancy testing [18]		X	X			X	X			8.3.15, 11.4
Safety laboratory test [19]		X	X	X	X	X	X	X		8.2.5, 11.2
Troponin [20]		X					X			8.2.7
PK sampling [21]			X			X	X	X		8.5.1, Table 2
ADA sampling [22]			X			X	X	X	X	8.5.2, Table 2
Biomarker sampling [23]			X				X			8.6
Study Intervention Administration										
DB-1303 Dosing [24]			Day 1 of each cycle							6.1.2, 6.2.1

Study Period	**Tissue Screening**	**SCN**	**Cycle 1 (21 days)**			**Cycle 2 and subsequent cycles (21 days per cycle)**	**EOT Visit**	**Safety FU [29]**	**Long Term FU or EOS [30]**	**For details see CSP Section**
Visit Time (Days)		**(Day -28 to -1)**	**C1D1[2]**	**C1D8 ±1 day**	**C1D15 ±1 day**	**CXD1±3 days**	**within 7 days of EOT [28]**	**35 days after last dose +7 days**	**Every 3 months ±14 days**	
Capecitabine			Administered twice daily orally for 2 weeks, followed by a 1-week rest period in 3-week cycles							6.1.1, 6.2.2
Paclitaxel			Administered intravenously every week in a 3-week cycles							6.1.1, 6.2.2
Nab-paclitaxel			Administered intravenously every week for 3 weeks, followed by a 1-week rest period in 4-week cycles							6.1.1, 6.2.2
Tumor Assessment										
Tumor assessment [25]		X	Every 6 weeks (±7 days) for the first 48 weeks; Every 9 weeks (±7 days) thereafter until the start of new systemic anticancer therapy, disease progression, lost to follow-up, withdrawal of consent, or death, whichever occurs first.							7.1.2, 8.1.1
Patient-reported Outcomes Assessments										
Allocate ePRO device [26]			X							8.1.4.5
ePRO subject training [27]			X							8.1.4.5
EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L, PRO-CTCAE			EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L: · Before administration on Cycle 1 Day 1 (up to -3 days); · Q3W (±3 days) relative to Cycle 1 Day 1 dosing until PFS2 regardless of delays in dosing;							8.1.4

Study Period	Tissue Screening	SCN	Cycle 1 (21 days)			Cycle 2 and subsequent cycles (21 days per cycle)	EOT Visit	Safety FU [29]	Long Term FU or EOS [30]	For details see CSP Section
Visit Time (Days)		**(Day -28 to -1)**	**C1D1[2]**	**C1D8 ±1 day**	**C1D15 ±1 day**	**CXD1±3 days**	**within 7 days of EOT [28]**	**35 days after last dose +7 days**	**Every 3 months ±14 days**	
			• At EOT visit unless already completed the same day; if discontinued treatment for reasons other than disease progression, also at disease progression visit unless already completed the same day. PRO-CTCAE: As above except assessments will stop at EOT rather than continue to PFS2							

ADA=anti-drug antibody; **AE**=adverse event; **AESI**=adverse event of special interest; **β-HCG**=β-human chorionic gonadotropin; **C1D1**=Day 1 of Cycle 1; **CSP**=Clinical Study Protocol**; ECG**=electrocardiogram; **ECHO/MUGA**=echocardiography or multiple-gated acquisition; **ECOG PS** =Eastern Cooperative Oncology Group performance status; **EORTC**= European Organization for Research and Treatment of Cancer; **EOS**=end of study; **EOT**=end of treatment; **ePRO**=electronic patient-reported outcome; **EQ-5D-5L**= EuroQoL 5-dimension, 5-level health state utility index; **FU**=follow-up; **HBsAg**=hepatitis B surface antigen; **HBV**=hepatitis B virus; **HCV**=hepatitis C virus; **HER2**=human epidermal growth factor receptor 2; **HIV**=human immunodeficiency virus; **HRCT**=high resolution CT of the chest; **IV**=intravenous; **LVEF**=left ventricular ejection fraction; **PFS2**=time to second progression or death; **PK**=pharmacokinetics; **PRO-CTACE**= patient-reported outcomes version of the common terminology criteria for adverse events; **Q3W**=every 3 weeks; **QLQ-C30**=30-item core quality of life questionnaire**; QLQ-BR45=**breast cancer-specific module**; QTcF**=Fredericia's formula-QT corrected interval; **SAE**=serious adverse event; **SCN**=screening visit.

SoA Notes:

1. **Tissue screening consent:** tissue screening informed consent must be signed before tumor tissue screening assessments.
2. **Main informed consent:** the main informed consent form must be signed before initiating all other screening assessments. If a procedure was completed as standard of care within 28 days of dosing prior to consent, this is permitted and does not need to be repeated. If the procedures to be repeated in C1D1 are performed within 7 days (3 days for safety laboratories) before C1D1 and the subject's condition has not changed, there is no need to repeat at C1D1, unless a specific procedure requires a narrower time window.
3. Every effort should be made to minimize the time between randomization and starting treatment (i.e., no more than 3 days from the date of randomization).
4. **Demographics:** demography information includes date of birth (or age), sex, and race/ethnicity. **Medical history** will include a directed series of questions.

5. **Targeted physical examination:** On Day 1 of each Cycle, targeted physical examination should be evaluated before infusion starting. Additional assessments may be performed when clinically indicated.
6. **Weight:** Initial infusion dose for each subject will be calculated based on the subject's weight at screening. If the subject's weight has changed by ≥ ± 10%, the subject's dose will be recalculated based on the subject's updated weight.
7. **ECOG PS**: ECOG PS for screening visit should be performed within 7 days prior to C1D1, details about the grade refer to Section 8.2.8.
8. **Vital sign:** include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions.
9. **SpO_2:** on SCN, C1D1, and D1 of subsequent cycles, SpO_2 should be evaluated within 3 days before DB-1303 infusion. If the SpO_2 of SCN is performed within 3 days before C1D1 and the subject's condition has not changed, there is no need to repeat the SpO_2 of C1D1.
10. **HRCT chest:** on SCN and C4D1. A non-contrast HRCT scan of the chest is preferred if feasible, otherwise a non-contrast CT is acceptable. The HRCT/CT chest scan will be performed for all subjects, in addition to standard CT/MRI scans of chest/abdomen/pelvis for tumor assessments. If both an HRCT/CT of the chest for assessment of ILD/pneumonitis and a diagnostic IV contrast enhanced chest CT scan for tumor response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT/CT should be performed first. HRCT scans are acquired on study as and when ILD/pneumonitis is suspected/as clinically indicated.
11. **Pulmonary function test:** PFT at a minimum should include spirometry (minimum requirement of: FVC [L], FVC % predicted, FEV1 [L], FEV1 % predicted, FEV1/FVC %). DLCO will be performed (when feasible), but for subjects with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement.
12. **ECHO/MUGA (LVEF):** perform either ECHO or MUGA to measure LVEF. This test will be performed at SCN, every 4 cycles starting with Cycle 5 (i.e., Cycle 5, 9, 13…) and the EOT visit.
13. **12-lead ECG:** at screening, ECGs will be obtained in triplicate. Subsequent ECGs will be performed in triplicate only if an abnormality is noted. When performed in triplicate, 3 individual ECG tracings should be obtained in succession within 10 minutes after being in a supine/semi-recumbent position for 5 minutes. 12-lead ECG should be performed before infusion on dosing days of every cycle and EOT. Additional assessments may be performed when clinically indicated.
14. **Ophthalmologic assessment:** include visual acuity testing, and slit lamp examination at the SCN and EOT, and as clinically indicated during treatment.
15. **Adverse events:** collection of all AEs regardless of attribution should begin from the time of signing of the ICF until Safety FU visit. Only ongoing or new AEs related to study drug should be collected during the Long-term FU period. All AE/SAE and AESI that are ongoing at the Safety FU

visit, whether related to study treatment, will be followed up in the follow-up period until recovery or return to baseline or become stable assessed by investigator, or death or lost to follow-up.

16. **Tumor sample**: a mandatory FFPE tumor sample must be provided, preferably obtained at the time of metastatic disease or later (most recent pre-randomization tumor sample).
17. **Viral infection laboratory testing:** Subjects should be tested for the presence of HIV antibody (as required by local regulations), HBV (Hepatitis B Serologic Test), and HCV antibody during the SCN period. Subjects with positive HBsAg and anti-HBc will need additional test for HBV-DNA. Subject with positive HCV antibody will need additional test for HCV-RNA.
18. **Pregnancy testing:** For female subjects of childbearing potential, a serum β-HCG pregnancy test should be performed during the SCN (within 7 days prior to randomization) and at the EOT visit, and a urine/serum pregnancy test should be performed within 3 days prior to infusion of every cycle. If the serum β-HCG pregnancy test of SCN is performed within 3 days before C1D1, there is no need to repeat the urine pregnancy test of C1D1. Any positive urine pregnancy test result must be confirmed immediately using a serum test.
19. **Safety laboratory test:** include hematology tests, chemistry tests, coagulation function tests, and urinalysis tests. Labs of SCN should be performed within 7 days prior to initiation of the first Treatment Cycle. Labs of C1D1 and Day 1 of subsequent cycles should be performed within 3 days before DB1303 infusion. If the safety Labs of SCN is performed within 3 days before C1D1 and the subject's condition has not changed, there is no need to repeat the safety Labs of C1D1. Labs of C1D8, C1D15 should be performed according to the visit time shown in the table above. Subjects in control arm with a weekly paclitaxel/nab paclitaxel study drug administration, safety labs of CnD8, CnD15 should be performed till EOT.
20. **Troponin:** blood samples for troponin (preferably high-sensitivity troponin-T) analysis should also be collected at screening, at EOT and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. If ECG is abnormal, follow institutional guidelines.
21. **PK sampling:** see Table 2 for detailed PK sampling schedule.
22. **ADA sampling:** see Table 2 for detailed ADA sampling schedule. PK assay can be performed on the ADA sample collected if a PK sample is not collected at that visit and deemed necessary.
23. **Biomarker sampling:** see Table 3 for detailed biomarker sampling schedule.
24. **DB-1303 Dosing:** DB-1303 is given as IV infusion under a 21-day Treatment Cycle. First infusion on C1D1: infusion time is not less than 90 minutes, and the subjects should be closely observed for infusion-related adverse reactions during and 90 minutes after the end of infusion. Subsequent infusion on C2D1 and after: If the first infusion is well tolerated, the following infusion may be administered at least 30 minutes; and the subject should be closely observed for infusion-related adverse reactions during and 60 minutes after the end of infusion.

25. **Tumor assessment:** the same CT or MRI method of assessment should be used to characterize each identified and reported lesion at baseline, during the study and follow-up. Subjects who discontinue study treatment early for reasons other than disease progression will continue to undergo tumor assessments following the original schedule until the start of new systemic anticancer therapy, disease progression, death, lost to follow-up, or withdrawal of consent, whichever occurs first. Requirements and details for tumor assessments are provided in Section 8.1.1.
26. **Allocate ePRO device:** the electronic PRO device should be charged and fully functional prior to the subject's arrival at the site for Cycle 1 Day 1 (-3 days) to ensure that the PROs can be completed at the start of the visit.
27. **ePRO subject training:** the subject should be trained on the use of the device, including the importance of completing the PRO questionnaires throughout the study in accordance with the completion schedule.
28. **End of Treatment** is defined as the investigator's decision date for treatment discontinuation. Detailed end of treatment criteria is described in Section 7.1.1.
29. **Safety FU**: Safety Follow-Up visit can be 35 days after last dose +7 days or prior to receiving next anti-cancer therapy whichever comes first. If the EOT visit assessments are performed within this period, there is no need to repeat the examinations. If the EOT occurs after this period, since EOT will include all the specified activities for Safety FU, there is no need to perform Safety FU examinations.
30. **Long-term FU:** If subjects have progressive disease or start a new anticancer treatment, they will be followed (by phone contact or chart review) to collect survival information every 3 months (±14 days) from the date of the 35-day (+7 days) follow-up visit until withdrawal of consent, lost to follow-up, death, or investigator or sponsor's decision to end the study, whichever occurs first, in this case AE and concomitant medication will not be collected.

Table 2 Pharmacokinetics, Anti-Drug Antibody Sampling Time Points of DB-1303

PK, ADA Sampling Time Point			PK Sample	Immunogenicity Sample
C1D1	Before infusion	Within 8 hours	X	X
	After the end of infusion	Within 30 mins	X	
	After the start of infusion	6 h ± 2h	X	
C2D1± 3 days	Before infusion	Within 8 hours	X	X
	After the end of infusion	Within 30 mins	X	
C3D1± 3 days	Before infusion	Within 8 hours	X	
	After the end of infusion	Within 30 mins	X	
C4D1± 3 days	Before infusion	Within 8 hours	X	X
	After the end of infusion	Within 30 mins	X	
C6D1± 3 days	Before infusion	Within 8 hours	X	
	After end of infusion	Within 30 mins	X	
C8D1± 3 days	Before infusion	Within 8 hours		X
C12D1± 3 days	Before infusion	Within 8 hours		X
C16D1± 3 days	Before infusion	Within 8 hours		X
EOT			X	X
Safety FU			X	X
Within 72 hours of occurrence of SAE (if possible)			X	X

Abbreviation: ADA=Anti-drug antibody; **EOT**=end of treatment; **FU**=follow-up**; PK**=Pharmacokinetics; **SAE**=serious adverse event.

Note:

1. PK assay may be performed on the Immunogenicity sample if there a PK sample is not collected at that visit and deemed necessary. If subject's ADA is tested positive (or ADA positive at EOT/Safety FU), ADA samples will be collected every 3 months (± 14 days) until 12 months after the last dose, or when subject's ADA become negative, or ADA titer is below baseline (if positive ADA observed at baseline), or subject starts a new therapy, or subject withdraws consent, whichever occurs first.
2. Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the timepoints indicated in the schedule of activities (SoAs).

Table 3 ctDNA Testing Sampling Time Points

Cycle/Day	Time Points
Cycle 1	Before Cycle 1 infusion
EOT	The date the investigator decides the discontinuation of the study treatment (+7 days)

Abbreviation: ctDNA = circulating tumor DNA; **EOT** = end of treatment.

2 INTRODUCTION

2.1 Study Rationale

Within breast cancers traditionally classified as HER2-negative, there exists a spectrum of HER2 expression. In addition to tumors with no detectable HER2 staining (classified by an IHC score of 0 in clinical guidelines), the category encompasses IHC 2+/ ISH negative and IHC 1+ cancers (defined in this study collectively as HER2-low).

Currently, patients with HR+, HER2-low advanced or metastatic breast cancer follow the same treatment paradigm as HR+, HER2-negative breast cancer patients. In general, ET is considered the preferred option for HR+, HER2-negative breast cancer. The optimal treatment sequence is considered to be the use of ET + CDK4/6 inhibitors first line, followed by subsequent ET with targeted therapies (e.g., mTOR or PI3-K inhibitors [for PI3-K mutant tumors]) (Cardoso et al 2020). In patients whose disease has progressed after multiple lines of ET with or without targeted therapies, chemotherapy may be appropriate (Cardoso et al 2018). In addition, for patients who have primary endocrine resistance (i.e., progressive disease within the first 6 months of first-line ET for advanced breast cancer), chemotherapy may also be appropriate as continued treatment with endocrine therapies following progression on ET + CDK4/6 inhibitors has been shown to provide less benefit (Rossi et al 2019, Sledge et al 2020, Turner et al 2018). In the DESTINY-Breast04 trial, trastuzumab deruxtecan (T-DXd) showed superior activity over standard chemotherapy options in patients with HER2-low advanced breast cancer, which highlights the clinical relevance of the HER2-low patient population and supports a need to redefine subgroups within HER2-negative breast cancers (Modi S et al 2022). Before this trial, few clinical trials were conducted specifically in patients with HER2-low metastatic breast cancer as defined here. Despite the approval of T-DXd for the treatment of HER2+ and HR+/HER2-low metastatic breast cancer, disease progression occurs in most patients, compelling the use of additional therapeutic options to overcome drug resistance. The best way is to investigate much safer and more efficacious new drugs, to further optimize the treatment and outcomes of this patient population.

In clinical trials in a heterogeneous breast cancer population, the standard of care with single agent chemotherapy leads to response rates of 10% to 30%, median PFS of 4-6 months and median OS of 15-25 months. Chemotherapy is also associated with significant AEs, including hematologic toxicities, nausea, vomiting, alopecia, and skin reactions; thus, there is a need for treatments with a better benefit/risk profile in this patient population who receive chemotherapy after endocrine treatment.

In the Phase 1 DB-1303-O-1001 clinical trial (NCT05150691), DB-1303 demonstrated promising antitumor activity with an unconfirmed ORR of 45.8% (95% CI: 32.72%-59.25%) in HER2-low breast cancer as of 31 August 2023, with the majority of patients experiencing tumor shrinkage with durable responses. Data from this study suggests that the antitumor activity of DB-1303 has the potential to provide meaningful clinical benefit to patients with

HER2-low, warranting further evaluation.

Therefore, in this Phase 3 study, DB-1303 will be compared against investigator's choice single agent chemotherapy to determine if DB-1303 can improve outcomes in HER2-low (IHC 2+/ISH- and IHC 1+), HR+ breast cancer patients whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6i in the metastatic setting (N=532).

In order to identify subjects who are likely to benefit from HER2 targeted therapies, validated companion diagnostic devices are needed in order to characterize HER2 expression / amplification in this setting. The prevalence of HER2-low in breast cancer has been characterized in the scientific literature. Duality Biologics has partnered with Roche to develop a companion diagnostic device [VENTANA HER2/neu (4B5) assay] in order to select subjects eligible for enrollment in DB-1303 (Clinical Performance Study No., RD006805; Protocol name, Performance of VENTANA HER2/neu (4B5) IUO assay with ultra-view detection on the benchmark ULTRA® instrument as a diagnostic device for determining HER2-low status in DualityBio Phase III study DYNASTY-Breast02).

Enrolling subjects in DB-1303 based on HER2-low tumor status, as indicated by the investigational VENTANA HER2/neu (4B5) assay, is expected to maximize the likelihood of clinical benefit from the study treatment based on the mode of action of HER2 targeted therapies and clinical experience to date using targeted therapies in the breast oncology setting. Therefore, DB-1303-O-3002 is a combined trial that includes the clinical performance assessment of the companion diagnostic VENTANA HER2/neu (4B5) assay in addition to the therapeutic evaluation of DB-1303. HER2 biomarker status will be tested during the screening period with the investigational HER2 companion diagnostic assay at a central laboratory.

2.2 Background

A detailed description of the chemistry and pharmacology of DB-1303, the non-clinical and clinical efficacy and safety results of DB-1303 are provided in the Investigator's Brochure (IB).

2.2.1 Background Information on the Disease to be Treated

Breast cancer is the most common cancer in the world and the most frequent cancer in women with an estimated 2.3 million new cases in 2020 globally (11.7% of all new cancers). Breast cancer is also the fifth most common cause of death from cancer with an estimated 685,000 deaths (Sung et al 2021). In Europe, an estimated 531,086 women were diagnosed with breast cancer in 2020 and 141,765 died from the disease (GLOBOCAN 2020). According to 2020 estimates, over 253,465 women in the United States (US) were diagnosed with breast cancer and 42,617 died from the disease (GLOBOCAN 2020). Despite advances in diagnosis and treatment, about 6% of women diagnosed with breast cancer in the US have metastatic disease at the time of first presentation and up to 30% of women with early stage non-metastatic breast cancer will develop distant metastatic disease (O'Shaughnessy 2005). Although

treatable, metastatic breast cancer remains largely an incurable disease with an estimated 5-year OS of only 25% (Cardoso et al 2018). Breast cancer treatment paradigms in the metastatic setting are defined by the expression of the HER2 and the estrogen receptor (ER) and progesterone receptor (PgR), which are collectively referred to as hormone receptors (HR).

In approximately 20% of breast cancer cases, there is overexpression and/or overamplification of HER2. According to ASCO/CAP guidelines, HER2 positivity is defined as tumors that have an IHC 3+ score or that show HER2 gene amplification by ISH; ISH testing is recommended in cases of IHC 2+ scoring. Several anti-HER2 targeted therapies such as HERCEPTIN® (trastuzumab), PERJETA® (pertuzumab), KADCYLA® (ado-trastuzumab emtansine [T-DM1]), TYKERB® (lapatinib), and ENHERTU® (fam-trastuzumab deruxtecan [T-DXd]) have improved outcomes in breast cancer patients who have HER2 overexpression/overamplification, classified as HER2-positive tumors. Any tumor not meeting these criteria for HER2-positivity has traditionally been referred to as "HER2-negative."

The ASCO/CAP testing guidelines and nomenclature used in this study are outlined in Table 4.

Table 4 ASCO/CAP HER2 2018 Testing Guidelines and Nomenclature Used in this Study

HER2 IHC testing result	IHC staining pattern			HER2 status per ASCO/CAP guidelines	Nomenclature used in this protocol
	Staining intensity	Membrane staining	Frequency		
IHC 3+	Intense	Complete, circumferential	>10% of tumor cells	HER2-positive (IHC2+ must be ISH+)	HER2-positive (IHC 2+ must be ISH+) [a]
IHC 2+[b]	Weak to moderate	Complete	>10% of tumor cells		
IHC 1+	Faint	Partial	>10% of tumor cells	HER2-negative (IHC 2+ must be ISH-; IHC 1+ must be ISH- or untested	HER2-low (IHC 2+ must be ISH-; IHC 1+ must be ISH- or untested)

ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization.

[a] HER2-positive patients will not be included in this study.

[b] Unusual staining patterns of HER2 by IHC can be encountered that are not covered by these definitions. In practice, these patterns are rare and if encountered should be considered IHC 2+ equivocal. As one example, some specific subtypes of breast cancers can show IHC staining that is moderate to intense but incomplete (basolateral or lateral) and can be found to be HER2-amplified. Another example is circumferential membrane IHC staining that is intense but in ≤10% of tumor cells (heterogeneous but limited in extent). Such cases can be considered 2+ equivocal, but additional samples may reveal different percentages of HER2-positive staining.

Currently, HR+ breast cancer patients whose tumors are HER2-low follow the treatment paradigm for HR+, HER2-negative breast cancer patients and receive single agent chemotherapy after disease progression on ET and/or targeted therapy (e.g., CDK4/6 inhibitor) regimens. Endocrine therapy, including aromatase inhibitors (aIs), selective ER modulators, and selective ER down-regulators, as well as targeted therapies such as CDK4/6 inhibitors, PI3-K inhibitors, and mTOR inhibitors have been shown to improve outcomes for patients with HR+, HER2-negative metastatic breast cancer and are considered standard of care for most patients in the metastatic setting (Andre et al 2019, Matutino et al 2018). Several studies have demonstrated a PFS benefit of aIs and fulvestrant, both of which have recently been used in combination with CDK4/6 inhibitors (Finn et al 2016, Goetze et al 2017, Hortobagyi et al 2018, Slamon et al 2018). The combination of ET and ribociclib has demonstrated an OS benefit among premenopausal women as first line therapy (Im et al 2019). In addition, combinations of abemaciclib (Sledge et al 2020) and ribociclib (Slamon et al 2019) with fulvestrant have demonstrated OS benefit.

The optimal treatment sequence for patients with HR+, HER2-negative metastatic breast cancer is considered to be the use of ET + CDK4/6 inhibitors first line, followed by subsequent ET with targeted therapies (e.g., mTOR or PI3-K inhibitors [for PI3-K mutant tumors]) (Cardoso et al 2020). In patients whose disease has progressed after multiple lines of ET with or without targeted therapies, or patients whose disease has primary endocrine resistance (progressive disease within the first 6 months of first-line ET for advanced breast cancer), chemotherapy may be appropriate. T-DXd has been approved by the FDA for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer. T-DXd recently demonstrated superior activity over standard chemotherapy options in patients with HER2-low advanced breast cancer in the DESTINY-Breast04 trial, highlighting the clinical relevance of the HER2-low patient population (Modi S et al 2022). However, the T-DXd prescribing information contains warnings for interstitial lung disease (ILD)/pneumonitis. Diagnosis of drug-related ILD/pneumonitis can be challenging and requires close attention from clinicians.

When chemotherapy is recommended, the choice between single agent and combination therapy is decided based on several factors to individualize therapy. Generally, sequential single agent therapy is preferred over combination therapy (Cardoso et al 2009, NCCN 2023). Chemotherapy combinations may be used in select patients with rapidly progressing disease and visceral crisis. Single agent therapy options include anthracyclines, taxanes (e.g., paclitaxel and nab-paclitaxel), and anti-metabolites (e.g., capecitabine). Because of the availability of many agents and the lack of clear superiority of one agent over others, there is no ideal sequence of treatments that can be applied to all patients. Most studies have demonstrated responses of approximately 10% to 30%, a median PFS between 4 and 6 months and a median OS between 15 and 25 months in a heterogeneous metastatic breast cancer setting, with chemotherapy being associated with many adverse effects including hematologic toxicities, alopecia, skin reactions, nausea, diarrhea and vomiting (Baselga et al 2017,

Gradishar et al 2005, Kaufman et al 2015, Miller et al 2007, Piccart-Gebhart et al 2008). Hence, a high unmet medical need exists and new treatment options are needed to further improve outcomes.

2.2.2 Background Information on DB-1303

DB-1303 is a HER2-targeting antibody-drug conjugate (ADC) that is being developed as a therapeutic candidate for breast cancer and other HER2-expressing tumors.

DB-1303 consists of an anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody, covalently linked to a proprietary DNA topoisomerase I inhibitor (P1003) via a cleavable linker containing maleimide tetrapeptide (GGFG), with a drug antibody conjugation ratio (DAR) of approximately 8. The antibody has the same amino acid sequence as HERCEPTIN® (trastuzumab), and thus DB-1303 is similarly targeted to HER2-expressing tumors. The drug P1003, a derivative of exatecan, is released after internalization and leads to apoptosis of the target tumor cells via the inhibition of topoisomerase I.

Due to incorporation of a novel linker, DB-1303 achieves a drug-to-antibody ratio (DAR) of approximately 8 with homogeneous conjugation of P1003. In addition, the cleavable linker in DB-1303 is stable in plasma, conferring a favorable safety profile as observed in nonclinical toxicology rat and monkey studies.

DB-1303 exhibits HER2-specific antitumor activity via a mechanism of action that combines the monoclonal antibody (mAb) specificity with the broad cytotoxicity of the released drug. After binding to HER2 and internalization, DB-1303 is cleaved by lysosomal enzymes preferentially expressed in tumor cells and releases the drug. DB-1303 is expected to exhibit antitumor activity through P1003-induced apoptosis and, potentially, the antibody-dependent cellular cytotoxicity (ADCC) activity and bystander killing effect.

For details on the schematic structures, molecular formula, finished product of DB-1303 and the overall safety and clinical efficacy data from different studies that involved DB-1303, refer to the most recent IB.

As of 31 August 2023, a total of 247 subjects have been treated with DB-1303 in an ongoing clinical study (DB-1303-O-1001, NCT05150691) across multiple HER2-expressing tumor types including breast cancer, gastric cancer, non-small cell lung cancer (NSCLC), endometrial carcionma, ovarian cancer, and esophageal carcinoma.

2.3 Benefit/Risk Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

More detailed information about the known expected benefits and risks and the overall efficacy and safety profiles of DB-1303 are found below and in the most recent IB.

2.3.1 Potential Risks of DB-1303

Based on data from clinical trials, toxicities considered to be associated with administration of DB-1303 include the identified risk of platelet count decreased (including thrombocytopenia) and ILD/pneumonitis, and potential risks of IRR and anaemia. Other identified risks of DB-1303 were primarily gastrointestinal in nature. These risks were generally manageable through dose modification and routine clinical practice. Refer to the most recent IB for details.

ILD/pneumonitis, LVEF decrease (≥Grade 3), and IRR (≥Grade 3) are considered adverse events of special interest (AESI).

DB-1303 has not been studied in subjects with severe/moderate hepatic impairment or severe renal impairment.

HER2-targeted Agents

Several ADC agents that target HER2 and prevent its activation or heterodimerization, such as T-DM1 and T-DXd, have been developed and marketed for the treatment of HER2-positive cancers or HER2-mutant tumors. The safety profile of these two HER2-targeted agents has been well described in product labels and published literature. The main safety risks identified in subjects receiving HER2-targeted products are described below; these could potentially be expected to occur in subjects receiving DB-1303.

Cardiotoxicity: cardiac dysfunction, mainly asymptomatic left ventricle ejection fraction (LVEF) decrease, has been observed in subjects receiving T-DXd and T-DM1. The Majority of cases have been asymptomatic decreases in LVEF.

Pulmonary Toxicity: cases of pulmonary toxicity, including ILD and pneumonitis, have been observed in patients receiving T-DXd and T-DM1. Occasionally, these cases have been severe in nature and have resulted in fatal outcomes. The incidence of ILD/pneumonitis of Grades 1-2 was higher in patients with moderate renal impairment who received T-DXd.

Hypersensitivity/Infusion-related Reactions: the administration of therapeutic proteins is associated with a risk of hypersensitivity and/or infusion reactions. Hypersensitivity/infusion-related reactions have been reported with T-DXd and T-DM1. These can range from mild reactions to severe anaphylactic shock with a fatal outcome.

Hepatic Toxicity: cases of hepatic toxicity have occurred with T-DXd and T-DM1. In subjects receiving T-DM1, hepatic toxicity has manifested mainly as transient asymptomatic liver transaminase elevations, although serious cases of drug-induced liver failure and nodular regenerative hyperplasia have also been reported.

Hematological Toxicity: hematological toxicity has been observed with all HER2-targeted therapies. Neutropenia, febrile neutropenia, leukopenia, and anemia have occurred commonly with T-DXd and T-DM1. Thrombocytopenia, including Grade 3 and Grade 4, is a common occurrence in T-DM1-treated subjects. Asian patients are reported to have a higher incidence

and severity of thrombocytopenia. Although rare, serious hemorrhagic events have been reported in the setting of thrombocytopenia.

Embryofetal Toxicity: in post-marketing reports, use of a HER2 receptor antagonist, during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

P1003 is a derivative of exatecan, a topoisomerase I inhibitor. The main risks associated with the use of topoisomerase I inhibitors include hematological toxicities and gastrointestinal toxicities. Hematological toxicities, manifesting as neutropenia, febrile neutropenia, anemia, thrombocytopenia, and pancytopenia, are commonly observed. The most common symptoms of gastrointestinal toxicity are nausea, vomiting, diarrhea, ileus, and intestinal perforation.

Refer to the current IB of DB-1303 for details.

Refer to Section 6.6.1.1 for toxicity management guidelines for DB-1303.

2.3.2 Potential Benefits of DB-1303

DB-1303 is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. Based on the clinical observations to date, DB-1303 demonstrates antitumor activity in HER2-expressing cancers.

Initial evaluation of DB-1303 in subjects with HER2-low advanced breast cancer refractory to or intolerant of standard treatment in the Study DB-1303-O-1001 (NCT05150691), demonstrated that the majority of subjects experienced tumor shrinkage; durable responses were observed. As of 31 August 2023, the majority of subjects with HR+/ HER2-low breast cancer had received DB-1303 at 8 mg/kg (59 subjects), with an unconfirmed ORR of 45.8% (95% CI: 32.72%-59.25%) and a DCR of 91.5% (95% CI: 81.32%-97.19%). The confirmed ORR was 33.9% (95% CI: 22.08%-47.39%) and the median DoR was 5.62 months (95% CI: 5.62, NE+). The median duration of follow-up was 6.27 months, while the median PFS was 8.48 months (95% CI: 5.19, NE). The median OS has not yet been reached. DB-1303 demonstrated promising antitumor activity in subjects with HR+/HER2-low breast cancer.

The results from study DB-1303-O-1001 comprise the primary data set to support initiation for this study.

2.3.3 Standard of Care (Investigator's Choice Chemotherapy)

The risks associated with capecitabine, paclitaxel and nab-paclitaxel are described in the local prescribing information.

2.3.4 Overall Benefit/Risk Conclusion

The standard of care with single agent chemotherapy in a heterogenous metastatic breast cancer population leads to response rates of 10% to 30%, median PFS of 4-6 months and median OS of 15-25 months. Chemotherapy is also associated with significant AEs, including hematologic toxicities, nausea, vomiting, alopecia, and skin reactions; thus, additional

effective treatment options are needed for this patient population.

DB-1303 is under development for the treatment of HER2-expressing cancers. Based on the clinical observations in the ongoing Phase 1/2a study (Study DB-1303-O-1001), DB-1303 demonstrates an acceptable safety profile and promising antitumor activity in HER2-expressing cancers.

Based on the cumulative review of the safety data, including available nonclinical, clinical, and epidemiologic information and scientific literature (published and unpublished) and taking into consideration biological plausibility, platelet count decreased (including thrombocytopenia) and ILD/pneumonitis are considered as identified risk of DB-1303, IRR and anaemia are classified as potential risks.

Several measures have been put in place to mitigate the incidence of pulmonary toxicities, including inclusion of eligibility criteria that prohibit subjects with pre-existing pulmonary comorbidities from entering the study. In addition, baseline pulmonary function tests will be performed for all subjects. For hematological toxicities, the use of growth factors is allowed, as per the Investigator's discretion. Subjects will be monitored closely throughout the study and clinical and laboratory assessments will be performed before every cycle. Toxicity management guidelines are also provided to assist with the management of the most commonly seen AEs.

Based on these considerations, DB-1303 has the potential to provide meaningful clinical benefit and given the measures put in place for mitigation, the benefit/risk assessment supports the proposed study.

Based on the mechanism of action of DB-1303, the use of the VENTANA HER2/neu (4B5) assay for the detection of HER2 protein expression to characterize HER2-low disease benefits the subjects and justifies the study of the *in vitro* diagnostic (IVD) assay in this study.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
· To assess the efficacy of DB-1303 compared with investigator's choice chemotherapy in terms of a hazard ratio (HR) for PFS assessed by blinded independent central review (BICR) in the HR+, HER2-low (IHC 2+/ISH- and IHC 1+) population. The intercurrent event of initiation of subsequent anti-cancer therapy will follow a hypothetical strategy, and discontinuation of study treatment will follow a treatment policy strategy.	· PFS by BICR according to response evaluation criteria in solid tumors (RECIST) 1.1 in the HR+, HER2-low population.
Secondary	
The key secondary objective is: · To assess the efficacy of DB-1303 followed by any other subsequent anti-cancer therapy compared with investigator's choice chemotherapy followed by any other subsequent anti-cancer therapy in terms of a HR for overall survival (OS) in the HR+, HER2-low (IHC 2+/ISH- and IHC 1+) population. Handling of intercurrent events will follow a treatment policy strategy. **The other secondary objectives are:** · To further assess the efficacy of DB-1303 compared with investigator's choice chemotherapy in terms of PFS by Investigator assessment, objective response rate (ORR), and duration of response (DoR) by BICR and Investigator assessment in the HR+, HER2-low population. · To assess the safety and tolerability profile of DB-1303 compared with investigator's choice chemotherapy. · To assess symptoms, functioning and health-	**The key secondary endpoint is:** · OS in the HR+, HER2-low population. **The other secondary endpoints are:** · ORR and DoR by BICR and Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population · PFS by Investigator assessment according to RECIST 1.1 in the HR+, HER2-low population · TEAEs and SAEs per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, physical examinations, changes from baseline in laboratory findings, electrocardiograms (ECGs), ECHO/MUGA and vital signs. · The patient reported outcomes (PROs) include: change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR45 scale scores, time to deterioration in EORTC QLQ-C30

Objectives	Endpoints
related quality of life (HRQoL) in subjects treated with DB-1303 compared with investigator's choice single agent chemotherapy. · To assess the impact of treatment and disease state on health utility using the EQ-5D-5L.	scores · EQ-5D-5L health state utility index
Exploratory	
· To assess the pharmacokinetics (PK) of DB-1303 (DB-1303 ADC and free payload P1003). · To investigate the immunogenicity of DB-1303. · To compare the effect of DB-1303 with investigator's choice chemotherapy in terms of disease control rate (DCR), and time to response (TTR) by BICR and Investigator assessment, time to second progression or death (PFS2) according to Investigator assessment, time to first subsequent treatment or death (TFST) and time to second subsequent treatment or death (TSST) in the HR+, HER2-low population · To define biological responses to DB-1303 and to investigate predictive markers of response, acquired resistance and other markers that may correlate with likelihood of clinical benefit or tolerability. · To assess patient-reported treatment tolerability. · To explore the population PK of DB-1303. · To explore the efficacy and safety Exposure-Response (ER) correlation.	· PK parameters (peak observed concentration [C_{max}], time to C_{max} [T_{max}], etc.) of DB-1303 ADC and free payload P1003. · ADA prevalence: the proportion of subjects who are ADA positive at any point in time (at baseline and post-baseline). ADA incidence: the proportion of subjects having treatment-emergent ADA. · DCR, TTR, PFS2, TFST, TSST in the HR+, HER2-low population · Biomarkers of DB-1303 sensitivity/resistance: o Protein expression (IHC analysis HER2) o Blood analysis for ctDNA at pre-treatment and EOT · Patient-reported treatment tolerability (PRO CTCAE) · To explore the population PK of DB-1303 ADC and released payload. · To explore the efficacy and safety Exposure- Response (ER) correlation with DB-1303 ADC and released payload.

4 STUDY DESIGN

4.1 Overall Design

The study is an open-label, multi-center, randomized study in HER2-low, HR+ breast cancer patients with disease progression on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6 inhibitor in the metastatic setting. The primary purpose of the study is to determine the efficacy and safety of DB-1303 compared with investigator's choice single agent chemotherapy in the target population. Approximately 532 subjects will be randomized 1:1 across approximately 230 centers globally to receive either 8 mg/kg DB-1303 Q3W or investigator's choice single agent chemotherapy (paclitaxel, nab-paclitaxel or capecitabine) until RECIST 1.1 defined progressive disease (PD), unless there is unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met. See Section 1.2 for details on study schema. The study will compare PFS, OS and other measures of efficacy between the study treatment groups and further characterize the safety and tolerability profile of DB-1303.

The randomization will be stratified by:

- prior CDK4/6 inhibitor use (Yes vs No)
- HER2 IHC expression (IHC 2+/ISH- vs IHC 1+)
- prior taxane use in the non-metastatic setting (Yes vs No)

Stratification factor status must be known at the time of subject's randomization to the study.

CDK4/6 inhibitors are being increasingly utilized as part of standard of care for patients with HR+ breast cancer. To ensure that majority of subjects have received prior CDK4/6 inhibitor therapy in the HER2-low population, no more than 53 subjects (10% of 532 subjects) who have not received prior therapy with CDK 4/6 inhibitors (e.g., palbociclib, abemaciclib, or ribociclib) will be randomized.

Tumor evaluation scans (computer tomography [CT]/magnetic resonance imaging [MRI] of chest/abdomen/pelvis) will be performed at screening (as baseline) with follow-ups at every 6 weeks (Q6W ± 1 week) from the date of randomization for 48 weeks, and then every 9 weeks (Q9W ± 1 week, starting at Week 48) until RECIST 1.1 disease progression.

An intravenous (IV) contrast-enhanced brain MRI (preferred) or IV contrast-enhanced CT of the brain is to be acquired for all subjects at baseline. Regularly scheduled follow-up brain scans (Q6W ±1 week from the date of randomization for 48 weeks, and then Q9W ±1 week, starting at Week 48 thereafter until RECIST 1.1 disease progression) are mandatory for all subjects who are enrolled with baseline stable brain metastases, while subjects without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated.

For subjects with bone-only disease that is non-measurable, X-Ray may also be used in

addition to the required CT or MRI of the chest, abdomen and pelvis. Any other areas of disease involvement or any other sites at which new metastatic disease is clinically suspected should be additionally imaged based on the signs and symptoms of individual subjects.

Digital copies of all scans performed during the conduct of this study must be retained at site as source data. Sites shall submit the digital copies electronically to the imaging contract research organization (iCRO) for centralized review by blinded independent central review (BICR). Submission via alternative method such as compact disc (CD)/digital versatile disc (DVD) may be accepted on discussion with the study team if electronic submission is not possible. Subjects will be followed for OS, regardless of whether study treatment is discontinued or delayed, unless the subject withdraws consent or study closure, whichever occurs first.

A mandatory formalin-fixed paraffin-embedded (FFPE) tumor sample must be provided, preferably obtained at the time of metastatic disease or later; the most recently collected pre-randomization tumor sample that meets the tissue requirements specified in Section 8.6 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. The tumor sample submitted should be of sufficient quantity to allow for assessment of HER2 status (for details of tumor tissue requirements see Laboratory Manual). Assessment of HER2 status will be performed via a central laboratory.

Central testing of HER2 status will be conducted using the VENTANA HER2/neu (4B5) assay, investigational for the IHC 2+ and IHC 1+ cut-offs. Tumor samples centrally confirmed to be HER2 IHC 2+ will be confirmed to be HER2 ISH negative (non-amplified) using a commercial HER2 ISH assay per manufacturers requirements. Testing will be carried out in a laboratory operating to GCP and with pathology staff fully trained by the diagnostic manufacturer to score reproducibly at all relevant HER2 IHC cut-offs (IHC1+ and IHC 2+).

4.1.1 Duration of the Study

Enrollment is planned to occur over approximately 20 months. For each subject there will be a 35 -day (+7 days) follow-up visit after the last study treatment administration, followed by long-term/survival follow-up visits every 3 months (±14 days) until death, withdrawal of consent, or study closure, whichever occurs first.

4.1.2 Duration of Subject Participation

The screening period is up to 28 days. Prior to the 28-day screening period, an tissue screening ICF will be signed by subjects to permit tumor tissue sample collection for central HER2 status testing. For DB-1303, each cycle of treatment will be 21 days. For capecitabine and paclitaxel, each cycle of treatment will be 21 days. For nab-paclitaxel, each cycle of treatment will be 28 days (see Table 1 for further details). The number of treatment cycles with DB-1303 and the investigator's choice chemotherapy (capecitabine, paclitaxel and nab-paclitaxel) is not fixed. Upon commencing study treatment, subjects may continue receiving study treatment until RECIST 1.1 disease progression, withdrawal of consent or any of the

discontinuation criteria as defined in Section 7.1.1 are met. Subjects cannot switch between the investigator's choice single agent chemotherapy control agents while on-treatment during the study.

After study treatment discontinuation, subjects will be contacted for the 35 -day (+7 days) follow-up visit, followed by long-term/survival follow-up visits every 3 months (±14 days) to obtain information about subsequent treatment(s) and survival status.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for DB-1303 in HR+, HER2-low, Advanced or Metastatic Breast Cancer

Preclinical data have demonstrated that DB-1303 inhibits tumor growth in a patient-derived HER2-low tumor xenograft model that is insensitive to T-DM1. Results from the first-in-human Phase 1 DB-1303-O-1001 study in subjects with HER2-low (defined by ASCO/CAP guidelines as HER2 IHC 2+/ISH- or HER2 IHC 1+) advanced breast cancer, refractory to or intolerant of standard treatment, demonstrated that the majority of subjects experienced tumor shrinkage; durable responses were observed.

Among the 79 subjects with HER2-low breast cancer treated with DB-1303 ranging from 4.4-10 mg/kg Q3W, the unconfirmed ORR was 45.6% (95% CI: 34.31%, 57.17%), and the unconfirmed DCR was 91.1% (95% CI: 82.59%, 96.36%). The confirmed ORR was 34.2% (95% CI: 23.87%-45.71%) and the median DoR was 5.78 months (95% CI: 5.62, NE+). Median PFS was 8.41 months (95% CI: 5.19, not estimable). Median OS has not been reached yet.

4.2.2 Rationale for Efficacy Endpoints

The primary endpoint is

- PFS by BICR according to RECIST 1.1.

PFS has been selected as the primary endpoint based on the following considerations:

- PFS is not confounded by subsequent therapies.
- Several meta-analyses demonstrate a statistically significant correlation between hazard ratios of PFS and OS in metastatic breast cancer patients (Adunlin et al 2015, Lux et al 2019).
- PFS has been used as the primary endpoint in studies leading to the registration of recently approved treatments for breast cancer where the magnitude of effect was sufficient to establish clinical benefit.
- PFS provides the evidence of drug activity and the improvement in PFS is of clinical benefit to patients.
- PFS is an acceptable primary endpoint as described in, for example, the EMA Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5)

and the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2018).

This is in line with the guidelines outlined by the National Cancer Institute Breast Cancer Steering Committee Working Group Report, which recommends that it is appropriate to have PFS as the primary endpoint (Seidman et al 2018) in HR+, HER2-negative disease in the first line setting of metastatic breast cancer. This recommendation was based on the expectation that post-progression survival is long and that subsequent therapies will have great influence on OS.

The **Key** secondary endpoints are:

- OS

The additional secondary endpoints are:

- ORR and DoR by BICR and Investigator assessment according to RECIST 1.1
- PFS by Investigator assessment according to RECIST 1.1

The secondary endpoints are in line with the recommendations outlined in the National Cancer Institute Breast Cancer Steering Committee Working Group Report, where for HR+/HER2-negative breast cancer in the first line setting it is appropriate to have the following secondary endpoints: OS, response rate and patient-reported outcomes (PROs) (Seidman et al 2018).

Furthermore, DCR, TTR, PFS2, TFST and TSST will be examined to further evaluate the antitumor effect of DB-1303 vs investigator's choice chemotherapy as exploratory endpoints to complement the antitumor effect noted from other, conventional endpoints (e.g., PFS, ORR, DoR and OS).

4.2.3 Rationale for Other Study Endpoints

The secondary patient-reported symptoms, functioning and overall health-related quality of life (HRQoL) endpoints, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) 30 Core Quality of Life Questionnaire and Breast Cancer-Specific Module, (QLQ-C30 and QLQ-BR45) will show the overall influence of the benefits and toxicity of the treatment from the subject's perspective and will aid in understanding the benefit/risk evaluation. The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal by payers. These PRO questionnaires are well-established instruments that have been previously included in cancer clinical studies.

As part of the exploratory endpoint assessment, blood samples will be taken to allow for research into the PK and immunogenicity of DB-1303.

Biological samples will be used to explore potential biomarkers in tumor and/or plasma, which may predict the progression of cancer (and associated clinical characteristics) and/or

tumor response.

4.3 Justification for Dose

DB-1303, and 3 investigator's choice of single agent chemotherapy are used in the study. The justification for dose for each of these interventions are provided below.

4.3.1 DB-1303 Dose Rationale

Based on all available information, a DB-1303 dose of 8 mg/kg Q3W has been chosen for this study.

- The 8 mg/kg Q3W dose was determined based on the totality of evidence generated from the current observed efficacy and safety summary, PK and exposure-response (E-R) analyses of safety and efficacy. The proposed dose of 8 mg/kg Q3W for the pivotal study was supported by clinical data collected from 217 subjects in the ongoing DB-1303-O-1001 study which comprised data from Phase 1 dose escalation part (2.2 to 10 mg/kg Q3W in solid tumor), as well as data from Part 2 at 8 mg/kg Q3W in subjects with HER2+ BC, HER low BC and EC. Utilizing the currently available data from DB-1303-O-1001 (data cutoff on May 29, 2023), integrated population PK (PopPK) and E-R analyses for safety and efficacy have been developed for DB-1303 (DB-1303 ADC and released payload P1003) to support the dose selection.
- In dose escalation part of DB-1303-O-1001 study, the majority of subjects with HER2 low BC were dosed with DB-1303 at 7 mg/kg (7 subjects) and 8 mg/kg (10 subjects), with a median follow-up time of 6.90 months and 5.65 months. At the time of the DCO (May-29, 2023), 1 subject in the 7 mg/kg group and 4 in the 8 mg/kg group had achieved confirmed PR with respective confirmed ORRs of 14.3% and 40.0%. Median DoR was not reached. The median PFS for subjects in the 7 mg/kg group was 4.27 months, while it was not reached for 8 mg/kg group. To further confirm the benefit of 8 mg/kg Q3W, total of 33 HER2-low BC subjects who received DB-1303 8 mg/kg Q3W (dose escalation and dose expansion) have been followed up for ≥13 weeks from the first dosing, with an unconfirmed ORR of 45.5% (30.3% confirmed response, and 12.1% pending confirmation of response); 10 subjects have been followed up for ≥19 weeks from the first dosing, with an unconfirmed ORR of 50.0% (40.0% confirmed response, 10.0% pending confirmation of response). Additionally, among subjects with HER2-low BC in dose escalation, patients at 8 mg/kg Q3W stayed on treatment longer than 7 mg/kg Q3W; where 40.0% (8 mg/kg Q3W) and 0% (7 mg/kg Q3W) of subjects were still on treatment beyond 8 cycles. The above evidence is suggested that 8 mg/kg Q3W conferred more clinical benefits than 7 mg/kg Q3W.
- In the Efficacy E-R analysis versus various PK exposure metrics across all dose levels, there was a statistically significant ($P<0.05$) positive relationship between the unconfirmed Best Overall Response (BOR) for subjects with all tumor type and their Cycle 1 DB-1303 AUC. Increased DB-1303 exposure levels were correlated with

increased response rate in these subjects and showed that 8 mg/kg elicited higher probability of response rate when compared to 6 or 7 mg/kg. A subgroup Efficacy E-R analysis also showed that the unconfirmed best overall response increases as Cycle 1 AUC of DB-1303 increases in subjects with HER2-low BC, even though no statistical significance was noted. Taken together, the current integrated efficacy analyses suggested that 8 mg/kg Q3W is the favorable dosing regimen to be implemented for the planned pivotal study.

- DB-1303 was well tolerated at all dose. During the Phase 1 dose escalation part of Study DB-1303-O-1001, the MTD of DB-1303 was not reached at doses up to 10 mg/kg and no DLT was observed in the DLT evaluation period (Cycle 1 Days 1 to 21) during dose escalation at all dose levels.
- The incidence of TEAEs, TEAEs ≥ Grade 3, SAEs, TEAEs leading to dose reduction, TEAEs leading to dose interruption, TEAEs leading to permanent drug discontinuation, and AESIs was similar between the subjects who received DB-1303 at 8 mg/kg and 7 mg/kg during dose escalation, though the treatment duration was slighter longer in the 8 mg/kg group (5.5 months vs. 4.9 months). Among patients treated with 8 mg/kg Q3W (N=159) to date, safety profile of DB-1303 is acceptable.
- Logistic regression was used to characterize E-R relationships between DB-1303 ADC and released P1003 exposure metrics and the probability of anemia (all grades and Grade ≥3), platelet count decrease (all grades and Grade ≥3), nausea or vomiting (all grades and Grade ≥3), dose interruption, and dose reduction. Exposure metrics included Cycle 1 AUC, Cycle 1 C_{MAX}, steady-state AUC, steady-state C_{MAX} and C_{AVG} over time through the cycle in which an event was experienced or the subject was censored. No statistically significant relationships between DB-1303 ADC and P1003 exposure metrics and safety endpoints were demonstrated in the logistic regression models, except the platelet count decrease (all grades) which was significantly correlated with DB-1303 ADC Cycle 1 CMAX (p-value < 0.05) and average concentration of P1003 through the event cycle (p-value < 0.05). The covariate analysis suggested that subjects with low baseline platelet and Asian subjects have a greater risk of developing platelet count decrease (of any grade) under the same drug exposure. However, no cases of bleeding caused by ≥ Grade 3 thrombocytopenia have been reported, indicating the lack of any clinically meaningful differences that warrant dose adjustment for these subjects within the limited sample tested to date. Furthermore, while PopPK and efficacy E-R analyses for DB-1303 ADC and P1003 did not reveal that race (Asian vs non-Asian) was a significant covariate that impacts exposure and treatment outcomes, the benefit-risk profile of DB-1303 dosing regimen should be maximized for the entire patient population.
- In addition to the E-R analyses, dose selection also considered the clinically observed PK characteristics of DB-1303. While dose-dependent increase in DB-1303 C_{max} and AUC was observed, increased clearance (i.e., shorter t1/2) was observed at lower doses (2.2

mg/kg (t1/2~ 3.2 days) to 4.4 mg/kg (t1/2~ 3.8 days)) and in the 6 mg/kg cohort (t1/2~ 5.6 days). The faster clearance observed in these subjects are likely due to target-mediated drug disposition (TMDD), which was not observed in dose levels ≥7 mg/kg (t1/2:6-7 days). Thus, to avoid this potential impact on the PK, higher doses than 6 mg/kg were considered for further dose selection.

- Taken together, the totality of evidence generated based on efficacy, safety, PK data and E-R analyses of safety and efficacy supports 8 mg/kg Q3W being an optimal dose regiment for DB-1303. The dose of 8 mg/kg Q3W was well tolerated and demonstrated more favorable efficacy profiles over lower dose levels tested in DB-1301-O-1001 and thus, provide the optimal benefit-risk outcome.

For information on dose modifications for DB-1303, see Section 6.6.

4.3.2 Chemotherapy Dose Rationale

Three chemotherapy options were chosen for the proposed study based on the strength of the efficacy data in the first line setting, and previously approved indications and the responses obtained in feasibility questionnaires (completed by DualityBiologics representatives in more than 200 sites from 16 countries [including the US] following outreach to sites in their respective region). The chosen options are capecitabine, paclitaxel, and nab-paclitaxel.

In addition, the decision to limit the investigator's choice comparator treatment to 3 options was taken to also limit the heterogeneity of the comparator arm without limiting effective treatment choices.

The rationale for the dose of each chemotherapy agent is provided below. All regimens proposed are based on standard practice and the National Comprehensive Cancer Network (NCCN) guidelines for HER2-negative recurrent or Stage IV breast cancer.

- **Paclitaxel:** Paclitaxel will be administered at a standard of care dose of 80 mg/m^2 every week as opposed to the United States Prescribing Information (USPI) labelled paclitaxel dose of 175 mg/m^2 Q3W. In a meta-analysis of randomized, controlled studies in advanced breast cancer (5 studies, 1471 patients), which compared weekly administration of paclitaxel with Q3W administration, the analysis concluded that there was an improvement in OS with weekly paclitaxel (pooled hazard ratio, 0.78; 95% CI: 0.67 to 0.89; p=0.001). Additionally, the incidence of neutropenia, neutropenic fever, peripheral neuropathy, and other SAEs was significantly lower with weekly paclitaxel compared with paclitaxel Q3W (Mauri et al 2010). Based on this meta-analysis and to be aligned to standard practice among breast cancer clinicians, the weekly regimen of 80 mg/m^2 is proposed for this study.
- **Nab-paclitaxel:** The Q3W labelled dose of nab-paclitaxel (260 mg/m^2), established from the Phase 3 study comparing paclitaxel with nab-paclitaxel (Gradishar et al 2005) is not generally used in current clinical practice. Instead, weekly administration of nab-paclitaxel at a dose of 100 mg/m^2 is the most commonly utilized schedule given the

better tolerability and suggestions of increased efficacy of weekly dosing compared with Q3W dosing. The superiority of the weekly regimen of nab-paclitaxel was first demonstrated in a randomized, Phase 2 study conducted in patients with previously untreated metastatic breast cancer (Gradishar et al 2009). In this study, the ORR and PFS by independent radiologist assessment were higher for the weekly regimens of nab-paclitaxel vs Q3W administration. The differences in PFS and ORR between the 100 and 150 mg/m^2 weekly dose levels of nab-paclitaxel were not statistically significant, but patients receiving the higher dose experienced a greater incidence of Grade 3 or 4 neutropenia (44% vs 25%) and Grade 3 sensory neuropathy (14% vs 8%). Subsequent clinical studies have not clearly demonstrated that weekly doses of nab-paclitaxel greater than 100 mg/m^2 are more efficacious. Therefore, for this study Duality Biologics proposes that subjects receive 100 mg/m^2 nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle.

- **Capecitabine:** The approved labelled dose of 1250 mg/m^2 twice daily on Days 1 to 14 followed by a 7-day rest period has demonstrated efficacy in ORR and PFS. However, 26% to 65% of patients had their dose reduced by at least 20% in these trials (Miller et al 2005, Pallis et al 2012). The main treatment-limiting toxicities at the labelled dosage were hand and foot syndrome (HFS) and diarrhea. Based on this experience, a number of Investigators have evaluated capecitabine at a lower starting dose (1000 mg/m^2 twice daily) and demonstrated similar efficacy to the approved dose and a more favorable safety profile with an incidence of dose reduction, ranging from 16% to 34% in Phase 2 studies (Baselga et al 2012, El-Helw and Coleman 2005). These results are further supported by a meta-analysis of data from 34 studies comprising of 4833 patients. The results showed a significantly lower incidence of dose reduction (15.9% vs 39.0%; p=0.007), high-grade HFS (12.0% vs 19.0%; p=0.01), diarrhea (5.3% vs 9.1%; p=0.01), and neutropenia (1.8% vs 7.3%; p<0.01) and all-grade neutropenia (5.8% vs 25.4%; p=0.01) for capecitabine 1000 mg/m^2 compared with 1250 mg/m^2 (Nishijima et al 2016). Therefore, for this study, Duality Biologics proposes that subjects have the option, based on Investigator's choice, to receive either the 1250 mg/m^2 dose as indicated in the label or the 1000 mg/m^2 dose.

For information on dose modifications for paclitaxel, nab-paclitaxel and capecitabine, see Section 6.6.1 and the respective local prescribing information.

4.4 End of Study Definition

The end of the study (EOS) is defined as completing the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed all phases of the study as per SoAs (including follow-up for OS).

Subjects must be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgement of Duality Biologics, study subjects are placed at undue risk

because of clinically significant findings. The study may be terminated at individual centers if the study procedures are not being performed according to ICH GCP or if recruitment rate does not allow to complete study in the planned timeframe.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and randomization criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to a study treatment. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, enrolled subjects are defined as those who sign informed consent including the tissue screening ICF. Randomized subjects are defined as those who undergo randomization and receive a randomization number. For procedures for withdrawal of incorrectly randomized subjects see Section 6.3.2.

The study population for this study will include pathologically documented advanced or metastatic HR+, HER2-low breast cancer patients whose disease has progressed on at least 2 lines of prior ET or within 6 months of first line ET + CDK4/6 inhibitor in the metastatic setting. Subjects must be RECIST 1.1 evaluable, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and have not received chemotherapy for metastatic disease.

5.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female adults (defined as ≥ 18 years of age or acceptable age according to local regulations at the time of voluntarily signing of informed consent).
2. Pathologically documented breast cancer that:
    1) Is advanced or metastatic
    2) Has HER2-low expression (IHC 1+ or IHC 2+/ISH-) as determined by the central laboratory result from the most recently collected pre-randomization tumor sample (see inclusion criterion 3)
    3) Was never previously reported as HER2-positive (IHC 3+ or ISH+) as per ASCO/CAP guidelines.
    4) Is documented as HR+ (either ER and/or PgR positive [ER or PgR ≥1%]) per ASCO/CAP guidelines (Allison et al 2020). If a subject has had multiple ER/PgR results after metastatic disease, the most recent test result will be used to confirm eligibility.
3. Must have an adequate tumor tissue sample available for assessment of HER2 by central laboratory, preferably in FFPE blocks based on a mandatory FFPE tumor sample obtained

at the time of metastatic disease or later; the most recently collected pre-randomization tumor sample that meets the tissue requirements specified in protocol Section 8.6 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. (See Section 8.6 and the laboratory manual for additional details).

4. ECOG performance status of 0 or 1
5. Must have had either:
   1) Disease progression on endocrine therapy + CDK4/6 inhibitor within 6 months of starting first line treatment for metastatic disease and considered appropriate for chemotherapy as the next treatment by the investigator, OR
   2) Disease progression on at least 2 previous lines of ET with or without a targeted therapy (such as CDK4/6, mTOR or PI3-K inhibitors) administered for the treatment of metastatic disease.

   Of note with regards to the ≥2 lines of previous ET requirement:

   - Single agent anti-CDK4/6 therapy for the treatment of metastatic disease is considered a line of therapy
   - Disease progression on adjuvant ET or progression within 12 months of stopping ET can be treated as one prior line ET; these subjects will only require 1 additional line of ET in the metastatic setting
   - Any progression >12 months after discontinuing adjuvant ET or completing a course of adjuvant ET will not be considered a line of therapy
   - Single agent PARP inhibitor therapy is not considered a line of ET
   - Changes in dosing schedules, or discontinuations/re-starting of the same drugs or the addition of a targeted therapy to an ET without progression (e.g., adding a CDK4/6 to a current aromatase inhibitor regimen) will not be considered separate lines of therapy.
6. No prior chemotherapy for advanced or metastatic breast cancer. Subjects who have received chemotherapy in the neo-adjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval (defined as completion of systemic chemotherapy to diagnosis of advanced or metastatic disease) of >12 months.
7. Life expectancy ≥12 weeks at screening.
8. Subjects must have at least one measurable lesion as defined per RECIST v1.1 or have non-measurable, bone-only disease that can be assessed by CT or MRI or X-Ray. Lytic or mixed lytic bone lesions that can be assessed by CT or MRI or X-Ray in the absence of measurable disease as defined above is acceptable; subjects with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible.
9. Has LVEF ≥ 50% by either echocardiography (ECHO) or multiple-gated acquisition

(MUGA) within 28 days before randomization.

10. Adequate organ and bone marrow function within 14 days before randomization. For all parameters listed below, the most recent results available must be used to meet the inclusion criteria:

Item	**Laboratory value**
Hematology (without receiving erythropoietin [EPO], granulocyte colony-stimulating factor [G-CSF], or granulocyte-macrophage colony stimulating factor [GM-CSF] within 14 days and blood, red blood cell (RBC), platelet transfusion within 7 days prior to the sampling)	
Platelet count	≥ 100,000/mm^3
Hemoglobin (Hb)	≥ 9.0 g/dL
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Chemistry	
Creatinine	Creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault equation, see Section 11.6.2)
AST and ALT	≤ 3 × ULN (if liver metastases are present, ＜ 5 × ULN)
Total bilirubin	≤ 1.5 × ULN if no liver metastases or <3 × ULN in the presence of Gilbert's syndrome or liver metastases at baseline
Serum albumin	≥ 2.5 g/dL
Coagulation	
INR/PT and either partial thromboplastin or activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

11. Has adequate treatment washout period before randomization, defined as table below.

Previous treatment	**Washout period**
Hormonal therapy	≥ 3 weeks
Immunotherapy (non-antibody-based therapy)	≥ 3 weeks

Previous treatment	**Washout period**
Small molecule targeted agents	≥ 2 weeks or 5 half-lives, whichever is longer
Antibody-based anti-cancer therapy	≥ 4 weeks with the exception of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g., denosumab for the treatment of complications resulting from bone metastases)
Chloroquine/Hydroxychloroquine	≥ 3 months
Traditional Chinese Medicine with anti-tumor activity	≥ 2 weeks
Major surgery	≥ 4 weeks (or 2 weeks for low-invasive cases [e.g., colostomy]), excluding operations or surgeries that can be recovered within 14 days prior to randomization, and have been recovered by the investigator's assessment, e.g., tumor biopsy, puncture, palliative operation, rectal/gastrostomy, etc.
Radiation therapy	≥ 4 weeks (radiation therapy including palliative radiation therapy to chest). ≥2 weeks (palliative radiation therapy to other areas).
CAR-T	≥2 weeks

12. Evidence of post-menopausal status (Section 11.4.1) or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner. For women of childbearing potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine beta-human chorionic gonadotropin (β-HCG) pregnancy test prior to each administration of study treatment.

    Women of childbearing potential are defined as those who are not surgically sterile (i.e., underwent bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

13. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Section 11.4.2) from the time of screening and must agree to continue using such precautions for 7 months after the last dose of study treatment. Not all methods of contraception are highly effective. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject for the duration of the study treatment and the drug washout period (7 months). Periodic abstinence (e.g., calendar ovulation, symptothermal, post ovulation methods), the rhythm method, and the withdrawal method

are not acceptable methods of contraception. Female subjects must not donate ova, or retrieve for their own use, from the time of screening and throughout the study treatment period, and for at least 7 months after the last dose of study treatment. They should refrain from breastfeeding throughout this time. Preservation of ova may be considered prior to randomization in this study.

14. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening and throughout the duration of the study treatment and the washout period (4 months after the last dose of DB-1303, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine). Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject for the duration of the study treatment and the drug washout period. Periodic abstinence (e.g., calendar ovulation, symptothermal, post ovulation methods), the rhythm method, and the withdrawal method are not acceptable methods of contraception. It is strongly recommended for the female partners of a male subject also use at least one highly effective method of contraception throughout this period, as described Section 11.4.2. In addition, male subjects should refrain from fathering a child or donating sperm throughout the duration of the study and the washout period (4 months after the last dose of DB-1303, 6 months after the last dose of paclitaxel or nab paclitaxel, and 3 months after the last dose of capecitabine). Preservation of sperm should be considered prior to randomization in this study

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Ineligible for all options in the investigator’s choice chemotherapy arm. Subjects with contraindications to capecitabine, paclitaxel, and nab-paclitaxel treatment, per local prescribing information, cannot be enrolled to the study.
2. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, uncontrolled or significant cardiovascular disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to give written informed consent.
3. Clinically uncontrolled pleural effusion, ascites or pericardial effusion requiring drainage, peritoneal shunt or cell-free concentrated ascites reinfusion therapy within 2 weeks prior to the randomization.
4. Uncontrolled or significant cardiovascular disease includes any of the following:
    1) Subjects with a medical history of myocardial infarction within 6 months before randomization or symptomatic CHF (NYHA Class II to IV). Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any

myocardial infarction related symptoms, should have a cardiologic consultation before randomization to rule out myocardial infarction.

2) Uncontrolled hypertension (defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg)

3) Uncontrolled and/or clinically important cardiac arrhythmias

4) Corrected QT interval by Fredericia's method (QTcF) prolongation to >470 ms (both females and males) based on average of screening triplicate 12-lead electrocardiogram (ECG)

5. Has as a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.

6. Subjects with prior use of immunosuppressive medication within 14 days prior to first study dose, except for intranasal and inhaled corticosteroids or systemic corticosteroids at doses less than 10 mg/day of prednisone or equivalent.

7. Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (i.e., pulmonary emboli within three months prior to study randomization, severe asthma, severe chronic obstructive pulmonary disorder [COPD], restrictive lung disease, significant pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e., rheumatoid arthritis, Sjogren's syndrome, sarcoidosis etc.), and/or prior pneumonectomy (complete).

8. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals

9. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study randomization.

10. Active primary immunodeficiency, known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjects should be tested for HIV prior to randomization if required by local regulations or by the institutional review board (IRB)/Independent ethics committee (IEC).

    Notes:

    1) Inactive hepatitis B surface antigen (HBsAg) carriers, treated and with stable hepatitis B (HBV DNA < 500 IU/mL or < 2500 copies/mL) can be enrolled. Subjects with detectable HBsAg or detectable HBV DNA should be managed per treatment

guidelines. Subjects receiving antivirals at screening should have been treated for > 2 weeks before randomization.

2) Subjects with a negative HCV antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for subjects testing positive for HCV antibody. Subjects receiving antivirals at screening should have been treated for > 2 weeks before randomization.

11. Receipt of live, attenuated vaccine (mRNA and replication-deficient adenoviral vaccines are not considered attenuated live vaccines) within 30 days prior to the first dose of study treatment. Note: Subjects, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of study treatment.

12. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline.

    Note: Subjects may be enrolled with chronic, stable Grade 2 toxicities (defined as no worsening to ≥Grade 2 for at least 3 months prior to randomization and managed with standard of care treatment) that the investigator deems related to previous anticancer therapy, such as:

    1) Chemotherapy-induced neuropathy

    2) Fatigue

    3) Residual toxicities from prior immune-oncology treatment: Grade 1 or Grade 2 endocrinopathies which may include:

    · Hypothyroidism/hyperthyroidism

    · Type 1 diabetes

    · Hyperglycemia

    · Adrenal insufficiency

    · Adrenalitis

    · Skin hypopigmentation (vitiligo)

13. Pregnant or breastfeeding female subjects, or subjects who are planning to become pregnant.

14. Subjects with a known hypersensitivity to either the drug substances, inactive ingredients in the drug product or to other monoclonal antibodies

15. History of another primary malignancy within 3 years, except adequately resected non melanoma skin cancer, curatively treated in situ disease, other solid tumors curatively treated, or contralateral breast cancer.

16. Previous treatment with anti-HER2 therapy.
17. Prior treatment with antibody-drug conjugate that comprised an exatecan derivative that is a topoisomerase I inhibitor.
18. Prior randomization or treatment in a previous DB-1303 study regardless of treatment assignment.
19. Participation in another clinical study with a study treatment administered in the last 30 days or if the washout period is less than five half-lives prior to first dose of study treatment or concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow up period of an interventional study. Of note, tissue screening for this study while a subject is on treatment in another clinical study is acceptable.
20. Has substance abuse or any other medical conditions such as psychological conditions, that may, in the opinion of the Investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.

5.3 Lifestyle Considerations

The safety-specific restrictions of DB-1303 are listed below and also in Section 6.5.

- It is important to inform subjects that they should refrain from taking any medications listed in Table 6 and minimize the use of restricted medications listed in Table 7 during the treatment period and for 35 days (+7 days) after the last study treatment. Subjects must consult with the Investigator before taking any medication during this period.
- During the course of the study, female and male subjects should strictly adhere to the contraception requirements and restrictions outlined in inclusion criteria #13 and 14.
- Due to the possibility of paclitaxel, nab-paclitaxel, and capecitabine chemotherapy causing irreversible infertility/testicular damage, men are advised to seek counselling on sperm storage before starting treatment, and preservation of sperm should be considered prior to randomization in this study.

Restrictions relating to concomitant medications are described in Section 6.5.

5.4 Screen Failures

Screen failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (i.e., subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (i.e., not randomized subjects). Subjects may be rescreened a single time, but they may not be re-randomized to treatment. In addition, subjects who are pre-screened may also be rescreened one single time, and may enter tissue screening on rescreen. Rescreened subjects should be assigned the subject number as for the initial screening. Rescreening should be documented so

that its effect on study results, if any, can be assessed.

Subjects who screen failed because of having a central HER2 test of HER2 IHC 0 cannot be rescreened unless a strong rationale can be provided to allow for HER2 retesting (e.g., subject received a subsequent line of therapy). In the event Investigators would like to rescreen subjects who have screen failed due to having a central HER2 test result of HER2 IHC 0, the rationale must be documented and a discussion with the Duality Biologics Medical Monitor is required.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, local HER2 testing results, details about sample sent for central HER2 testing and any SAE for screen failures including subjects who are identified in the tissue screening phase as not eligible.

6 STUDY INTERVENTIONS (TREATMENTS)

Study intervention or study treatment is defined as any investigational intervention/treatment (including marketed product comparator and placebo) or medical device(s) intended to be administered to a subject according to the study protocol. Study treatment in this study refers to DB-1303 and investigator's choice chemotherapy (paclitaxel, nab-paclitaxel and capecitabine).

6.1 Study Interventions (Treatments) Administered

6.1.1 Study Treatments

The study treatments to be administered in this study are shown in Table 5.

Table 5 Study Treatments

Study treatment name	Dosage Presentation	Unit Dose Strength	Dosage level	Route of administration	Schedule	Packaging and labeling	Sourcing
DB-1303	Vial	Powder for concentrate for solution for infusion 100 mg/vial	8 mg/kg	IV	Q3W	DB-1303 will be provided in 100 mg vials. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement	Provided centrally by Duality Biologics
Paclitaxel	Vial	Variable	80 mg/m^2	IV	QW in 3-week cycles	If centrally sourced [a], product will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per regulatory country requirements.	Sourced locally by site [a]
Capecitabine	Tablet	Capecitabine 500 mg film-coated tablets and/or Capecitabine 150 mg film-coated tablets	1000 or 1250 mg/m^2	Oral	Twice daily orally for 2 weeks followed by a 1 week rest period in 3-week cycles	If centrally sourced [a], product will be provided either in blister packs in carton, bottles or in a wallet. If applicable, the blister pack and carton, or bottle, will be labeled. If provided in a wallet, only the wallet will be labelled. All labels will be labelled in accordance with GMP Annex 13 and per country requirements.	Sourced locally by site [a]
Nab-paclitaxel	Vial	Variable	100 mg/m^2	IV	QW for 3 weeks followed by a one-week rest period in 4-week cycles	If centrally sourced [a], product will be provided in vials. Each vial will be labelled in accordance with GMP Annex 13 and per regulatory country requirements.	Sourced locally by site [a]

a. Under certain circumstances when local sourcing is not feasible, paclitaxel/nab-paclitaxel/capecitabine may be supplied centrally through Duality Biologics

6.1.2 DB-1303

DB-1303 will be supplied by Duality Biologics as a 100 mg lyophilized powder for infusion after reconstitution and dilution. The reconstituted drug product is a clear and colorless to yellow liquid and practically free from visible particles.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product should be kept in original packaging until use to prevent prolonged light exposure.

6.2 Preparation/Handling/Storage/Accountability of Study Treatments

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatments.
- Only subjects randomized in the study will receive study treatment and only authorized site staff will supply or administer study treatment. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

The study treatments provided for this study will be used only as directed in this protocol and the Pharmacy Manual. The study site staff will account for all study treatments dispensed to and returned from the subject. The study site staff will account for all study treatments received at the site, unused study treatments and for appropriate destruction of all unused study treatments. Certificates of delivery and destruction should be signed and filed in the study documentation.

6.2.1 DB-1303

DB-1303 will be administered at room temperature by controlled infusion into a peripheral or central vein. The standard infusion time for DB-1303 is over approximately 90 minutes for the first infusion. If the first infusion is well tolerated and the subject does not experience an infusion-related reaction, then the minimum infusion time for subsequent cycles is 30 minutes. However, if there are interruptions during the infusion, the total time from the start of reconstitution to the end of infusion should not exceed 4 hours. An 90-minute observation period is recommended after the first infusion of DB-1303. Refer to Pharmacy Manual for

details.

Subjects will receive a dose of 8 mg/kg Q3W. Note: Subjects with mild and moderate hepatic impairment may start at a lower starting dose of DB-1303 based on emerging clinical evidence prior to implementation. The number of treatment cycles with DB-1303 is not fixed. Upon commencing study treatment, subjects will continue receiving DB-1303 until RECIST 1.1 disease progression, withdrawal of consent or any of the discontinuation criteria are met.

The subject's weight at screening will be used to calculate the initial dose. If, during the course of treatment, the subject's weight has changed by ≥ ± 10%, the subject's dose will be recalculated based on the subject's updated weight. However, sites can modify the dosage if the weight changes after screening and if the site's local practice is more conservative than the 10% threshold for dose adjustment (e.g., dose adjustment if 5% variance in the subject's weight).

Do not co-administer other drugs through the same infusion line.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. If either preparation time or infusion time exceeds the time limit a new dose must be prepared from new vials. DB-1303 does not contain preservatives, and any unused portion must be discarded.

Refer to the Pharmacy Instructions for detailed information about preparation and administration of DB-1303.

6.2.2 Paclitaxel, Capecitabine and Nab-paclitaxel

Subjects will receive the investigator's choice chemotherapy in doses specified in Table 5. Refer to the local label for details on handling. The investigator's choice of chemotherapy should be predefined, prior to randomization. The investigator's choice chemotherapies, paclitaxel, capecitabine and nab-paclitaxel, will either be locally sourced or centrally supplied by Duality Biologics and will be administered according to local prescribing information or treatment guidance in general use by the investigation site or drug label for centrally sourced medications. An 1-hour observation period is recommended after the first infusion of chemotherapy drugs that are administered intravenously The number of treatment cycles for the investigator's choice chemotherapy is not fixed.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Subject Enrollment and Randomization

All subjects will be randomly assigned to an arm using IRT. Before the study is initiated, the login information and directions for the IRT will be provided to each site.

If a subject withdraws from the study, then his/her randomization code cannot be reused.

Withdrawn subjects will not be replaced.

Investigators should keep a record of subjects (i.e., the subject screening log) who entered screening and/or tissue screening.

At tissue screening/screening, the Investigators or suitably trained delegate will do the following:

- Tissue screening ICF will be signed by subjects to permit for tumor tissue sample collection (HER2 status) and testing prior to the 28-day screening window. At the time of signing tissue screening ICF, Investigators should ensure that there is a reasonable possibility that the subject would be candidate for this study based on available information (e.g., medical history, availability of required number of slides for study). Subjects who signed the tissue screening ICF will be considered enrolled. The main informed consent form must be signed before initiating all other screening assessments. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the subject. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization. For subjects with a single target lesion (TL), if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.
- Obtain a unique subject number at tissue screening. This number is the subject's unique identifier and is used to identify the subject on the electronic case report forms (eCRFs).
- Obtain tumor sample and send for centralized HER2 testing. A mandatory FFPE tumor sample must be provided, preferably obtained at the time of metastatic disease or later; the most recently collected pre-randomization tumor sample that meets the tissue requirements specified in Section 8.6 is required. If no archival specimens are available, a newly acquired biopsy specimen is acceptable. Obtaining the tumor sample should be given very high priority and as such, a tissue screening ICF should be signed for subjects to permit for sample collection and testing prior to the 28-day screening window in order to permit for analysis in a timely manner. Screening procedures may be carried out while HER2 status is being tested, however it is recommended that the main ICF and other study procedures not be started until the sample submitted for HER2 testing is accepted for central laboratory testing. Tumor lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy; and in this instance only core needle (not excisional/incisional) biopsy is allowed.
- Determine subject eligibility (see Sections 5.1 and 5.2).

If the subject is ineligible and not randomized, such a subject should be recorded by site personnel in the IRT system as "screen-failure" and the IRT should be contacted to terminate the subject in the system.

The day subjects receive the first dose of study treatment is Cycle 1 Day 1. Every effort

should be made to minimize the time between randomization and dosing. Dosing should occur no more than 3 days after randomization. If it is anticipated that dosing cannot occur within 3 days, a discussion with the Sponsor Medical Monitor is required. Subjects must not be randomized and must not receive study treatment unless all eligibility criteria have been met.

6.3.2 Procedures for Handling Incorrectly Randomized Subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized to treatment, and they must be withdrawn from the study.

When a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Duality Biologics Medical Monitor immediately, and a discussion should occur between the Duality Biologics Medical Monitor and the Investigator regarding whether to continue or discontinue the subject from treatment. The Duality Biologics Medical Monitor must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the subject.

6.3.3 Methods for Assigning Treatment Groups (Randomization)

The actual treatment given to subjects will be determined by the randomization scheme in the IRT. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization stratum. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of subjects randomized to each treatment group.

Randomization codes will be assigned strictly sequentially, within each stratum (refer to the 3 stratification factors in Section 4.1), as subjects become eligible for randomization. When medication is provided centrally by Duality Biologics, the IRT will allocate kit identification numbers at each treatment visit. If medication is provided locally, IRT will not provide kit numbers.

6.3.4 Methods for Ensuring Blinding

This is an open-label study for the personnel at study sites; however, the trial will be conducted as “sponsor-blind” and the specific treatment to be taken by a subject will be assigned using an IRT (see Section 6.3.3 for details). To maintain the integrity of the study, Duality Biologics personnel directly involved in the study conduct will not undertake or have access to efficacy data aggregated by treatment arm prior to final data readout for the primary endpoint. Before the first subject is randomized, a Trial Integrity Document will be generated in which data access levels for relevant Duality Biologics personnel will be pre-specified.

6.4 Study Treatment Compliance

When subjects are dosed at the site, they will receive study treatment directly from the

Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study treatment start and stop dates, including any changes from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations should be recorded in the eCRF. The reason should also be documented. The Investigator or pharmacist must retain records of all study treatments administered at the site. The Study Monitor will check these records to confirm compliance with the protocol administration schedule.

Capecitabine is the only oral intervention in this study and will be self-administered by the subjects at home. Subjects will be instructed to bring capecitabine dosing diaries and all blister packs, bottles, or wallets of capecitabine (empty, partially empty, or full) to the clinic for each study visit. For each cycle, subjects should return all unused tablets during the dispensation visit of the subsequent cycle, at which point a new set of tablets will be dispensed to the subjects. In this case, the compliance will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Accountability records should be maintained by the site staff and should be current and up to date. In case of low compliance, subjects should be retrained by the site staff, and the retraining should be documented.

6.5 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening (signing main ICF) until the end of the clinical treatment phase of the study including the 35-day (+7 days) follow-up period following the last dose of study treatment.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrollment or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, unit and frequency

6.5.1 Restrictions on Concomitant Medications/Therapies

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables (Table 6, Table 7 and Table 8) and apply to all treatment arms. Refer also to the dose

modification and toxicity management guidelines (see Section 6.6.1.1). Refer to the local prescribing information for capecitabine, paclitaxel and nab-paclitaxel, with regards to warnings, precautions, contraindications and prohibited medications during treatment.

Table 6 Prohibited Concomitant Medications/Therapies

Prohibited medication/class of drug	**Usage**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment
mAbs against HER2 other than those under investigation in this study	Should not be given concomitantly whilst the subject is on study treatment
Any concurrent anti-cancer therapy, including chemotherapy, targeted therapy, radiotherapy, immunotherapy, traditional Chinese medicine or herbs, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	• Should not be given concomitantly whilst the subject is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable). • For DB-1303 treatment, palliative radiotherapy to the chest area is prohibited. • For both treatment arms, palliative radiotherapy (outside of palliative radiotherapy to the chest area) is permitted after consultation with the Medical Monitor. The lesions must be known to be present at the time of study entry and the Investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. For subjects with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (e.g., lesions at risk for spontaneous micro-fractures or painful lesions).
Live attenuated vaccines	Should not be given during the study and up to 35 days after the last dose of study treatment.
Immunosuppressive medications	DB-1303 cannot be administered when the subject is taking immunosuppressive medications, including corticosteroids with the exception of: • Short-term courses (< 2 weeks) • Low to moderate dose (less than 10 mg/day of prednisone or equivalent) • Long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy) • Administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection. Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed.

Table 6 Prohibited Concomitant Medications/Therapies

Prohibited medication/class of drug	Usage
	Corticosteroids used as premedication for the prevention of nausea and vomiting is allowed. A temporary period of steroid treatment will be allowed for different indications after discussion with the Medical Monitor (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.). Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study. Use of immunosuppressive medications for the management of treatment-related AEs or in subjects with contrast allergies is acceptable. Immunosuppressive medications also include drugs like methotrexate, azathioprine, and tumor necrosis factor-alpha blockers.
Chloroquine/hydroxychloroquine	Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. If treatment with chloroquine or hydroxychloroquine treatment is absolutely required, study treatment must be interrupted. If chloroquine or hydroxychloroquine is administered, then a wash-out period of more than 3 months is required before restarting study treatment.

AE = adverse event; HER2 = human epidermal growth factor receptor 2; mAb = monoclonal antibody

Table 7 Restricted Medications/Therapies

Restricted medication/class of drug	Usage
Strong CYP3A4 inhibitors	If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying DB-1303 treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is co-administered and DB-1303 treatment cannot be delayed, subjects should be closely monitored for adverse reactions. See Section 11.9 Appendix 9 for the list of strong CYP3A4 inhibitors.

Table 7 Restricted Medications/Therapies

Restricted medication/class of drug	Usage
Tobacco products, e-cigarettes and vaping	Use of tobacco products, e-cigarettes and vaping is strongly discouraged but not prohibited. Any prior or current use of these products must be recorded in the eCRF.
Dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments	Concomitant use is doscouraged, but not prohibited.
QT-prolonging medications	Drugs that prolong the QTc interval should be restricted unless it is absolutely necessary per the investigator's discreption

eCRF = electronic case reported form; CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4

Table 8 Supportive Medications/Therapies

Supportive medication/class of drug	Usage
Anti-emetic agents including 5-hydroxytryptamine receptor (5-HT3) antagonists, Neurokinin-1 (NK1) receptor antagonists and steroids (e.g., dexamethasone)	DB-1303 is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of DB-1303, subjects should be premedicated with a combination regimen of two or three medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting**.**
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all subjects
Inactivated viruses, such as those in the influenza vaccine	Permitted

Supportive medication/class of drug	Usage
Coumadin anticoagulants	Permitted
Hematopoietic growth factors	Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator
Approved bone-modifying agents (e.g., bisphosphonates or RANKL-targeting agents) to treat or control bone disease	Permitted.
Required for management of other medical conditions.	As required except for those identified as "prohibited," as listed in Table 6.

6.5.2 Other Concomitant Medications

Other medications other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.6 Guidelines for Dose Modification

6.6.1 Individual Subject Dose Modifications

6.6.1.1 DB-1303

The following dose modifications apply to toxicities that are attributable to DB-1303:

- Dose delays are permitted for DB-1303 therapy. In instances for delays in dosing, the dosing interval for the next DB-1303 cycle may be shortened as clinically feasible to gradually align with the schedule of tumor efficacy assessment. Two consecutive doses must be administered at least 19 days apart.
- Every effort should be made to limit DB-1303 delay, however in circumstances of AE management or medical intervention, DB-1303 can be held up to 7 weeks (49 days) from the last DB-1303 dose. If a subject is assessed as requiring a dose delay longer than 28 days from the planned date of administration, the subjects will permanently discontinue the study treatment. In such cases, the subject may continue the study treatment per the discretion of the Investigator after consultation with the Sponsor Medical Monitor or designee. During this time scheduled CT/MRI scans should continue as per protocol, and subjects should fulfil all of the following criteria:
  - DB-1303 may be resumed with confirmation of continued benefit per RECIST 1.1. Scans should be performed at the frequency defined per protocol, while the drug is being held. At minimum, 1 scan must be done within 6 weeks prior to restarting the study drug.
  - DB-1303 is restarted within the guidance of the toxicity management for DB-1303.
  - No prohibited concomitant medications have been administered since the last dose of DB-1303.

- For management of dose delays due to DB-1303-related events, the dose modification and toxicity management guidelines should be followed, as applicable.

In summary, if a subject experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted (or discontinued) or supportive therapy administered as required.

Investigators may consider dose interruptions, reductions or discontinuations of DB-1303 according to the subject's condition or refer to the table below.

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
No toxicity	Maintain dose and schedule
Infusion-related reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, and/or hypotension) is observed during administration, the infusion rate should be reduced by 50%, and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, and/or IV fluids); prophylactic medications indicated for ≤24 hrs)	Administration of DB-1303 should be interrupted and symptomatic treatment started (e.g., antihistamines, NSAIDs, narcotics, and/or IV fluids). If the event resolves or improves to Grade 1, infusion can be restarted at a 50% reduced infusion rate. Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences; urgent intervention indicated)	Administration of DB-1303 should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation, etc., should be administered.
Hematologic toxicity (if supportive therapy fails [as clinically indicated and according to local practice], consider additional toxicity management guideline as below).	
Neutrophil count decreased and/or white blood cell count decreased	
Grade 3	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
Febrile neutropenia (absolute neutrophil count < 1×10^9/L, fever > 38.3°C, or a sustained temperature of ≥ 38 °C for more than 1 hour)	Delay dose until resolved, then reduce dose 1 level
Lymphocyte count decreased [a]	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (< 0.2×10^9/L)	Delay dose until resolved to ≤ Grade 2: If resolved in ≤ 14 days from day of onset, then maintain dose If resolved in > 14 days from day of onset, then reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin < 8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet count decreased	
Grade 3 (platelets < 50 to 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4 (platelets < 25×10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac toxicity	
Symptomatic CHF	Discontinue subject from study treatment
Decrease in LVEF 10% to 20% (absolute value), but LVEF > 45%	Continue treatment with DB-1303
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	Continue treatment with DB-1303 Repeat LVEF assessment within 3 weeks
LVEF 40% to ≤ 45% and decrease is 10% to 20% (absolute value) from baseline	Interrupt DB-1303 dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment If LVEF recovers to within 10% from baseline, resume study drug treatment

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
LVEF < 40% or > 20% (absolute value) drop from baseline	Interrupt DB-1303 dosing. Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study treatment If LVEF has recovered to > 40% and decrease is < 20% from baseline, follow appropriate guidance above
Electrocardiogram QTc prolonged	
Grade 3 (Average QTc > 500 ms or > 60 ms change from baseline)	Delay dose until resolved to ≤ Grade 1 (corrected QT ≤ 480 ms), then determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. If attributed to DB-1303, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
Pulmonary Toxicity	Work-up of suspected ILD/pneumonitis: If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. Evaluations should include: High resolution CT Pulmonologist consultation (infectious disease consultation as clinically indicated) Blood culture and complete blood count. Other blood tests could be considered as needed Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible Pulmonary function tests and pulse oximetry (SpO_2) Arterial blood gases if clinically indicated One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered, as needed. If the AE is confirmed to have an etiology other than treatment-related ILD/pneumonitis, follow the management guidance outlined in the “Other Non-Laboratory Adverse Events” dose modifications. If another etiology for the AE cannot be identified and it could be related to DB-1303, then follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness should be followed until resolution.

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
Grade 1	Management: Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry Consider follow-up imaging in 1-2 weeks (or as clinically indicated) Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines * Dose modification: The administration of DB-1303 must be interrupted. DB-1303 can be restarted only if the event is fully resolved to Grade 0: If resolved in ≤ 28 days from day of onset, maintain dose If resolved in > 28 days from day of onset, reduce dose 1 level Management of Grade 1 ILD/Pneumonitis: If the event Grade 1 ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 7 weeks (49 days) from the last infusion, the drug should be discontinued. * If a subject is asymptomatic, then the subject should still be considered as Grade 1 even if steroid treatment is given.
Grade 2	Dose Modification: Permanently discontinue subject from study treatment. Management: Promptly start and treat with systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) for at least 14 days followed by a gradual taper over at least 4 weeks Monitor symptoms closely Re-image as clinically indicated If worsening or no improvement in clinical or diagnostic observations in 5 days, Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and switching treatment administration to intravenous (e.g., methylprednisolone) Re-consider additional work-up for alternative etiologies as described above Escalate care as clinically indicated

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
Grade 3 or 4	Dose modification: Permanently discontinue subject from study treatment. Management: Hospitalization required Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days followed by gradual taper over at least 4 weeks Re-image as clinically indicated If still no improvement within 3 to 5 days, Re-consider additional work-up for alternative etiologies as described above Consider other immunosuppressants and/or treat per local practice
Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Blood creatinine increased	
Grade 3 (> 3.0 to 6.0 × ULN)	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose 1 level
Grade 4 (> 6.0 × ULN)	Discontinue subject from study treatment
Hepatic toxicity	
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with simultaneous blood bilirubin increased	
AST/ALT ≥ 3.0 x ULN with simultaneous total bilirubin > 2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline.

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	
Grade 2 (> 3.0 to 5.0 × ULN if baseline was normal; > 3.0 to 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT
Grade 3 (> 5.0 to 20.0 × ULN if baseline was normal; > 5.0 to 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1 if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline, then: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 3: (> 8.0 to 20.0 × ULN if baseline was normal; > 8.0 to 20.0 × baseline if baseline was abnormal) In subjects with liver metastases, if the baseline level was > 3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4 (> 20 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Blood bilirubin increased	
Grade 2 (> 1.5 to 3.0 × ULN if baseline was normal; > 1.5 to 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (> 3.0 to 10.0 × ULN if baseline was normal; > 3.0 to 10.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then reduce dose 1 level If resolved in > 7 days from day of onset, then discontinue DB-1303 If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 2: If resolved in ≤ 7 days from day of onset, then reduce dose 1 level If resolved in > 7 days from day of onset, then discontinue DB-1303

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	**Management guidelines for DB-1303**
Grade 4 (> 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Blood alkaline phosphatase increased	
Grade 3 (> 5.0 to 20.0 × ULN if baseline was normal; > 5.0 to 20.0 × baseline if baseline was abnormal) Or Grade 4 (> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
<u>Gastrointestinal</u>	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 3 days from day of onset, then maintain dose If resolved in > 3 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue subject from study treatment
<u>Other laboratory adverse events</u>	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue subject from study treatment
<u>Other non-laboratory adverse events</u>	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: If resolved in ≤ 7 days from day of onset, then maintain dose If resolved in > 7 days from day of onset, then reduce dose 1 level
Grade 4	Discontinue subject from study treatment

Table 9 Dose Modification and Toxicity Management Guidelines for DB-1303

Worst toxicity CTCAE v 5.0 Grade (unless otherwise specified)	Management guidelines for DB-1303

AE = adverse event; ALT = alanine transaminase; AMI = acute myocardial infarction; AST = aspartate transaminase; CHF = congestive heart failure; CT = computer tomography; CTCAE = common terminology criteria for adverse events; ECG = electrocardiogram; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; NSAIDS = non-steroidal anti-inflammatory drugs; PK = pharmacokinetics; SpO_2 = pulse oximetry; TMGs = toxicity management guidelines; ULN = upper limit normal

[a] There will be no dose modifications for Grade 1 to Grade 3 lymphopenia

Note: All dose modifications should be based on the worst preceding toxicity

Dose Modification Criteria for Suspected or Confirmed COVID-19

Please see Section 11.8 for dose modification and management plan for subjects with confirmed or suspected COVID-19 who are being treated with DB-1303.

6.6.1.2 Investigator's Choice Chemotherapy

Investigators should follow the local prescribing information and standard clinical practice regarding management of paclitaxel, nab-paclitaxel and capecitabine-related toxicities. The investigator's choice chemotherapy treatment can be interrupted for up to 28 days from the planned date of administration. If a subject requires a dose delay longer than 28 days, resumption of treatment should be discussed with the Duality Biologics Medical Monitor. The investigator's choice of chemotherapy should be predefined, prior to randomization.

Prophylactic therapy, supportive care prior to and after chemotherapy treatment should be given as needed on a prophylactic and treatment basis in compliance with institutional standards. Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator in compliance with the standards of the center.

6.7 Intervention after the End of the Study

No intervention is planned after the end of the study. After the final analysis, Duality Biologics will continue to supply open-label drug to subjects receiving DB-1303 and to subjects receiving centrally supplied capecitabine, paclitaxel, and nab-paclitaxel up to the time that they discontinue the treatment for whatever reason.

In the event that a roll-over or safety extension study is available at the time of the final data cut off (DCO) and database closure, subjects currently receiving DB-1303 may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any subject who would be proposed to move to such a study would be asked to sign a new ICF.

7 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

7.1.1 Permanent Discontinuation of Study Treatment

Subjects may be discontinued from study treatment in the following situations. Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study. Subjects who permanently discontinue study treatment will continue to have follow-up assessments per the protocol. Subjects will be permanently discontinued from the treatment if the following criteria are met:

- Withdrawal of consent by subject. The subject is, at any time, free to discontinue treatment, without prejudice to further treatment. A subject who discontinues study treatment is normally expected to continue to participate in the study (e.g., for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 1.3).
- Occurrence of any AE that, in the opinion of the Investigator or Duality Biologics, contraindicates further dosing
- Occurrence of any AE that meets the criteria for permanent discontinuation as defined in toxicity management guidelines for DB-1303 (Section 6.6.1.1) or as defined in the local prescribing information for paclitaxel, nab-paclitaxel and capecitabine
- Pregnancy or intent to become pregnant
- Severe non-compliance with the study protocol that, in the opinion of the Investigator or Duality Biologics, warrants withdrawal from study treatment (e.g., refusal to adhere to scheduled visits)
- When a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Duality Biologics Medical Monitor immediately, and a discussion should occur between the Duality Biologics Medical Monitor and the Investigator regarding whether to continue or discontinue the subject from treatment (Section 6.3.2). The Duality Biologics Medical Monitor must ensure all decisions are appropriately documented. The Investigator should make documentation in the medical record as appropriate.
- Initiation of alternative anticancer therapy including another investigational agent
- Objective progressive disease, as determined by the investigator per criteria set forth in RECIST 1.1 (refer to Section 11.5)
- Death
- Study terminated by Duality Biologics
- Lost to follow-up

All subjects who are discontinued from study treatment should complete protocol-specified procedures for discontinuation of study treatment (details in Section 7.1.2) and follow-up procedures (details in Section 1.3). Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (e.g., death certificates) as allowed by local laws.

The EOT visit should be performed as soon as the subject is permanently discontinued from study treatment. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

7.1.2 Procedures for Discontinuation of Study Treatment

Discontinuation of study treatment does not impact the subject's participation in the study. A subject who decides to discontinue the study treatment will always be asked about the reason(s) for discontinuation and the presence of any AE. The subject should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the subject does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the subject, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Subjects who are permanently discontinued from further receipt of study treatment, regardless of the reason, will be identified as having permanently discontinued treatment. Subjects who are permanently discontinued will enter follow-up (for details, see Section 1.3). Subjects who have permanently discontinued from further receipt of study treatment will need to be recorded in the IRT.

Subjects who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 scans performed Q6W ±1week for the first 48 weeks from randomization, and then Q9W ±1week (starting at Week 48) thereafter until RECIST 1.1 disease progression followed by an additional tumor evaluation scan, if feasible. (see Section 1.3).

All subjects will be followed for survival until the end of the study. Survival information may be obtained via telephone contact with the subject, subject's family, or by contact with the subject's current physician. Subjects who decline to return to the site for evaluations should be contacted by telephone, following the timing and procedures indicated in the SoAs (see Section 1.3), as an alternative.

7.2 Subject Withdrawal from the Study

- A subject may withdraw from the study at any time at her/his own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an EOT visit should be conducted, as shown in the SoA and for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The subject will discontinue the study treatment and be withdrawn from the study at that time.
- If the subject withdraws consent for disclosure of future information, Duality Biologics may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed and there is insufficient information to determine the subject's vital status at that time. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study. Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get study treatment. Public sources may be searched for vital status

information. If vital status is determined as deceased, this will be documented and the subject will not be considered lost to follow-up. Duality Biologics personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 11.1.6.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (see Section 1.3)
- The Investigator will ensure that data are recorded on the eCRFs.
- The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.
- Immediate safety concerns should be discussed with Duality Biologics immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoAs (see Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Data management will be performed by Duality Biologics or a delegate according to the Data Management Plan.
- AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the World Health Organization (WHO) Drug. Classification coding will be performed by Duality Biologics or a delegate. The data collected through third party sources will be obtained and reconciled against study data.
- Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.
- When all data have been coded, validated, signed, and locked, a clean file will be declared.
- SAE reconciliation reports are produced and reconciled with the Subject Safety database and/or the investigational site.

8.1 Efficacy Assessments

8.1.1 RECIST 1.1 Assessments

RECIST 1.1 tumor assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis at screening (as baseline) with follow-ups at Q6W ± 1 week from the date of randomization for 48 weeks, and then Q9W ± 1 week, starting at Week 48, until objective disease progression (see SoAs in Section 1.3). For subjects with bone-only disease that is non-measurable, RECIST 1.1 tumor assessments may be performed using X-Ray in addition to the required CT or MRI scans of the chest, abdomen and pelvis.

In addition, an IV contrast-enhanced MRI (preferred) or IV contrast-enhanced CT of the brain is to be included for all subjects at screening/baseline. Regularly scheduled follow-up brain scans (Q6W ±1 week from the date of randomization for 48 weeks, and then Q9W ±1 week, starting at Week 48 and continuing until RECIST 1.1 disease progression) are mandatory for all subjects who were enrolled with baseline stable brain metastases, while subjects without brain metastases do not need additional brain scans for subsequent tumor assessments, unless clinically indicated.

The on-study imaging schedule MUST be followed regardless of any delays in dosing. Additional anatomy should be imaged based on signs and symptoms of individual subjects at baseline and follow-up. If an unscheduled assessment was performed (e.g., to investigate clinical signs/symptoms of progression) and the subject has not progressed, every attempt should be made to perform the subsequent imaging at their next regularly scheduled visit. A bone scan will be performed for all subjects at baseline and subsequent scans will be performed on subjects with bone-only disease or those where bone metastases are their evaluable site of disease. The bone scan will be conducted Q12W±1 week from the date of randomization for 24 weeks, and then Q18W±1 week thereafter. During study treatment, response assessment scans must be reviewed for evidence of disease progression and ILD/pneumonitis prior to administration of the next scheduled dose of study treatment.

8.1.1.1 Central Reading of Scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an Duality Biologics-appointed iCRO for quality control (QC), storage, and for BICR. Guidelines for image acquisition, de-identification, storage of digital copies at the investigative site as source documents, and electronic transfer to the iCRO will be provided in a separate document.

All decisions made during the study will be based on the local investigator’s assessment of radiographic images, clinical status, and relevant examination of the subjects. Sites will submit specific radiographic image files to the centralized data review facility during the study at an ongoing basis or at the Sponsor’s request. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of subjects will be based upon the

results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter (IRC).

8.1.2 Overall Survival (OS)

Assessments for survival must be made every 3 months (±14 days) from the date of 35-day (+7 days) follow-up visit, until death, withdrawal of consent, or study closure, whichever occurs first. Survival information may be obtained via telephone contact with the subject or the subject's family, or by contact with the subject's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, subjects on treatment or in survival follow-up will be contacted following the DCO for the subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the DCO.

8.1.3 PFS2

PFS2 is defined as time from randomization to second progression (the earliest of the progression event subsequent to first subsequent therapy) or death, which comes first. Second progression will be defined according to local standard clinical practice. Following discontinuation of study treatment due to disease progression, as determined by Investigator according to RECIST 1.1 assessment, subjects will continue to be followed at the 35-day (+7 days) follow-up visit, and every 3 months (± 14 days) thereafter for documentation of progression on subsequent anticancer therapy.

8.1.4 Patient-Reported Outcome (PRO) Measures

PRO measures will be used to examine the impact of treatment on symptoms, functioning, HRQoL and overall health status, subject-perceived treatment tolerability, and benefit/risk from the subjects' perspective. The PROs included in this study are as follows and will be administered in this order:

- EORTC QLQ-C30
- EORTC QLQ-BR45
- EQ-5D-5L
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The PROs will be assessed in accordance with the SoA (see Section 1.3).

8.1.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group to assess HRQoL, functioning, and symptoms in cancer clinical trials (see Section 11.12.1). It is a 30-item self-administered questionnaire for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item

symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global QoL scale, 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and 1 item on the financial impact of the disease. All but 2 questions have 4-point scales: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much”. The 2 questions concerning global health status and QoL have 7-point scales with responses ranging from “Very poor” to “Excellent”. For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning, better HRQoL, or greater level of symptoms (Aaronson et al 1993).

8.1.4.2 EORTC QLQ-BR45

The EORTC QLQ-BR45 is an updated version of the BR23, a validated breast cancer-specific module used in conjunction with the core QLQ-C30 to assess breast cancer-specific HRQoL (Bjelic-Radisic et al 2020, Sprangers et al 1996) (see Section 11.12.2). New breast cancer treatments and diagnostics prompted the update of the QLQ-BR23 to include an additional 22 items. The self-administered instrument includes the original 23-items yielding 5 multi-item scores (body image, sexual functioning, arm symptoms, breast symptoms, and systemic therapy side effects). The additional 22 items yield four additional multi-item scales (breast satisfaction, endocrine therapy symptoms, skin mucosis symptoms, and endocrine sexual symptoms). In addition, single items assess sexual enjoyment, future perspective and being upset by hair loss. Items are scored on a 4-point verbal rating scale: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much”. Scores are transformed to a 0 to 100 scale, where higher scores for functioning scales or items indicate better functioning, whereas higher scores for symptom scales or items represent a higher level of symptoms. The free text item in the EORTC QLQ-BR45 instrument is not included in the study, as the utility of this information and the analysis method have not been established.

8.1.4.3 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility. The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (van Reenen et al 2014) (see Section 11.12.3). The questionnaire comprises six questions that cover five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Respondents also assess their health today using the EQ-VAS (visual analogue scale), which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

8.1.4.4 PRO-CTCAE

The PRO-CTCAE, developed by the NCI is included to address tolerability from the subjects’ perspective (see Section 11.12.4). The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available. All applicable translations

available during the study will be used. PRO-CTCAE is an item library of symptoms experienced by subjects while undergoing treatment of their cancer. The items pre-selected for this study are based on a review of the treatment-related symptoms of DB-1303, capecitabine, paclitaxel and nab-paclitaxel and in consideration of symptoms that are already captured in the other PRO instruments with a view to minimize burden. The free text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established.

8.1.4.5 Administration of Patient-Reported Outcome Measures

The PRO measures will be self-administered by subjects using a handheld electronic device in accordance with the SoA (see Section 1.3). In case of handheld device failure, subjects may complete the PRO measures using a web-based version or an appropriate back-up option may be considered with prior approval from Duality Biologics. PROs will be provided in the language of the country in which it will be administered. However, the PRO-CTCAE will only be administered in the languages where a linguistically validated version is already available.

Subjects will complete PRO assessments at home or at the study sites if the assessment timepoint coincides with a scheduled site visit. Similarly, during the follow-up period, subjects will complete PROs at home or at the study site if a scheduled visit coincides with the timepoint. If subjects have had scans or other tests at an outside facility or missed a scheduled data collection site visit, PRO questionnaires should still be completed by subjects at home according to the PRO completion schedule.

While PROs may be completed at home or site visits, subjects should always bring the handheld electronic device to all site visits. It will take approximately 20 to 30 minutes for subjects to complete the questionnaires.

The following instructions should be followed when collecting PRO data:

- The research nurse or appointed site staff must explain to subjects the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is not routinely shared with study staff. Therefore, if subjects have any medical problems, they should discuss them with the doctor or research nurse separately from the PRO assessment.
- The research nurse or appointed site staff must train the subject on how to use the PRO device, using the materials and training provided by the PRO vendor, and provide guidance on whom to call if there are problems with the device if the subject is completing the PRO at home.
- It is vital that the PRO reporting is initiated at the baseline visit (Cycle 1, Day 1), as specified in the SoA (Section 1.3) to capture the effect of study treatment. The handheld

device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.

- All questionnaires must be completed using an electronic device; paper questionnaires are not allowed in this study. It is therefore very important to set up the device in advance of the subject's first treatment visit, ideally at least the day before, to ensure the device is functioning properly and to identify and address any technical issues prior to the visit.
- Study sites must ensure that subjects complete baseline questionnaires before revealing the treatment arm allocated to the subject.
- PRO questionnaires completed at site visits must be completed before treatment administration and ideally before any discussions of health status to avoid biasing the subject's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures, such as collection of laboratory samples, to further minimize bias.
- For PROs collected at site visits, PRO questionnaires must be completed by the subject in a quiet and private location and the subject given enough time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff must remind subjects that there are no right or wrong answers and avoid introducing bias by not interpreting or clarifying items.
- The subject should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a subject uses visual aids (e.g., glasses or contact lenses) for reading and does not have them when he or she visits the site, the subject will be exempted from completing the PROs at the visit.
- Site staff must not read the PRO questionnaires on behalf of the subject. If the subject is unable to read the questionnaire (e.g., is blind, illiterate or not fluent in the available language), that subject should be exempted from completing PRO questionnaires but may still participate in the study. If the subject cannot complete the PRO questionnaires due to reasons other than being blind, illiterate or not fluent in the available language, the Duality Biologics study team must be contacted to determine if they can be exempted. Subjects exempted in this regard should be flagged appropriately by the site staff in the source documents and the Review of PRO/Questionnaire/Diary eCRF.
- Site staff must administer questionnaires available in the language that the subject speaks and understands. Questions should not be read in an available language and translated into another language for the subject.
- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits and document the reason(s) why a subject could not complete assessments in the eCRF. The research nurse or appointed site staff must monitor compliance since minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If the site receives an email notification regarding the subject's

compliance, a check-in call from the study site to ask the subject if they have any difficulties is highly recommended. A solution to enhance/resolve compliance should be discussed with the subject. Discussions and compliance review should be reflected in source documents.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Informed Consent

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including tissue screening/screening/baseline evaluations.

All subjects will be required to provide tissue screening consent to supply a sample of their tumor (HER2 status) for entry into this study. At the time of signing tissue-screen ICF, Investigators should ensure that there is a reasonable possibility that the subject would be a candidate for this study based on available information (e.g., medical history, availability of required number of slides for study).

If laboratory or imaging procedures were performed for alternate reasons prior to signing main consent, these can be used for screening purposes with consent of the subject. However, all results from the screening assessments must have been obtained within 28 days of randomization.

8.2.2 Physical Examinations

Physical examinations will be performed according to the assessment schedules (see Section 1.3).

Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

A targeted physical examination will include, at a minimum, assessments of the lungs, skin, oral, cardiovascular system, and abdomen (liver and spleen).

Body weight is recorded at Day 1 of each Cycle, at EOT and at the 35-day (+7 days) follow-up visit.

8.2.3 Vital Signs

Vital signs (blood pressure [BP], pulse rate, temperature, and respiration rate) will be evaluated according to the SoAs (see Section 1.3).

Vital signs will be evaluated and recorded in eCRF at baseline, before infusion, end of infusion on Day 1 and before infusion on Day 8 and Day 15 of the first cycle; they will be collected before infusion and end of infusion on Day 1 of Cycles 2 and 3; starting from Cycle 4, they will be evaluated only before infusion on Day 1 of each cycle until the end of treatment. Vital signs will be evaluated at the 35-day (+7 days) follow-up visit as well.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.2.4 Electrocardiograms

At screening, ECGs will be obtained in triplicate. Subsequent ECGs will be performed in triplicate only if an abnormality is noted. During the treatment period, ECGs are performed within 3 days prior to dosing (see Section 1.3). ECGs will be taken while the subject is in a supine/semi-recumbent position. Twelve-lead ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QTcF intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

At each time point at which a triplicate ECG is required, 3 individual ECG tracings should be obtained in succession. The full set of triplicates should be completed within 10 minutes. ECGs will be obtained after the subject has been resting. All ECGs should be recorded with the subject in the same physical position. A standardized ECG machine should be used, and the subject should be examined using the same machine throughout the study, where feasible. After ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the subject's medical records. If an abnormal ECG finding at screening or pre-dose is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, ECG intervals and an overall evaluation will be recorded. Any clinically significant abnormalities detected require a confirmatory ECG.

8.2.5 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry, coagulation, hematology, and urine samples for urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Section 1.3).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. For women of childbearing potential, a negative result for serum pregnancy test must be available at the screening visit. A pregnancy test (urine or serum test per institutional guideline) 72 hours before randomization is required. Within 72 hours before randomization, if a positive

urine pregnancy test result is confirmed using a serum test in a female subject of child bearing potential, then the subject should not be randomized into the study. Repeat pregnancy tests (urine or serum test per institutional guideline) are performed 72 hours before treatment administration of each cycle and at EOT.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Section 11.2.

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies (as per local regulations). Hepatitis C polymerase chain reaction (PCR) test may also be done if HCV antibody test is positive.

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN will need to be reported as SAEs.

All subjects should have hematology and clinical chemistry tests performed at screening, Cycle 1, Day 1 (before infusion), Day 8 and Day 15 of Cycle 1, and before infusion on Day 1 of all subsequent cycles until EOT. After permanent treatment discontinuation, follow-up hematology and clinical chemistry assessments are performed at 35 days (+7 days) after last dose of study treatment (see Section 1.3). Coagulation tests and urinalysis should be performed at screening and as clinically indicated during treatment period (see Section 1.3).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

All subjects with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.6 Pulmonary Assessments

Pulse oximetry (SpO_2) should be obtained at the timepoints specified in the SoAs (Section 1.3). SpO_2 should be evaluated by Investigator or the delegate physician prior to the administration of study treatment and at the end of infusion (as applicable per SoA) at each visit.

Pulmonary function tests should include basic spirometry at a minimum with optional additional components as mentioned in Table 10.

Table 10 Spirometry Components

Required spirometry components	Optional spirometry components
FVC (L)	PEF
FVC % predicted	DLCO – see exception in the below text where DLCO is mandatory
FEV1 (L)	FEV6
FEV1 % predicted	TLC
FEV1/FVC %	RV

DLCO = diffusion capacity of the lungs for carbon monoxide; FEV = forced expiratory volume; FVC = forced vital capacity; PEF = peak expiratory flow; FEV1 = FEV-1 second; FEV6 = FEV-6 seconds; L = liters; RV = residual volume; TLC = total lung capacity

Diffusion capacity of the lungs for carbon monoxide (DLCO) will be performed (if feasible), but for subjects with prior severe and/or clinically significant pulmonary disorders, DLCO is a requirement. In event of suspected ILD/pneumonitis, refer to Section 8.2.10.1 for additional pulmonary assessments.

HRCT of the chest will be performed at screening, C4D1, and if ILD/pneumonitis is suspected. Chest CT and/or chest HRCT scans will be reviewed separately for safety for the presence of ILD/pneumonitis prior to administration of the next scheduled dose of DB-1303. If both a non-contrast chest HRCT scan for assessment of ILD/pneumonitis and a diagnostic IV contrast-enhanced chest CT scan for tumor response assessment (as part of chest-abdomen-pelvis imaging) are to be acquired in the same imaging session, HRCT should be performed first.

8.2.7 Echocardiograms/Multiple Gated Acquisition Scans

LVEF will be measured by either echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan. ECHO/MUGA scans will be performed at screening and before infusion on Day 1 of Cycle 5 and every 4 cycles (±7 days) thereafter until the EOT. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function. The modality of the cardiac function assessments must be consistent within a subject (i.e., if ECHO is used for the screening assessment, then ECHO should also be used for subsequent scans if required). The subjects should also be examined using the same machine and operator whenever possible. Subjects should have high-quality, standardized 2-dimensional with Doppler echocardiographic examinations performed by an experienced sonographer. LVEF determinations will be made quantitatively based on bi-plane measurements of end-diastolic and end-systolic left ventricular volumes.

Blood samples will be collected for troponin (preferably high-sensitivity troponin-T) analysis at screening, EOT and as needed based on subject reported cardiac signs or symptoms

suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. If at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis, a sample should be collected for troponin testing and an ECG will be performed in triplicate. If ECG is abnormal, follow institutional guidelines.

Situations in which ECG results should be reported as AEs are described in Section 8.3.7.

8.2.8 ECOG Performance Status

Functional status will be assessed at the times specified in the assessment schedules (see Section 1.3) by using the ECOG PS described in Section 11.6.1.

Any significant change from baseline or screening must be reported as an AE.

8.2.9 Ophthalmologic Assessments

Ophthalmologic assessments including visual acuity testing, and slit lamp examination will be performed at screening, EOT and as clinically indicated.

8.2.10 Other Safety Assessments

8.2.10.1 Pneumonitis (ILD) Investigation

If new or worsening pulmonary symptoms (e.g., dyspnea, cough or fever) or radiological abnormality suggestive of ILD/pneumonitis is observed, treatment with study drug should be interrupted and a full investigation is required as described in detail in the dose modification and toxicity management guidelines for DB-1303 (Section 6.6.1.1). Evaluations should include:

- High resolution CT of the chest
- Pulmonologist consultation
- Pulmonary function tests and pulse oximetry (SpO_2)
- Arterial blood gases if clinically indicated
- Bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible
- One blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.
- Other tests could be considered, as needed.

The results of the full diagnostic workup (including HRCT, blood and sputum culture, SARS-CoV-2 [COVID-19] test, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the toxicity management guidelines should be followed. Troponin measurements will be done to rule out cardiac etiology.

The following assessments should be performed, if feasible, to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc.) including auscultation for lung field will be assessed.
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    a) ILD markers (KL-6, SP-D) and β-D-glucan
    b) Tumor markers: particular tumor markers that are related to disease progression
    c) Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

8.3 Adverse Events and Serious Adverse Events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Section 11.3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate informaiton both to determine the outcome and to assess whether it meets the criteria for classifcation as an SAE or that caused the subject to discontinue the study.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

The safety recording and reporting requirements as it pertains to the clinical investigators for the clinical performance (IVD) study are described in the *in vitro* diagnostic regulation (IVDR) Safety Plan.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

For subjects who sign the tissue screening ICF, only SAEs directly related to tissue screening procedure (i.e., if a subject undergoes a tumor biopsy) will be reported during tissue screening period. All other SAEs will be recorded from the time of signing of the main ICF.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study treatment but after obtaining informed

consent will be recorded on the Medical History of eCRF, not the AE section.

AEs and SAEs will be collected from the time of the subject signing the ICF until the follow-up period is completed (35 [+7] days after the last dose of study treatment). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late-onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Duality Biologics concurs with that assessment.

8.3.2 Investigator's Reporting of AEs to Duality Biologics Safety

All SAEs will be recorded and reported to Duality Biologics Safety or its designee within 24 hours after the first aware of the event(s) by the Investigator. The Investigator will submit any updated SAE data to Duality Biologics Safety or its designee within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 11.3.

If the Investigator becomes aware of an SAE with an at least reasonable possibility of being related to the study treatment that occurs after the end of the clinical study in a subject treated by him or her, the Investigator shall, without undue delay, report the SAE to Duality Biologics Safety or its designee.

The following types of events should be reported by the Investigator in eCRF electronic data capture (EDC) AE page(s) in the clinical study database within 24 hours of becoming aware for the purposes of reporting in the global safety database:

- SAEs
  - Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥ 3 × ULN and an elevated TBL ≥ 2 × ULN that may occur either at different timepoints or simultaneously during the study should be reported as important medical events, see Section 11.10 Appendix 10 for details.
- AESIs
  - All potential ILD/pneumonitis cases, including both serious and non-serious potential ILD/pneumonitis cases.
  - IRR ≥ Grade 3
  - LVEF decrease ≥ Grade 3
- Overdose that associated with SAEs.

- Medication error that associated with SAEs.
- Pregnancy, see Section 8.3.15 for details.

8.3.3 Submission and Distribution of Serious Adverse Event Reports

Per regulatory requirements, if an event is assessed as a suspected unexpected serious adverse reaction (SUSAR), Duality Biologics and/or its designee will submit the SUSAR to Regulatory Authorities according to applicable regulations.

In addition, the SUSAR will be distributed to Investigators/site, IRB/IEC per the governing institutional requirements and in compliance with local laws and guidelines. The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the trial.

8.3.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. Each event must be monitored and followed up by the investigator to obtain adequate information until resolution or stabilization unless the subject is lost to follow-up. It is also the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed

Any AE that is unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 35 days after the last dose of study treatment), but without further recording in the eCRF. Duality Biologics retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE Grade reported
- Changes in CTCAE Grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatments
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE
- Date the Investigator became aware of SAE

- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of the SAE

The grading scales found in the revised NCI CTCAE v5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE v5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5 Causality Collection

The Investigator should assess causal relationship between study treatment and each AE with respect to each study treatment (DB-1303, capecitabine, paclitaxel and nab-paclitaxel), and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?’

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: ‘Have you had any health problems since the previous visit/you were last asked?’ or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse Events Based on Examinations and Tests

The results from the Protocol mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, or are the reason for discontinuation of treatment with the investigational product or are considered to be

clinically relevant as judged by the Investigator (which may include but are not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g., dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.8 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN will need to be reported as SAEs. Refer to Section 11.10 Appendix 10 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.9 Disease Progression

Disease progression can be considered a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new metastases or progression of existing metastasis to the primary cancer under study should be considered disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.10 Disease Under Study

Symptoms of disease under study (DUS) are those which might be expected to occur as a direct result of breast cancer. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of study treatment.

8.3.11 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the subject's inclusion in this study.

8.3.12 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as

follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the DUS, the AE causing the death must be reported to the Sponsor Medical Monitor as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results should be forwarded to Duality Biologics Safety or its designee within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study drug, then it should also be reported as an SAE.

8.3.13 Adverse Events of Special Interest

An AESI is an AE of scientific and medical interest specific to understanding of the study treatment and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of a study treatment.

AESIs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the Investigator for severity, relationship to the study treatment, possible etiologies, and whether the event meets criteria for an SAE.

Based on the available pre-clinical and clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, ILD/pneumonitis, LVEF decrease (≥Grade 3), and IRR (≥Grade 3) are considered to be AESIs. Any relevant information regarding the AESIs regardless of seriousness is to be reported to Duality Biologics Safety or its designee within 24 hours of learning the event by the E-SAE Form.

8.3.13.1 Interstitial Lung Disease/Pneumonitis

ILD/pneumonitis is considered an important potential risk based on a comprehensive cumulative review of potential ILD/pneumonitis cases, the available safety data from the clinical development program, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a

summary of preliminary clinical study data.

- High resolution CT of the chest and pulmonary function will be measured at baseline. If the AE is suspected to be ILD/pneumonitis during the study, treatment with study drug should be interrupted pending further evaluations. Evaluations for ILD/pneumonitis should include high resolution CT, SARS-CoV-2 (COVID-19) test, pulmonologist consultation, pulmonary function tests and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible and one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.

Refer to Section 6.6.1.1 and Section 11.11 for guidelines on management of drug-induced ILD.

8.3.13.2 LVEF Decrease (≥Grade 3)

LVEF decrease in association with DB-1303 is considered to be a potential risk based on the available pre-clinical data, literature and available safety information for drugs of similar class. Refer to the current IB for a summary of preliminary clinical trial data.

- LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function.
- Troponin will be measured at screening, EOT and as needed based on subject reported cardiac symptoms.
- At screening, ECGs will be obtained in triplicate (3 individual ECG tracings should be obtained in succession within 10 minutes). Subsequent ECGs will be performed in triplicate only if abnormalities are noted. 12 lead ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QTcF intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

8.3.13.3 Infusion-related Reaction (≥Grade 3)

As with any therapeutic antibodies, there is a possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions following the administration of DB-1303. Immune responses causing allergic or anaphylactic reactions that are classified as ≥ Grade 3 are considered as AESIs for the DB-1303 clinical program.

Subjects receiving DB-1303 should be monitored by means of vital signs, physical examination, and signs and symptoms of infusion related reaction: fever, chills, nausea, vomiting, headache, cough, dizziness, rash, and/or lower back pain usually of mild to moderate severity and may lead to shortness of breath and severe lowering of blood pressure.

8.3.14 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Duality Biologics representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Duality Biologics representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the Duality Biologics Safety and/or its representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the Duality Biologics Safety or its designee by telephone followed by completion of EDC reporting.

The Duality Biologics Safety will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Section 11.3.

The reference documents for definition of expectedness/listedness are the current IB for DB-1303 and the Summaries of Product Characteristics (SmPC) for the investigator's choice of chemotherapy (Latest effective SmPC for Paclitaxel, Hospira UK Limited; Latest effective SmPC for Xeloda, Roche Products Limited; Latest effective SmPC for Abraxane, Celgene Limited).

8.3.15 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to Duality Biologics except:

- If the pregnancy is discovered before the subject has received any study treatment.

If a pregnancy is reported during the course of study, the Investigator should inform Duality Biologics Safety or its representative within 24 hours of learning of the pregnancy and the study treatment should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the

subject was discontinued from the study.

The same timelines apply when outcome information is available.

8.3.15.1 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study treatment and during the washout period (4 months after the last dose of DB-1303, 6 months after the last dose of paclitaxel or nab-paclitaxel, and 3 months after the last dose of capecitabine) after the last dose of study treatment. Preservation of sperm should be considered prior to randomization in this study. In addition, local prescribing information relating to contraception and the time limit for such precautions should be followed for marketed products used in this study.

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality), occurring from the date of the first dose until 4 months or as per local prescribing information (marketed products) after the last dose and as indicated by previous studies (pre-clinical and clinical) should be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

When a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant IRB/IEC prior to use.

Subjects who are permanently discontinued from further receipt of study treatment, regardless of the reason will enter follow-up (see the SoAs [Section 1.3]).

8.3.16 Management of Study Treatment-related Toxicities

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including withholding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the randomized study treatment along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (See Section 6.6).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE v5.0.

8.3.16.1 Specific Toxicity Management and Dose Modification Information for DB-1303

All dose modifications (interruption, reduction and/or discontinuation) should be based on the worst preceding toxicity (CTCAE v5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of DB-1303 are listed in the dose modification and toxicity management guidelines for DB-1303 (see Section 6.6.1.1), which is applicable only to TEAEs that are assessed as related to use of DB-1303 by the Investigator(s). A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after initiating the study drug until the 35-day (+7 days) safety follow-up visit.

For non-drug related TEAEs, follow standard clinical practice. Appropriate clinical experts should be consulted as deemed necessary.

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Section 11.8 for additional information on dose modification for suspected or confirmed COVID-19 infection for subjects treated with DB-1303.

ILD/Pneumonitis Management Guidance:

Refer to the ILD/pneumonitis management summary flow chart in Section 11.11 for the management of drug-induced ILD.

ILD/pneumonitis should be ruled out if a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is confirmed to have an etiology other than ILD, follow the management guidance outlined in the in the dose modification section of the study protocol (Section 6.6).

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation, pulmonary function tests, SARS-CoV-2 [COVID-19] test, and SpO_2, arterial blood gases if clinically indicated, bronchoscopy and bronchoalveolar lavage as clinically indicated and feasible and one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines.

If the AE is confirmed to be ILD/pneumonitis, follow the dose modification and toxicity management guidelines, and the summary flow chart for management of drug-induced ILD (DI-ILD)/pneumonitis (Section 6.6.1.1, Section 11.11). All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after study treatment discontinuation.

To ensure adequate and relevant evaluation, systematic additional data collection will be conducted for all cases that will be brought for evaluation. This additional data collection will

cover a more in-depth relevant medical history (e.g., smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event.

LVEF Decrease Management Guidance:

LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function.

- Troponin will be measured at screening, EOT and as needed based on subject reported cardiac signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. If at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis, a sample should be collected for troponin testing and an ECG will be performed in triplicate. If ECG is abnormal, follow institutional guidelines.
- ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QTcF intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities prior to the infusion days of each cycle. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

Dose Reduction Levels for DB-1303

Once the dose of DB-1303 has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required (Table 11). More than 2 dose reductions are not allowed, and the subject will be discontinued from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

Table 11 Dose Reduction Levels for DB-1303

Starting Dose	Dose Level -1	Dose Level -2
8 mg/kg	7 mg/kg	6 mg/kg

Dose Interruption and Modification/Toxicity Management Guidelines:

- Every effort should be made to limit DB-1303 delay, however in circumstances of AE management or medical intervention, DB-1303 can be held up to 7 weeks (49 days) from the last DB-1303 dose. During this time scheduled CT/MRI scans should continue as per protocol, and subjects should fulfil all of the following criteria:
  - DB-1303 may be resumed with confirmation of continued benefit per RECIST 1.1. Scans should be performed at the frequency defined per protocol, while the drug is being held. At minimum, 1 scan must be done within 6 weeks prior to restarting the study drug.
  - DB-1303 is restarted within the guidance of the toxicity management guidelines for DB-1303.

- No prohibited concomitant medications have been administered since the last dose of DB-1303.

Treatment cycles for a subject for whom DB-1303 dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last DB-1303 dose.

In addition, Investigators may consider dose reductions or discontinuation of DB-1303 according to the subject's condition.

Refer to Section 6.6.1.1 for more detailed guidance on toxicity management.

8.3.16.2 Toxicity Management and Dose Modification Information for Investigator's Choice of Chemotherapy

Investigators should follow local standard clinical practice regarding dose modification and toxicity management for the selected investigator's choice chemotherapy. Refer to the local prescribing information for paclitaxel, nab-paclitaxel and capecitabine. If a subject is assessed as requiring a dose delay of longer than 28 days, resumption of treatment must be discussed with the Duality Biologics Medical Monitor.

8.4 Overdose

Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, i.e., poses an actual or potential risk to the subject.

Details of the overdose including DB-1303 dosage, clinical course, associated AEs, and outcome must be captured in the narrative form of the CRF within EDC. Use of DB-1303 (20% more than the intended w/v dose), capecitabine, paclitaxel, and nab-paclitaxel (according to labels) in doses that are in excess of those specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of the study treatments used in the study, and possible symptoms of overdose are not established. Refer to the local prescribing information for treatment in cases of an overdose related to paclitaxel, capecitabine and nab-paclitaxel. The Investigator will use clinical judgement to treat any overdose. Investigators should be advised that any subject who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly.

- An overdose without associated symptoms is only reported on the overdose CRF module and not the AE module.
- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the overdose CRF module. If the AE is reconginized as an SAE, it should be reported to the safety database within 24 hours of the investigator's awareness.

8.4.1 Medication Error

If a medication error occurs in the course of the study and associated with an SAE, then the Investigator or other site personnel should inform the Duality Biologics Safety or designee immediately but no later than 24 hours of when he or she becomes aware of it.

The definition of a Medication Error can be found in Section 11.3.5.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples are provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

8.5.1 Pharmacokinetics

PK for DB-1303 will be assessed as a secondary objective for this study.

Blood samples for determination of DB-1303 ADC and free payload P1003 concentrations in serum will be obtained as according to the SoAs (see Section 1.3) and will be analyzed by a designated third party on behalf of Duality Biologics.

If DB-1303 is restarted, routine DB-1303 PK blood sample collection will continue per the SoA.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be collected in accordance with Table 2.

For subjects with positive ADA at the 35-day (+7 days) follow-up visit, additional serum ADA samples may be collected every 3 months (± 14 days) up to 1 year after the last dose of DB-1303, or until the ADA becomes negative, or until the ADA titer becomes less than the baseline (applicable when pre-existing ADA was observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

Samples will be measured for the presence of ADAs and also potentially for ADA-neutralizing antibodies for DB-1303 using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be employed.

Full details of the methods used will be described in a separate report. ADA samples may also

be further tested for characterization of the ADA response and/or other exploratory safety biomarkers.

See Laboratory Manual for further details on requirements including sample collection, and shipping.

8.6 Human Biological Sample Biomarkers

Samples and generated data will be used to support diagnostic development.

By consenting to participate in the study the subject consents to participate in the mandatory research components of the study. Samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA (see Section 1.3).

The following mandatory samples will be collected from all subjects including screen failures wherever possible.

- A mandatory FFPE tumor sample must be provided, preferably obtained at the time of metastatic disease or later (most recent pre-randomization tumor sample). Subjects must be willing and able to provide the most recently available formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks (or freshly sectioned slides, see Laboratory Manual for details), obtained prior to treatment initiation, to a sponsor -designated central laboratory for biomarker analysis. If archival tissue is not available, then a newly-obtained biopsy of an accessible tumor lesion is required.
-
  - HER2 IHC analysis will be performed at a central reference laboratory testing service using the investigational VENTANA HER2/neu (4B5) assay. Testing will be carried out in a laboratory operating to GCP and with pathology staff fully trained by the diagnostic manufacturer to score reproducibly at the HER2 IHC cut-offs.
  - Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy. For subjects with a single TL, if tissue screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow time for healing (e.g., 1-2 weeks) before imaging scans are acquired; and, if imaging occurs prior to biopsy, in order to ensure that lesion size is unaffected by biopsy, biopsy sampling should be no larger than core needle size.

See Laboratory Manual for further details on requirements including sample collection, and shipping.

Baseline measures will be correlated with outcomes. Note that samples will be obtained from subjects randomized to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with treatment. The following assessments will be performed with the samples collected, where applicable.

- Tumor samples will be tested for HER2-low expression (IHC 2+/ISH- and IHC 1+) to evaluate their association with the observed clinical responses PFS, OS, ORR to DB-1303 and investigator's choice of chemotherapy.
- Tumor samples centrally confirmed to be HER2 IHC 2+ will be confirmed to be HER2 ISH negative using a commerical HER2 ISH assay per manufacturers requirements.

9 STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 1 for the Tissue Screening, Screening, treatment, and follow-up periods.

9.1 Tissue Screening

To determine eligibility, subjects must have breast cancer with low HER2 expression, as determined by the investigational VENTANA HER2/neu (4B5) assay and a commercial ISH assay evaluated at a central laboratory in accordance with the ASCO-CAP 2018 HER2 testing guidelines.

Note: Subjects may continue prior therapy while tissue testing takes place.

A sequential screening process must be followed. Tissue screening must be followed by the main screening procedures in Section 9.2.

Please refer to the study laboratory manual for required tumor sample specifications and shipping instructions.

Fine Needle Aspirate (FNA) and bone biopsies will not be accepted for tissue samples.

The following procedures will be conducted:

- Obtain a signed and dated written Tissue Screening ICF from the subject prior to collecting tissue.
- Obtain the most recently collected pre-randomization tumor sample for HER2 testing. Refer to the study laboratory manual for preparation, number of slides required, storage, and shipment procedures.
- If archival tumor tissue is not available, collect a fresh tumor tissue sample. If applicable, a coagulation sample should be taken 24 hours prior to tumor biopsy.
- If a tumor biopsy is needed, report any SAEs directly related to tissue screening procedure (i.e., tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.
- Send the samples to the central laboratory to assess HER2 status.

9.2 Screening

A sequential screening process must be followed. Tissue screening (see Section 9.1) must be completed before the main screening procedures below.

The duration of the screening/baseline period is up to 28 days. Informed consent will be obtained from the subject before any study-specific procedures are initiated.

The following activities and/or assessments will be performed **within 28 days before**

randomization during the screening period:

- Unless required by local regulations or IRB/IEC, an HIV antigen/antibody test is not required prior to randomization/enrollment.
- Perform a hepatitis B surface antigen/hepatitis C antibody test. Subjects who have a positive HCV antibody test will require a negative polymerase chain reaction for HCV RNA.
- Perform ophthalmologic assessments including visual acuity testing, and slit lamp examination.
- Perform an ECHO or MUGA (**Note:** The same test must be used for the subject throughout the study).
- Perform tumor assessment by CT or MRI scans of the chest, abdomen, pelvis, and any other sites of disease. A CT or MRI of the brain is to be included for all subjects.
- Perform high resolution computed tomography (HRCT) chest and pulmonary function test.
- Obtain:
    - Demographics (e.g., birth date, sex, race, ethnicity);
    - Medical (including smoking) and surgical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, estrogen/progesterone receptor status, and previous cancer therapies (including prior radiation therapy);
    - Oncology surgical history.

If there are screening procedures that are performed within 28 days of randomization during the standard treatment of the subject, these procedure results can be used for the trial even if conducted prior to consent as they were performed during the normal course of subject care.

Note: To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use it as comparator for subsequent measurement.

The following activities and/or assessments will be performed during the screening period **within 7 days before randomization** except as indicated:

- Confirm subject eligibility.
- Perform a physical examination, including weight and height.
- Assess functional status using the ECOG PS.
- Record concomitant medications and AEs at every visit (from the time the subject signed the Main ICF). For details on AE collection and reporting, refer to Section 8.3.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body

temperature) and peripheral oxygen saturation (SpO_2).

- Perform triplicate 12-lead ECG.

  The ECGs will be taken in close succession while in a supine/semi-recumbent position. The ECGs should preferably be performed before blood draws at respective time points.

  - Note that subsequent ECGs will be performed in triplicate only if an abnormality is noted.

- Collect and send blood samples to the laboratory for the following tests:

  - Hematology
  - Chemistry
  - Coagulation (should also be performed as clinically indicated throughout the study)
  - Troponin (preferably high-sensitivity troponin-T); the test used to test troponin should be the same at Screening and at EOT. If ECG is abnormal, follow institutional guidelines.

- Obtain urine sample for urinalysis (protein, glucose, blood, microscopy assessment [if indicated], and specific gravity).
- For women of childbearing potential, within 72 hours before randomization perform a serum pregnancy test and document the results.

9.3 Randomization

Eligible subjects will be randomized by the IRT in a 1:1 ratio into the treatment arms: DB-1303 vs physician's choice, which has

3 available treatment paradigms (refer to Section 6.1.1).

Randomization will be stratified by

- Prior CDK4/6 inhibitor use (Yes vs No)
- HER2 IHC status of tissue samples assessed by a central laboratory (HER2 IHC 2+/ISH- vs HER2 IHC 1+)
- Prior taxane in non-metastatic setting (Yes vs No)

Investigators will choose 1 of the control treatments for every subject before randomization.

Treatment and procedures performed on Day 1 of Cycle 1 and beyond are specified in Table 1 and further described below. Procedures are to be performed within 3 days of the Day 1 visit of each cycle unless otherwise specified.

A subject's first dose at Cycle 1 Day 1 should occur within 3 days after the date the subject is randomized.

9.4 Treatment Period

9.4.1 Cycle 1 to 4 and Subsequent Cycles

9.4.1.1 Between -3 Days Before Dosing Through Immediately Before Dosing (All Cycles)

- Perform a physical examination, including weight. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Assess functional status using the ECOG PS.
- Record concomitant medications and AEs at every visit.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO_2. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Perform 12-lead ECG. ECGs will be performed in triplicate if an abnormality is noted. The ECGs will be taken in close succession while in a supine/semi-recumbent position. The ECGs should preferably be performed before blood draws at respective time points.
- Collect and send blood/urine samples to the laboratory for the following tests:
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
- Perform HRCT chest on C4D1.
- For all female subjects of childbearing potential, perform a serum or urine pregnancy test within 72 hours prior to the beginning of dosing and document the results. A positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug administration. For subjects who are of non-childbearing potential, no pregnancy test will be required.

Note: Vital signs (including SpO_2) evaluations, clinical laboratory tests, physical examination, weight, ECG, and ECOG PS need not be repeated if they were performed within 3 days of the first dose in each cycle.

9.4.1.2 Day 1 Before Dosing (All Cycles, Unless Otherwise Noted)

- The subject must complete the health economics and outcomes research (HEOR) outcomes: EORTC QLQ-C30, EORTC QLQBR45, EQ-5D-5L, and PRO-CTCAE questionnaires before any other assessments or procedures are done on the day of clinic visit each cycle during the treatment period.

- Obtain blood samples for ctDNA analysis, see Table 3.
- Only subjects randomized to DB-1303:
  - PK and ADA assessments, see Table 2.
- Record concomitant medications, and AEs records at every visit.

9.4.1.3 Day 1 Dosing and End of Dosing (All Cycles, Unless Otherwise Noted)

DB-1303 should only be initiated and administered by a healthcare professional experienced in the administration of cytotoxic chemotherapy. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment, should be available for immediate use.

Comparator treatments should be administered and monitored as per label approved in the country of drug administration or the NCCN guidelines.

- For DB-1303 treatment, administer study treatment IV infusion at least 90 minutes for the initial dose and, if no infusion related reaction after the initial dose, infuse subsequent doses over 30 minutes. Record start and stop times of any study treatment and amount of drug administered.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- For subjects randomized to DB-1303, collect blood samples for PK and ADA analysis, see Table 2.

Note that end of infusion assessments are not required for subjects on capecitabine.

9.4.1.4 Day 8 (±1 day) and Day 15 (±1 day) (Cycle 1 Only)

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Collect and send blood/urine samples to the laboratory for the following tests:
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
- Record concomitant medications and AEs at every visit.

9.4.2 Every 4 Cycles (±3 days) After Cycle 1

- Perform an ECHO or MUGA (**Note:** The same test must be used for the subject throughout the study) before infusion at Cycle 5, 9, 13, etc.

9.5 End of Treatment

The EOT is defined as the date the Investigator decides to discontinue study treatment and the visit should occur within 7 days of the decision. All assessments required as part of EOT must occur within 7 days from the date the Investigator decides to discontinue study treatment. The following procedures will be performed as specified in Table 1. If the EOT assessments have been performed within 35 days (±7 days) of their last treatment, they can be considered to be the EOT data and there is no need to repeat them; otherwise, these assessments need to be repeated.

- The subject must complete the HEOR outcomes EORTC QLQ-C30, EORTC QLQBR45, EQ-5D-5L, and PRO-CTCAE questionnaires before any other assessments or procedures are done on the day of clinic visit.
- For women of childbearing potential, perform a serum pregnancy test and document the results. For subjects who are of nonchildbearing potential, no pregnancy test will be required.
- Perform a physical examination, including weight.
- Perform ophthalmologic assessments including visual acuity testing, and slit lamp examination.
- Assess functional status using the ECOG PS.
- Record concomitant medications and AEs at every visit.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO_2.
- Perform 12-lead ECGs.
    - If an abnormality is noted, perform triplicate ECG. The ECGs will be taken in close succession while in a supine/semi-recumbent position. The ECGs should preferably be performed before blood draws at respective time points.
- Perform an ECHO or MUGA (**Note:** The same test must be used for the subject throughout the study).
- Blood sample for troponin (preferably high-sensitivity troponin-T).
- Collect and send blood/urine samples to the laboratory for the following tests:
    - Hematology
    - Chemistry
    - Coagulation
    - Urinalysis

- Blood sample for ctDNA analysis in plasma will be collected.
- For subjects randomized to DB-1303, collect blood samples for PK and ADA analysis, see Table 2.
- Tumor assessments should include all sites of disease identified at Screening and any other locations where PD is suspected (e.g., MRI of the brain if brain metastases are suspected) should also be imaged. If the previous scan was within the last 6 weeks (±7 days) from the date of EOT, this assessment does not need to be performed at EOT. If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review.
- A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need brain scan for tumor assessment unless clinically indicated.

9.6 Safety Follow-up (35+7 days)

Thirty-five days (+7 days) after last study treatment administration or before starting new anticancer treatment, whichever comes first, the following procedures will be performed as specified in Table 1. If EOT is >35 days (+7 days) after last treatment, then the EOT assessments can also function as the 35-Day (+7 days) Follow-up assessments.

- The subject must complete the HEOR outcomes EORTC QLQ-C30, EORTC QLQBR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done on the day of clinic visit.
- Perform a physical examination, including weight.
- Assess functional status using the ECOG PS.
- Record concomitant medications and AEs.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature).
- Collect and send blood/urine samples to the laboratory for the following tests:
  - Hematology
  - Chemistry
  - Coagulation
  - Urinalysis
- For subjects randomized to DB-1303, collect blood samples for PK and ADA analysis, see Table 2.
- Record subsequent anticancer treatments, their outcomes, and survival.

9.7 New Cancer Treatment and Survival Follow-up

After completion of the 35-Day (+7 days) Follow-up assessments, the Long-term/Survival Follow-up assessments will be performed every 3 months (±14 days) from the date of 35-Day (+7 days) Follow-up assessments until death, withdrawal of consent from the study, loss to follow-up, or study closure, whichever occurs first.

The following activities will take place during Long-term/Survival Follow-up at the study site or by telephone contact:

- The subject must complete the EORTC QLQ-C30, EORTC QLQBR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day (before the second disease progression or death).
- For subjects with positive ADA at the 35-Day (+7 days) Follow-up assessment, additional serum ADA samples may be collected every 3 months (±14 days) up to 1 year from the last dose of study drug, until the ADA becomes negative, until the ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), until the subject starts another therapy for cancer or withdraws consent from the study, whichever occurs first.
- Record subsequent anticancer treatments, their outcomes, and survival.
- Further follow-up may be required for ongoing AEs.
- All subjects will be followed for survival until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

If direct contacts are not possible because of withdrawal of consent or the subject becomes lost to follow-up, the site must make every effort to collect survival status from public records (e.g., death certificates) in accordance with local laws. See Section 7.2 for further details on how subjects will be followed for survival status if they withdraw consent.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

Primary hypothesis (H1):

DB-1303 is superior to investigator's choice chemotherapy in terms of PFS according to RECIST 1.1 assessed by BICR in patients with HR+, HER2-low breast cancer.

H_0: $S(t)_{PFS,experimental} = S(t)_{PFS,control}$;

H_1: $S(t)_{PFS,experimental} > S(t)_{PFS,control}$

Where $S(t)_{PFS,experimental}$ is the survival function of PFS per RECISIT 1.1 assessed by BICR at time t for the experimental arm and $S(t)_{PFS,control}$ is the survival function of PFS per RECISIT 1.1 assessed by BICR at time t for the control arm.

Key secondary hypothesis (H2):

DB-1303 is superior to investigator's choice chemotherapy in terms of OS in patients with HR+, HER2-low breast cancer.

H_0: $S(t)_{OS,experimental} = S(t)_{OS,control}$;

H_1: $S(t)_{OS,experimental} > S(t)_{OS,control}$

Where $S(t)_{OS,experimental}$ is the survival function of OS at time t for the experimental arm and $S(t)_{OS,control}$ is the survival function of OS at time t for the control arm.

10.1.1 Multiple Testing Procedure

The ITT population will be used for all efficacy endpoints and will be analyzed according to randomized treatment regardless of the treatment received (ITT principle).

PFS will be tested once, when PFS reaches the planned 262 events in the ITT population. This is estimated to occur 22 months after the first subject is randomized (2 months after randomization is completed) assuming a non-uniform accrual of subjects with a duration of 20 months including 6 months of ramp up period.

OS will be tested at two interim and one final analyses as described below:

1. The first interim OS analysis will be performed at the time of the final PFS analysis. It is expected that 135 OS events (40% information fraction) will have been observed.
2. The second interim OS analysis will occur when approximately 226 OS events have been observed (67% information fraction). This is anticipated to occur approximately 32 months after the first subject is randomized.
3. The final OS analysis will be performed when approximately 337 OS events have been observed, which is expected to occur approximately 51 months after the first subject is randomized.

To strongly control the family wise error rate at 5% (2-sided) in terms of the primary and key secondary endpoints, a multiple testing procedure (MTP) with the following gatekeeping strategy will be employed:

Step 1: Test PFS at a 5% alpha level. If significance is achieved, go to Step 2.

Step 2: Test OS at the 5% alpha level.

For the OS hypothesis, the alpha allocated will be distributed between the two interim and final analyses using the Lan DeMets spending function that approximates the O'Brien Fleming alpha-spending approach (Lan and DeMets 1983). Under this procedure, the adjusted significance levels at the interim and final analyses are determined by the information fraction available at the time of analysis (i.e., actual number of events observed at interim / planned number of OS events at the final analysis) and the correlation computed from the actual number of events from each analysis, giving greater weight to analyses performed at the end of the study than those performed earlier. If the study continues to final analysis, all remaining alpha will be spent at the final analysis, and the nominal significance level will be adjusted by the actual number of events.

10.2 Sample Size Determination

The study provides adequate power to show a statistically significant between-treatment difference in PFS. Based on a 2-sided significance level of 5%, a total of 262 PFS events will provide approximately 90% power to detect a hazard ratio of 0.67 (increase in median PFS from 6 to 9 months), assuming an exponential distribution for both treatment groups.

If PFS is significant, the study also provides sufficient power to demonstrate a statistically significant difference in OS. Based on a 2-sided alpha of 5% and taking into account two interim OS analyses, a total of 337 OS events will be required to achieve 80% power to detect a hazard ratio of 0.72 (increase in median OS from 20 to 27.8 months), assuming an exponential distribution for both treatment groups.

Assuming dropout rate of 20% for PFS and 10% for OS, an enrollment duration of 20 months, and the final analysis of PFS and OS occur at approximately 22 and 51 months, respectively, approximately 532 subjects will need to be randomized.

Approximately 887 subjects will be screened with an approximate screen failure rate of 40% to achieve randomization of approximately 532 subjects to the study treatment.

10.3 Populations for Analyses

Table below defines the populations upon which the analyses are based.

Table 12 Populations for Analyses

Population/Analysis set	Description
Full analysis set (FAS) (ITT)	The ITT population, also termed as FAS, will include all randomized subjects. Treatment arms will be compared on the basis of randomized study treatment, regardless of the study treatment actually received. Subjects who were randomized but did not subsequently go on to receive study treatment

Table 12 Populations for Analyses

Population/Analysis set	Description
	are included in the analysis in the treatment arm to which they were randomized.
Safety (SAS)	All subjects who received at least 1 dose of study treatment. Safety data will be summarized according to the treatment received. Erroneously treated subjects (e.g., those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.
Per-protocol analysis set (PPS)	PPS will include all randomized subjects who are absence of major protocol deviations likely to impact primary efficacy outcome.
PK	The PK analysis set will include all subjects who receive at least 1 dose of DB-1303 per the protocol for whom any postdose data are available.
ADA	All subjects who receive at least 1 dose of DB-1303 per the protocol, have non-missing baseline ADA and at least 1 non-missing post-baseline ADA results. All major ADA analyses will be based on the ADA evaluable set.

ADA = anti-drug antibody; FAS = full analysis set; ITT = intent-to-treat; PK = pharmacokinetic; PPS = per-protocol analysis set; SAS = safety analysis set.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized before the first subject is randomized and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

10.4.1 General Considerations

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
Efficacy data	
PFS	ITT, PPS
OS	ITT
ORR	ITT
DoR	ITT
DCR	ITT
TTR	ITT
PFS2, TFST, TSST	ITT
PROs	SAS
Study population/Demography data	
Demography characteristics	ITT
Baseline and disease characteristics	ITT

Table 13 Summary of Outcome Variables and Analysis Populations

Outcome variable	Populations
Important deviations	ITT
Medical/surgical history	ITT
Previous anti-cancer therapy	ITT
Concomitant medications/procedures	ITT
Subsequent anti-cancer therapy	ITT
PK data	
PK data	PK analysis set
Immunogenicity data	
Immunogenicity data	Listings will be based on SAS Summaries will be based on ADA evaluable set
Safety data	
Exposure	SAS
AEs	SAS
Laboratory measurements	SAS
Vital signs	SAS
ECGs	SAS

ADA = anti-drug antibody; AEs = adverse events; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; HER2 = human epidermal growth factor receptor 2; ITT = intent-to-treat population; KM = Kaplan Meier; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression or death; PK = pharmacokinetic; PPS = per-protocol analysis set; PROs = patient reported outcomes; SAS = safety analysis set; TFST = time to first subsequent treatment or death; TSST = time to second subsequent treatment or death.

Depending on the extent of any impact, summaries of data relating to subjects diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated. More detail will be provided in the SAP.

10.4.2 Handling of intercurrent events

Expected intercurrent events of interest for this trial are initiation of subsequent anti-cancer treatment and discontinuation of trial treatment. Further, unexpected intercurrent events may occur during trial conduct and will consequently be defined in the SAP.

Strategy 1 will be used for PFS primary analysis (Table 14). Strategy 2 will be used for OS primary analysis (Table 14).

Table 14 Strategies for handling intercurrent events

Intercurrent events of interest	Strategy 1 (PFS)	Strategy 2 (OS)
Initiation of subsequent anti-cancer treatment	Hypothetical strategy	Treatment policy strategy
Discontinuation of study treatment	Treatment policy strategy	Treatment policy strategy

OS = overall survival; PFS = progression-free survival.

The further sections will define which strategy will be used for which analysis especially for the analysis of the primary and key secondary endpoint analyses. The strategies for handling intercurrent events as defined in this section together with the detailed clinical objectives for the primary and key secondary objectives define the estimands for the primary and key secondary objectives.

10.4.3 Efficacy

10.4.3.1 Primary Endpoint (PFS by BICR)

The primary endpoint of the study is PFS by BICR according to RECIST 1.1.

PFS is defined as the time from the date of randomization until the date of disease progression, as defined by RECIST 1.1, or death (by any cause in the absence of progression), whichever comes first.

The primary analysis of the primary endpoint PFS will be performed using the ITT set and strategy 1 for handling intercurrent events as defined in Section 10.4.2. Moreover, sensitivity and supplementary analyses will be performed.

Subjects who have not had disease progression or death at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the subject has disease progression or dies immediately after two or more consecutive missed visits, the subject will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits. If the subjects have no evaluable visits or do not have baseline data, they will be censored at Day 1 unless they die within two visits of baseline (12 weeks plus 1 week allowing for a late assessment within the visit window). More details will be specified in the SAP.

PFS distribution will be compared between DB-1303 and investigator's choice chemotherapy using a stratified log-rank test adjusting for prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC 1+ vs IHC 2+/ISH-), and prior taxane use in the non-metastatic setting (yes vs no). The stratification variables in the statistical modelling will be based on the values entered in IRT. If there are insufficient events per stratum, the strata will be pooled following a pooling strategy that will be prespecified in the SAP. The hazard ratio and its CI will be estimated from a stratified Cox Proportional Hazards model with strata being the same as the stratification variables from IRT.

Kaplan-Meier plots of PFS will be presented by treatment arm.

Sensitivity analyses for PFS will be described in the SAP.

10.4.3.2 Key Secondary Endpoints (OS)

The key secondary endpoint of the study is OS.

OS is defined as the time from the date of randomization until death due to any cause regardless of whether the subject withdraws from randomized therapy or receives another anticancer therapy.

The primary analysis of the key secondary endpoint OS will be performed using the ITT set and strategy 2 for handling intercurrent events as defined in Section 10.4.2. Moreover, sensitivity and supplementary analyses will be performed.

Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Analysis of OS will be performed to compare DB-1303 vs investigator's choice chemotherapy using the same methodology as for PFS.

10.4.3.3 Other Secondary Endpoints

PFS by Investigator Assessment

PFS by Investigator assessment according to RECIST 1.1 will be analyzed as described for the primary endpoint.

Objective Response Rate

ORR is defined as the percentage of subjects with at least one visit response of complete or partial response (using RECIST 1.1) and will be based on all randomized subjects. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, subjects who receive subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) after discontinuing study treatment without progression and then respond will not be included as responders in the ORR.

At the time of the formal PFS and OS analyses, the confirmed ORR (by BICR according to RECIST 1.1) will be compared between DB-1303 and investigator's choice chemotherapy using CMH adjusting for the same stratification factors as the primary endpoint. The ORR using Investigator assessments according to RECIST 1.1 will be analyzed using the same methodology as supportive analyses.

Summaries will be produced that present the number and percentage of subjects with a tumor response (complete response [CR]/partial response [PR]), and overall visit response data will be listed. Best overall response (BOR) will be summarized by n (%) for each category (CR,

PR, stable disease [SD], progressive disease [PD], and not evaluable [NE]) for each treatment arm in ITT analysis set. No formal statistical analyses are planned for BOR.

Duration of Response

For subjects who achieve complete or partial response per RECIST 1.1, DoR is defined as the time from the date of first documented response until date of documented progression (using RECIST 1.1) or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a subject does not progress following a response, then their DoR will use the PFS censoring time.

Descriptive data will be provided for the DoR by BICR and by Investigator assessment according to RECIST 1.1 in responding subjects, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

Patient-reported Outcomes

The main PRO endpoints identified in the secondary objectives are symptoms, functioning and HRQoL of the EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L health state utility index. PROs are not part of the main MTP and will be analyzed as supportive endpoints. Further details of the analyses will be described in the SAP.

10.4.3.4 Exploratory Endpoints

Disease Control Rate (DCR)

DCR is defined as the percentage of subjects who have a BOR of CR or PR or who have SD (without subsequent cancer therapy) after randomization. Similar to ORR, DCR will be summarized by treatment arm.

Time to Response (TTR)

TTR is defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR), descriptive statistics for TTR will be provided by treatment arm.

PFS2

PFS2 is defined as time from randomization to second progression (the earliest of the progression event subsequent to first subsequent therapy) or death, which comes first. Second progression will be defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.

Analysis of PFS2 will be performed to compare DB-1303 vs investigator’s choice chemotherapy using the same methodology as for PFS.

TFST

TFST is defined as time from randomization to the start date of the first subsequent anti-cancer therapy after discontinuation of randomized treatment or death due to any cause.

Analysis of TFST will be performed to compare DB-1303 vs investigator's choice chemotherapy using the same methodology as for PFS.

TSST

TSST is defined as time from randomization to the start date of the second subsequent anti-cancer therapy after discontinuation of randomized treatment or death due to any cause.

Analysis of TSST will be performed to compare DB-1303 vs investigator's choice chemotherapy using the same methodology as for PFS.

10.4.4 Safety

Safety summaries will be provided using the safety analysis set (SAS). Safety data will be presented using descriptive statistics unless otherwise specified.

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study treatment. Details are described in the SAP.

Adverse Events

Adverse events will be coded using the most recent version of MedDRA that will be released for execution at Duality Biologics.

A TEAE is defined as an AE observed or worsened after starting administration of the study drug until 35 days after the last dose of the study treatment and prior to the start of a new anticancer treatment. Any drug related AE will be considered as TEAE regardless of onset timing. Only TEAE will be included in the AE summaries. Any other AEs will be flagged in the data listings, but not included in the summaries.

An overview of TEAEs will be provided for each treatment group: the number and percentage of subjects with any TEAE, TEAEs with outcome of death, serious TEAEs, Grade ≥3 TEAEs, drug-related TEAEs, and TEAEs leading to discontinuation of study treatment, TEAEs leading to study treatment dose interruption, and TEAEs leading to study treatment dose reduction.

TEAEs will be presented for each treatment group by system organ class (SOC) and/or preferred term covering number and percentage of subjects reporting at least one event and number of events where appropriate.

Separate TEAE tables will be provided taking into consideration the relationship of TEAE to study treatment as assessed by the Investigator, the CTCAE Grade, seriousness, death and

events leading to discontinuation of study treatment as well as other action taken related to study treatment, AESIs and other significant TEAEs (if applicable).

An additional table will be presented for the number and percentage of subjects with most common TEAEs. Most common TEAEs will be defined in the SAP.

Key subject information will be presented for subjects with TEAEs with outcome of death, serious TEAEs, and TEAEs leading to discontinuation of study treatment.

An AE listing will cover details for each individual AE.

AEs occurring prior to start of study treatment, TEAEs and post-treatment AEs will be presented separately.

Full details of AE analyses will be provided in the SAP.

Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover number of subjects (n), mean, standard deviation, median, minimum (Min.) and maximum (Max).

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Details of vital sign analyses will be provided in the SAP.

Laboratory Parameters

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover number of subjects (n), mean, standard deviation, median, Min. and Max. Frequency tables and shift tables cover number and percentage of subjects in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and hematology parameters will be presented for observed values and change from baseline.

Elevation in liver parameters for assessment of Hy’s Law will be done and reported appropriately if potential cases have been identified during the course of the study.

A shift table for urinalysis will be presented with baseline assessment against the maximum on treatment category if a sufficient number of urinalysis assessments are recorded.

Supportive laboratory listings will cover observed values and changes from baseline for each individual subject as well as abnormalities.

Details of laboratory analyses will be provided in the SAP.

Other safety analyses will be detailed in the SAP.

10.4.5 Other Analyses

10.4.5.1 Pharmacokinetic Data

The PK analyses will be performed on the PK Analysis Set using actual sample times and noncompartmental analysis method. Blood concentration-time data for DB-1303 ADC and unconjugated payload P1003 will be listed and summarized using descriptive statistics by study cycle at each nominal collection time. Applicable plots will illustrate the appropriate data. PK parameters will be estimated. The PK parameters of DB-1303 ADC, and unconjugated payload P1003(including, C_{max} and T_{max}) will be listed and summarized using descriptive statistics. Descriptive statistics will be provided for the PK parameters for each analyte as appropriate.

Population PK modeling method can also be used for PK characterization and PK covariate analysis to explore effect of intrinsic factors (e.g., disease, age, sex, body weight) and extrinsic factors altering systemic exposure, which will be planned and reported separately.

If deemed appropriate, ER between DB-1303 ADC and payload (PK matrices such as C_{max}) and clinical activity (e.g., ORR) or probability of safety events of interest will also be explored combining Phase 1 and Phase 2a data together to facilitate to inform rational safety and effective dose regimens selection. These analyses will be planned and reported separately.

10.4.5.2 Immunogenicity Data

Immunogenicity results will be listed by subject, and a summary will be provided by the number and percentage of subjects who develop ADA for DB-1303.

ADA prevalence, which is the percentage of subjects who were ADA positive at any time point (baseline or post-baseline), will be summarized. The ADA incidence will also be reported, which is the proportion of subjects having treatment-emergent ADA during the study period. Treatment-emergent ADA includes subjects who were ADA negative at baseline and became ADA positive post-baseline (treatment-induced ADA), subjects who were ADA positive at baseline and post-baseline but had an increase in ADA titer of defined threshold from baseline to post-baseline (treatment -boosted ADA), and subjects who had missing ADA data at baseline and were positive post-baseline.

The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of DB-1303 antibodies.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the Duality Biologics Clinical Pharmacology group or designee.

10.5 Interim Analyses

OS will be tested at two interim analyses as described in Section 10.1.

The SAP will describe the planned interim analyses in greater detail.

10.6 Data Monitoring Committees

10.6.1 IDMC Committee

The safety of all Duality Biologics clinical studies is closely monitored on an ongoing basis by Duality Biologics representatives in consultation with Subject Safety. An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 60 subjects have been randomized, whichever occurs later. The IDMC will review unblinded safety data and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter, or more frequently if indicated or requested by the Medical Monitor based on available safety data, and at each meeting make recommendations to continue, amend, or stop the study based on safety findings.

In addition, the IDMC will be asked to review efficacy data at pre-specified timepoints. Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

10.6.2 ILD Adjudication Committee

An ILD Adjudication Committee will review all cases of potential ILD/pneumonitis. To ensure adequate evaluation, relevant additional data from within the clinical database and other sources, including imaging data, may be provided to the adjudication committee to fully characterize medical history (e.g., smoking, radiation and pulmonary history), diagnostic evaluation, treatment and outcome of the event. Further details can be found in the ILD Adjudication Charter.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations

11.1.2 Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject or their legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or their legally authorized representative.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

11.1.3 Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.4 Data Quality Assurance

All subject data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided and reviewed with participating site personnel before the start of the study. The Sponsor will review CRFs for accuracy and completeness after transmission to the Sponsor; any discrepancies will be resolved with the participating physician or designee, as appropriate.

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

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CRO).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator after study completion according to local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

11.1.5 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

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.

11.1.6 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first subject is consented.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development for commercial reasons/safety issues/ethical issues.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

11.1.7 Publication Policy

The publication policy will be addressed in the clinical trial agreement with the investigative sites.

11.1.8 Financing and insurance

The sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Provided that the subject has been treated according to the protocol and sponsor's instructions, any injury caused to a subject which is the direct result of his/her participation to the clinical study shall be covered by the sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

11.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by the local laboratory according to the time points indicated in the SoA (Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 15 Protocol-required Safety Laboratory Tests

<table>
<tr><th>Laboratory Tests</th><th colspan="2">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet (PLT) count</td><td rowspan="4">White blood cell (WBC) count with differential:
Neutrophils (absolute)
Lymphocytes (absolute)
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>Red blood cell (RBC) count</td></tr>
<tr><td>Hemoglobin (HGB)</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td>Clinical chemistry</td><td colspan="2">○ Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH).
○ Creatinine, total protein, albumin, total bilirubin, direct and indirect bilirubin, blood urea nitrogen (BUN)/urea.
○ Phosphorus, potassium, sodium, calcium, chloride, magnesium.
○ Troponin</td></tr>
<tr><td>Coagulation function parameters</td><td colspan="2">○ Prothrombin time (PT)
○ International normalized ratio (INR)
○ Activated partial thromboplastin time (APTT)</td></tr>
<tr><td>Urinalysis</td><td colspan="2">○ Specific gravity, pH, glucose, blood, protein, ketones, bilirubin, urobilinogen.
○ Sediments: casts, RBCs, WBCs.
○ Protein: If the subject's urine protein is 2+ or above during the study, a 24-hour urine should be collected for a 24-hour urine protein quantitative test.
○ Microscopic examination (if indicated).</td></tr>
<tr><td>Pregnancy testing</td><td colspan="2">○ Highly sensitive serum β-human chorionic gonadotropin (β-HCG) pregnancy test (as needed for women of childbearing potential)
○ Urine pregnancy test (as needed for women of childbearing potential)</td></tr>
<tr><td>Other screening tests, if needed</td><td colspan="2">Serology human immunodeficiency virus (HIV) antibody (as per local regulations), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis B e antibody (HBeAb), hepatitis B e antigen (HBeAg), and hepatitis C virus (HCV) antibody. Subject with positive HBsAg will need additional test for HBV-DNA. Subject with positive HCV antibody will need additional test for HCV-RNA.</td></tr>
</table>

The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report.

11.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1 Definition of AE

AE Definition
● An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug. ● Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Events Meeting the AE Definition
● Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease) ● Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition ● New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study ● Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction ○ Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. ● “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
● Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition ● The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition ● Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

11.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

11.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information. The following variables will be collected for each AE:
    - AE diagnosis/description
    - The date when the AE started and stopped
    - CTCAE grade maximum intensity
    - Whether the AE is serious or not
    - Investigator causality rating against the investigational product (yes or not)

- Action taken with regard to investigational product (drug withdrawn; drug interrupted; dose reduced; dose not changed; not applicable; unknown)
- Outcome (recovered/resolved; recovering/resolving; recovered/resolved with sequelae; not recovered/not resolved; fatal; unknown).

- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

Investigators will make an assessment of severity for each AE and SAE reported during the study referencing the NCI-CTCAE, version 5.0. A general severity grading scale is provided at the beginning of the above referenced document, and specific event grades are also provided. The general NCI-CTCAE definitions of Grade 1 through Grade 5 are:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self.

Assessment of Causality

- The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator is obligated to assess the reasonable possibility between study drug and each occurrence of each AE/SAE.
- The investigator will use clinical judgment to determine the relationship, also consulting the IB and/or product information, for marketed products, in his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The following terms are used to describe the causality of the AE:
    - **Related**: There is a reasonable possibility that the study drug caused the AE/SAE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE/SAE
    - **Not Related**: There is not a reasonable possibility that the administration of the study drug caused the event. for example, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

Follow-up of AEs and SAEs

- After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AE/SAE and AESI that are ongoing at the end of Safety follow-up, whether or not related to study treatment, will be followed up in the follow-up period until recovery or return to baseline or become stable assessed by investigator, or death or lost to follow-up.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by guidelines or the Sponsor 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 with a copy of any postmortem findings including histopathology (if applicable).
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of awareness.

11.3.4 Reporting of SAEs

SAE Reporting to the Sponsor's Safety or designee

- The primary mechanism for reporting a SAE to the sponsor will be the electronic data collection tool. In rare circumstances, if the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool. The study center will enter the SAE data into the electronic system as soon as it becomes available
- Initial notification via telephone does not replace the need for the investigator to complete and report the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Safety Management Plan and Monitoring Plan.

11.3.5 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an Duality Biologics study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion

- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IRT errors)
- Wrong drug administered to subject (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background, or standard of care medication in open label studies.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

11.4 Appendix 4: Contraceptive and Barrier Guidance

11.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - ✓ A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

11.4.2 Contraception Guidance

Contraceptives [a] allowed during the study include:

1. Highly effective methods [b] that have low user dependency (*Failure rate of < 1% per year when used consistently and correctly)*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation [b]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS) [b]
- Bilateral tubal occlusion
- Vasectomized partner

  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)

2. Highly effective methods [b] that are user dependent (*Failure rate of < 1% per year when used consistently and correctly)*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [c]
  - ✓ oral
  - ✓ intravaginal
  - ✓ transdermal
  - ✓ injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation [c]
  - ✓ oral
  - ✓ injectable
- Note: Sexual abstinence not an acceptable contraceptive method.

3. Acceptable methods [d]

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide [e]
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) [e]

Notes:

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b. Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d. Considered effective, but not highly effective-failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

e. Male condom and female condom should not be used together (due to risk of failure with friction).

11.5 Appendix 5: Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1)

11.5.1 Definitions

Response will be evaluated in this study using the international criteria (version 1.1) proposed by the RECIST Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST version 1.1 criteria. Lesions are either measurable or non-measurable using the criteria provided below.

11.5.1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] in the plane of measurement to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm),
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

11.5.1.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue

components, that can be evaluated by cross sectional imaging techniques (i.e., CT or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

11.5.1.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

11.5.1.4 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:

- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥10 but < 15 mm
- Normal if short axis < 10 mm

For baseline, add the actual short axis measurement to the sum of LD of non-nodal lesions.

11.5.1.5 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression”. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

11.5.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest x-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is acceptable in certain situations (e.g., for body scans).

Ultrasound. Ultrasound should not be used to measure tumor lesions. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date because they are operator dependent. If new lesions are identified by ultrasound, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

11.5.3 Response Evaluation Criteria (RECIST version 1.1)

11.5.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target Lesions that Become "too small to measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

Lesions that Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced, the vector of the longest diameter should be the maximal longest diameter for the "coalesced lesion".

11.5.3.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions (the appearance of one or more new lesions is also considered progression). To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation.

11.5.3.3 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a "new" healing bone lesion). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate progressive disease. If a new lesion is equivocal, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

11.6 Appendix 6: Reference Standards

11.6.1 Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status scale scores are summarized below.

Table 16 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG
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, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care; 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

Source: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

11.6.2 Cockcroft-Gault Equation

The Cockcroft-Gault calculation will be made using the appropriate equation from the following:

Conventional (serum creatinine in mg/dL):

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) (serum creatinine in µmol/L):

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

11.6.3 Fridericia Formula for QT Interval Correction

Fridericia Formula for QT Interval Correction: $QTc=QT/RR^{0.33}$

11.6.4 New York Heart Association (NYHA)

The NYHA classifications are summarized below.

Table 17 New York Heart Association Classifications

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.

Source: American Heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition March 14, 1994.

11.7 Appendix 7: Drugs Commonly Associated with QT Prolongation

The drugs associated with QT prolongation and TdP are listed in Table 18. But this is not an exclusive list of drugs commonly associated with QT prolongation, if the investigator considers the use of other drugs that are not involved in the table may also prolong the QTc interval, it is necessary to discuss with the Sponsor's medical monitor to confirm whether the drugs can be used.

Table 18 Drugs Associated with QT Prolongation and TdP

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolimitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Ketoconazole	Veniafaxine		
	Itraconazole			

11.8 Appendix 8: Management of Subjects Who Are Unable to Attend Onsite Study Visit with Unavoidable Circumstances (e.g., Coronavirus Disease 2019 or Other Pandemics or Natural Disasters)

Regulatory authorities have recognized that the coronavirus disease 2019 (COVID-19) (i.e., severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection) or other pandemics or natural disasters may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the study drugs, or other considerations if site personnel or study subjects become infected with these diseases. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the study drugs or adhering to protocol-mandated visits and laboratory testing. To accommodate these challenges and mitigate safety risks, protocol modifications may be required and additional health checks including COVID-19 testing, body temperature monitoring, etc. may be performed during the trial, even if not planned within the protocol. Dose modifications will be based on the worst CTCAE version 5.0 grade. All dose modifications (discontinuations, interruptions, or reductions) must be recorded on the AE and drug administration eCRFs. Please use CTCAE version 5.0 general grading criteria to evaluate COVID-19, and then refer to the table below for detailed information about the dose modification.

Table 19 COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity (unless otherwise specified)	**Dose Modification**
Grade 1	• Resume DB-1303 at the same dose.
Grade 2	• If chest CT findings are completely resolved, maintain same dose; • If chest CT findings are nearly resolved, reduce dose one level.
Grade 3	• If chest CT findings are completely resolved, reduce dose one level; • If chest CT findings are not completely resolved, discontinue DB-1303.
Grade 4	• Permanently discontinue DB-1303.

COVID-19=coronavirus disease.

Note:

- Closely monitor signs/symptoms after resuming study intervention, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

- In addition to the recommendations outlined above, investigators may consider dose modifications of the study intervention according to the subjects' conduction and after discussion with the study Medical Monitor.

If subjects are not able to visit the study site due to unavoidable circumstances (e.g., COVID-19 or other pandemics or natural disasters), the following provisions may be made:

- Study visits may be performed by phone/virtually.
- Study visits may be performed in subjects' home residence by a visiting health care professional assigned by principal investigator and approved by Sponsor.
- Study visits may be performed in a local hospital close to subjects' home residence with Sponsor's approval.

The visiting health care professional or local hospital must be confirmed as qualified and approved by the investigator and Sponsor before performing study assessments.

Training will be provided to ensure assessments' quality and reduce discrepancy between on-site and remote assessments.

11.9 Appendix 9: Strong CYP3A inhibitors

Table 20 below provide an overview of strong CYP3A4 inhibitors.

Table 20 Strong CYP3A4 inhibitors

Strong CYP3A4 inhibitors	
boceprevir	lopinavir and ritonavir
clarithromycin	nefazodone
cobicistat	nelfinavir
conivaptan	paritaprevir and ritonavir and (ombitasvir
danoprevir and ritonavir	and/or dasabuvir)
diltiazem	posaconazole
elvitegravir and ritonavir	ritonavir
grapefruit juice	saquinavir and ritonavir
idelalisib	telaprevir
indinavir and ritonavir	tipranavir and ritonavir
itraconazole	troleandomycin
ketoconazole	voriconazole

CYP3A4 = Cytochrome P450, family 3, subfamily A, polypeptide 4.

Note: This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical/clinical pharmacological judgement is required.

Source: FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available online: https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems#table%201

11.10 Appendix 10 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

11.10.1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits even if collected outside of the study visits.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with Sponsor Medical Monitor or designee, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the study treatment.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

11.10.2 Definitions

11.10.2.1 Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3×Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

11.10.2.2 Hy's Law (HL)

AST or ALT ≥ 3×ULN **together with** TBL ≥ 2×ULN, where no other reason, other than the study treatment, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

11.10.3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3×ULN
- AST ≥ 3×ULN
- TBL ≥ 2×ULN

Local laboratories being used:

The Investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor Medical Monitor or designee
- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

11.10.4 Follow-up

11.10.4.1 Potential Hy's Law Criteria not Met

If the subject does not meet PHL criteria the Investigator will:

- Inform the Sponsor Medical Monitor or designee that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 11.10.8.

11.10.4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the Sponsor Medical Monitor or designee who will then inform the central study team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting study treatment, the Investigator is not required to submit a PHL SAE unless there is a significant change (see **note** below) in the subject's condition

- The Sponsor Medical Monitor or designee contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Sponsor Medical Monitor or designee.
  - Complete the relevant Liver eCRF Modules as information becomes available

Note: 'A significant change' in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Sponsor Medical Monitor or designee if there is any uncertainty.

11.10.5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Sponsor Medical Monitor or designee contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study treatment, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Duality Biologics Safety or designee will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the Duality Biologics standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study treatment:

- Send the updated SAE (report term 'Hy's Law') according to Duality Biologics standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

11.10.6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to subjects with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a **significant change** in the subjects' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required
- If there is a significant change, notify the Duality Biologics representative, who will inform the central study team, then follow the subsequent process described in Section 11.10.4.2.

11.10.7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g., chronic or progressing malignant disease, severe infection or liver disease or did the subject meet PHL criteria prior to starting study treatment and at their first on-study treatment visit.

If **No**: follow the process described in Section 11.10.4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change, follow the process described in Section 11.10.4.2 for reporting PHL as an SAE

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Sponsor Medical Monitor or designee if there is any uncertainty.

11.10.8 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory, this list may be modified according to clinical judgement. Any test result must be recorded.

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA [a] IgG anti-HCV HCV RNA [a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	CD-transferrin [b]
Autoimmune hepatitis	ANA Anti-Liver/Kidney Microsomal Ab (Anti-LKM) ASMA
Metabolic diseases	alpha-1-antitrypsin

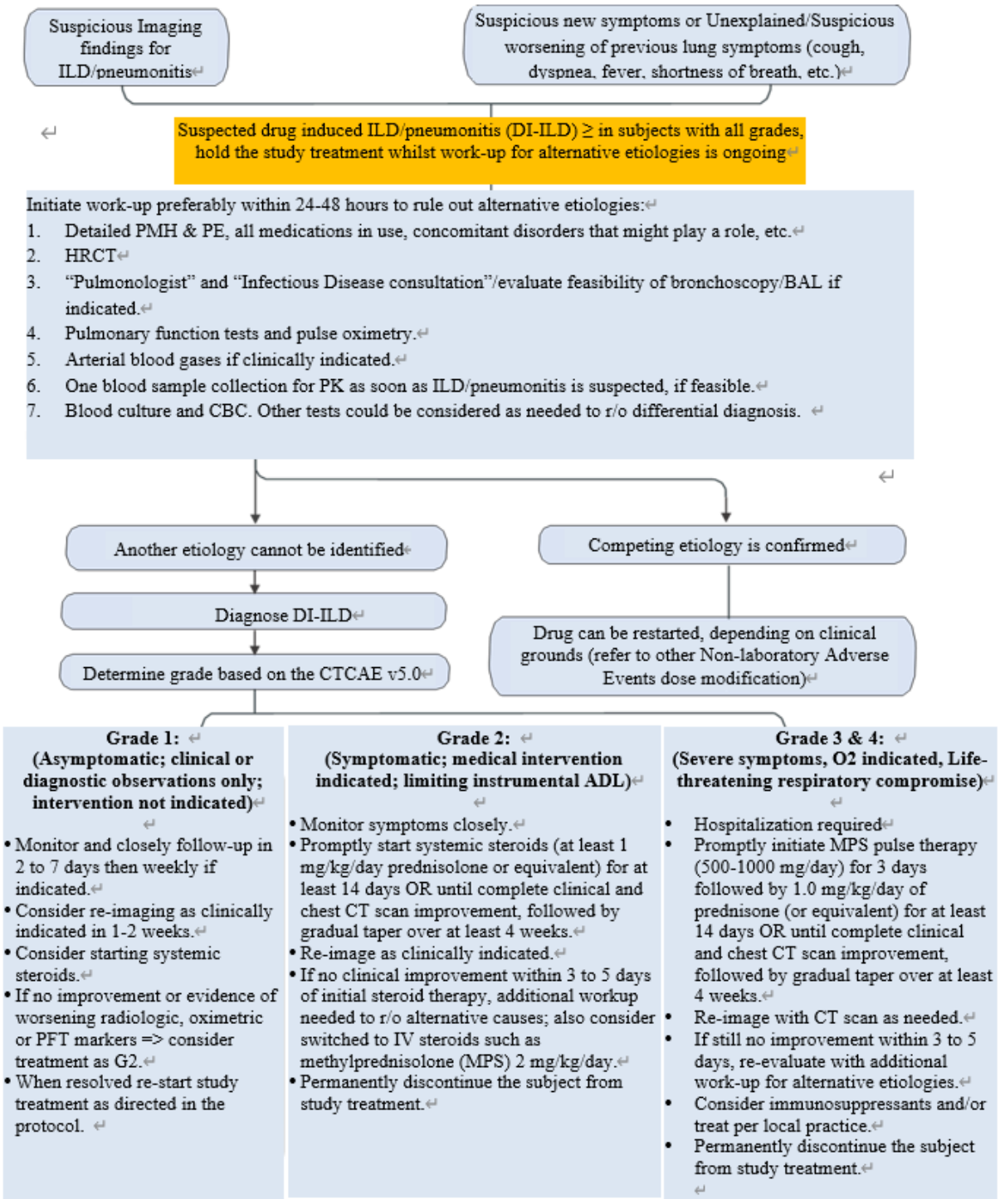
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
	Ceruloplasmin Iron Ferritin Transferrin [b] Transferrin saturation

ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = epstein-barr virus; GGT = gamma glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBsAg = surface antigen of the hepatitis B virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; INR = international normalized ratio; IgG = immunoglobulin G; IgM = immunoglobulin M; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal; RNA = ribonucleic acid;

[b] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive

[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

11.11 Appendix 11: Guidance for Management of Subjects with Drug-Induced ILD/Pneumonitis



ADL = activities of daily living; BAL = bronchoalveolar lavage; CBC = complete blood count; CT = computer tomography; CTCAE = Common Terminology Criteria for Adverse Events; DI = drug induced; HRCT = high resolution computed tomography; ILD = interstitial lung disease; IV = intravenous; MPS = methylprednisolone; PE = physical examination; PFT = pulmonary function test; PK = pharmacokinetic; PMH = past medical history.

11.12 Appendix 12: Quality of Life Questionnaire

11.12.1 EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

11.12.2 EORTC QLQ-BR45

EORTC QLQ-BR45

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Have you had a dry mouth?	1	2	3	4
32.	Have food and drink tasted different than usual?	1	2	3	4
33.	Have your eyes been painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you have lost any hair: Have you been upset by the loss of your hair?	1	2	3	4
36.	Have you felt ill or unwell?	1	2	3	4
37.	Have you had hot flushes?	1	2	3	4
38.	Have you had headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
41.	Have you had problems looking at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Have you worried about your health in the future?	1	2	3	4
During the past four weeks:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44.	Have you been interested in sex?	1	2	3	4
45.	Have you been sexually active (with or without intercourse)?	1	2	3	4
46.	Has sex been enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Have you had any pain in your arm or shoulder?	1	2	3	4
48.	Have you had a swollen arm or hand?	1	2	3	4
49.	Have you had problems raising your arm or moving it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Has the area of your affected breast been swollen?	1	2	3	4
52.	Has the area of your affected breast been oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4
54.	Have you sweated excessively?	1	2	3	4
55.	Have you had mood swings?	1	2	3	4
56.	Have you been dizzy?	1	2	3	4
57.	Have you had soreness in your mouth?	1	2	3	4
58.	Have you had any redness in your mouth?	1	2	3	4
59.	Have you had pain in your hands or feet?	1	2	3	4
60.	Have you had any redness on your hands or feet?	1	2	3	4
61.	Have you had tingling in your fingers or toes?	1	2	3	4
62.	Have you had numbness in your fingers or toes?	1	2	3	4
63.	Have you had problems with your joints?	1	2	3	4
64.	Have you had stiffness in your joints?	1	2	3	4
65.	Have you had pain in your joints?	1	2	3	4
66.	Have you had aches or pains in your bones?	1	2	3	4
67.	Have you had aches or pains in your muscles?	1	2	3	4
68.	Have you gained weight?	1	2	3	4
69.	Has weight gain been a problem for you?	1	2	3	4

Please go on to the next page

During the past four weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
70. Have you had a dry vagina?	1	2	3	4
71. Have you had discomfort in your vagina?	1	2	3	4

Please answer the following two questions only if you have been sexually active:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
72. Have you had pain in your vagina during sexual activity?	1	2	3	4
73. Have you experienced a dry vagina during sexual activity?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
74. Have you been satisfied with the cosmetic result of the surgery?	1	2	3	4
75. Have you been satisfied with the appearance of the skin of your affected breast (thoracic area)?	1	2	3	4

11.12.3 EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

11.12.4 PRO-CTCAE

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 31 January 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
4.	In the last 7 days, did you have any RASH?				
	○ Yes		○ No		
5.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
6.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 31 January 2020

7.	In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

11.13 Appendix 13: Clinical Laboratory Details

Refer to the table below for details on the central laboratories to be used in this study.

#	**Involving Laboratories**	**Address**	**Scope**
1	Labcorp Central Laboratory Services S.À.R.L.	Rue Moïse-Marcinhes 7 CH - 1217 Meyrin/Genève Switzerland	Tumor Sample (for HER2), PK/ADA/ctDNA sample receiving from sites
2	Labcorp Central Laboratory Services LP	8211 SciCor Drive Indianapolis, IN 46214-2985 USA	PK/ADA/ctDNA sample receiving from sites
3	Labcorp Pharmaceutical Research and Development	Building 9, No.338 Jialilue Road, Zhangjiang Hi-Tech Park, Shanghai, China	Tumor Sample (for HER2), PK/ADA sample receiving from sites
4	Labcorp Development (Asia) Pte. Ltd.	1, International Business Park #03-14 The Synergy Singapore 609917	Tumor Sample (for HER2), PK/ADA sample receiving from sites
5	Laboratory Corporation of America Holdings	19750 South Vermont Avenue Suite 200 Torrance, CA 90502	Tumor Sample (for HER2)
6	Labcorp Pharmaceutical Research and Development	Area B, S4 Door, Building #9, No.338 Galileo (Jialilue) Road, Zhangjiang Hi-Tech Park, Pudong, Shanghai, China	PK/ADA testing
7	Labcorp Development (Asia) Pte. Ltd	1 International Business Park #03-12 The Synergy Singapore 609917 Singapore	PK/ADA testing
8	Shanghai Solid Waste Disposal Co., Ltd	2491 Jiazhu Road, Jiading District, Shanghai, China	Labcorp sample destruction
9	Beijing Yingji Pharmaceutical Cold Chain Technology Co., Ltd	147 Kehai Avenue, East District, Economic Development Zone, Tongzhou District, Beijing, China	Labcorp sample transit
10	Burning Rock Dx	121 Innovation Dr, Suite 100, Irvine, CA 92617	ctDNA testing

#	**Involving Laboratories**	**Address**	**Scope**
11	Guangzhou Burning Rock Dx Co., Ltd	China Burningrock Guangzhou lab Burning Rock Medical Testing Department (PBD) No. 5, North Xingdao Ring Road, international biological island, Guangzhou, Guangdong Province, China	ctDNA testing
12	Guangzhou Environment Protection Investment Group Co., Ltd.	Room 1218, No. 121 Liuhua Road（South Tower）, Yuexiu District, Guangzhou, Guangdong Province, China	ctDNA sample destruction
13	Shanghai Shengsheng Logistics Co., Ltd.	Building 3, #327 Jifeng Road, Minhang District, Shanghai, China	ctDNA sample transit

As required by China National Center for Biotechnology Development, the items 3, 6, 8, 9, 11, 12, 13 are the names and the locations of the central laboratories that will be operating in China and will touch the human genetic resources for this study including vendors involved on sample disposal and transport activities.

11.14 Appendix 14: Abbreviations and Definitions

Abbreviation Term	Definitions
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
β-HCG	β-human chorionic gonadotropin
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CAP	College of American Pathologists
CDK	Cyclin-dependent Kinase
C_{max}	Peak observed concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CR	Complete response
CRO	Contract research organization
CSP	Clinical Study Protocol
ctDNA	circulating tumor DNA
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CTFG	Clinical Trial Facilitation Group
C_{trough}	Trough concentration
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
DAR	Drug-to-antibody ratio
DCO	Data cutoff

Abbreviation Term	Definitions
DCR	Disease Control Rate
DLCO	Diffusion capacity of the lungs for carbon monoxide
DLT	Dose-limiting toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic data collection
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of study
EOT	End of treatment
EPO	Erythropoietin
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-dimension, 5-level health state utility index
ER	Exposure response
ET	Endocrine therapy
FAS	Full analysis set
FDA	US Food and Drug Administration
FEV	Forced expiratory volume
FFPE	Formalin fixation and paraffin embedding
FIH	First in human
FSH	Follicle stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good laboratory practice
GM-CSF	Granulocyte-macrophage colony stimulating factor
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

Abbreviation Term	**Definitions**
HER2	Human epidermal growth factor receptor 2
HFS	Hand and foot syndrome
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hormone receptor
HRCT	High resolution computed tomography
HRQoL	Health-related quality of life
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRC	Independent review charter
IRR	Infusion-related reaction
IRT	Interactive response technology
ISH	In situ hybridization
ITT	Intent-to-treat
ILD	Interstitial lung disease
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVD	*in vitro* diagnostic
IVDR	*in vitro* diagnostic regulation
LAM	Lactational amenorrhoea method
IV	Intravenous
LD	Longest diameter
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
ms	Millisecond

Abbreviation Term	Definitions
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MTP	Multiple testing procedure
MUGA	Multiple-gated acquisition
NCI	National Cancer Institute
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
NYHA	New York heart association
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PFS2	Time to second progression or death
PFT	Pulmonary function test
PK	Pharmacokinetic
PLT	Platelet
PopPK	Population pharmacokinetics
PPS	Per-protocol analysis set
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PT	Prothrombin time
PT	Preferred term
Q3W	Once every 3 weeks
Q6W	Once every 6 weeks
Q9W	Once every 9 weeks
QLQ-BR45	Breast cancer-specific module
QLQ-C30	30-item core quality of life questionnaire
QTc	QT corrected interval
QTcF	Fredericia’s formula-QT corrected interval
QW	Every week
RBC	Red blood cell

Abbreviation Term	**Definitions**
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SD	Stable disease
SFU	Safety follow-up
SoA	Schedule of activities
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
TBIL	Total bilirubin
T_{max}	Time to peak concentration
TEAE	Treatment emergent adverse event
TFST	Time to first subsequent treatment or death
TSST	Time to second subsequent treatment or death
TTR	Time to response
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of childbearing potential

11.15 Appendix 15: Protocol Amendment History

Protocol Version	Version Date	General Description of Changes
Version 1.0	30 Jun 2023	Original document.
Version 2.0 (Protocol Amendment 1)	19 Jul 2023	Updating the rationale for the selection of RP2D.
Version 3.0 (Protocol Amendment 2)	14 Sep 2023	The protocol was updated per the discussion with FDA.

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