

Clinical Study Protocol

Chemotherapy-Free pCR-Guided Strategy with Subcutaneous Pertuzumab-Trastuzumab and T-DM1 in HER2-Positive Early Breast Cancer (PHERGain-2)

Code: MEDOPP293

Drugs Tested	<ul style="list-style-type: none">• Pertuzumab and trastuzumab for subcutaneous administration (PH FDC SC)• Ado-trastuzumab emtansine (T-DM1)
EU CT #	<u>2023-508738-32-00</u>
Clinicaltrials.gov #	NCT04733118
Protocol Code	MEDOPP293
Protocol Date	11-February-2025
Protocol Review History	<ul style="list-style-type: none">• CSP version 1.0, 10-Feb-2021• CSP version 2.0, 02-Jun-2021• CSP version 3.0, 23-Nov-2021• CSP version 4.0, 04-April-2022• CSP version 5.0, 11-Feb-2025

I. SPONSOR'S SIGNATURE PAGE

Study title: Chemotherapy-Free pCR-Guided Strategy with Subcutaneous Pertuzumab-Trastuzumab and T-DM1 in HER2-Positive Early Breast Cancer (PHERGain-2)

Study code: MEDOPP293

Version number: 5.0

Version date: 11-February-2025

_____ Sponsor's Medical Scientist	_____ Signature	_____ Signature date (DD-Mmm-YYYY)
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_____ Scientific Global Coordinator	_____ Signature	_____ Signature date (DD-Mmm-YYYY)
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II. KEY CONTACTS**Sponsor**

Name: Medica Scientia Innovation Research (MEDSIR)
Contact Name: [REDACTED]
Address: C/ Pere IV, 128, 3rd floor, 08005 Barcelona (Spain)
Phone: [REDACTED]
Fax: [REDACTED]
E-mail: [REDACTED]

Sponsor's Safety Risk Management

Name: Medica Scientia Innovation Research (MEDSIR)
Address: C/ Pere IV, 128, 3rd floor, 08005 Barcelona (Spain)
Phone: [REDACTED]
Fax: [REDACTED]
E-mail: pharmacovigilance@medsir.org

Scientific Global Coordinator

Name: Javier Cortés, MD, PhD
Email: [REDACTED]
Position: [REDACTED]
Institution: [REDACTED]

Principal Investigator

Name: Antonio Llombart-Cussac, MD
Email: [REDACTED]
Position: [REDACTED]
Institution: [REDACTED]

Sponsor's Medical Scientist

Name: [REDACTED]
E-mail: [REDACTED]

III. STEERING COMMITTEE

Name	Role
Dr. Antonio Llombart-Cussac	<i>Clinical Expert</i>
Dr. Javier Cortés	<i>Clinical Expert</i>
██████████	<i>Medical Scientist</i>
PHERGain-2 Study Investigators	

IV. DECLARATION OF INVESTIGATORS

Protocol Title: Chemotherapy-Free pCR-Guided Strategy with Subcutaneous Pertuzumab-Trastuzumab and T-DM1 in HER2-Positive Early Breast Cancer (PHERGain-2)

Version: 5.0

Version date: 11-February-2025

Protocol number: MEDOPP293

I have received, reviewed, and understood the following:

- a) Protocol version: 5.0, dated 11-February-2025
- b) Summary of Product Characteristics (SmPC) for ado-trastuzumab emtansine (T-DM1) and Investigator's Brochure (IB) of pertuzumab and trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC), with details of clinical and nonclinical data that are relevant to the study of the products in human subjects.
 - I have been adequately informed about the development of the investigational products to date. I will confirm the receipt of updated SmPCs and IB. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.
 - I fully understand that any changes instituted by the investigator(s) without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the wellbeing of the patients). I am aware that I cannot deviate from or apply changes to the protocol without prior approval or the favorable opinion of the Institutional Review Board (IRB) or Ethics Committee (EC) and/or before Sponsor's agreement to avoid immediate risk to the trial patients. If this occurs, I agree to inform the Sponsor as to the deviation or changes in writing and their reasons, as soon as possible.
 - I will not enroll the first patient in the study until I have received approval from the appropriate IRB/EC and until all legal and regulatory requirements in my country have been fulfilled.
 - The study will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (ICH E6(R2) GCP) and applicable regulations and laws.

- I agree to obtain, in the manner described in this protocol and in (ICH E6[R2] GCP), signed informed consent form (ICF) by the patient or witnessed verbal ICF to participate for all patients whose participation in this study is proposed to and before any patient's study specific procedure is done.
- I will ensure that the study drug(s) supplied by the Sponsor are being used only as described in this protocol.
- I am aware of the requirements for the correct reporting of serious adverse events, and I commit to document and to report such events as required by the Sponsor and in accordance with Health Authority Regulatory requirements.
- I agree to supply – upon request – the Sponsor or Sponsor's representative with evidence of current laboratory accreditation, the name and address of the laboratory, and a list of normal values and ranges.
- I agree with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.
- I agree to keep all source documents and case report forms as specified in the relevant sections of this protocol.
- I will provide all required Regulatory Authority forms, up-to-date curriculum vitae of myself, sub-investigators and of any member of my study team (if requested) before the study starts, which may be submitted to regulatory authorities.
- I am aware of the possibility of being audited by the Sponsor or its delegate or inspected by regulatory authorities for the performance of this study. I will permit monitoring, auditing and inspection and provide direct access to source data/documents and reports for these purposes.
- Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

Name: _____

Signature: _____

Date: _____

V. PROTOCOL SYNOPSIS

Investigational Medicinal Products:	<ul style="list-style-type: none"> • Pertuzumab and trastuzumab for subcutaneous administration (PH FDC SC) • Ado-trastuzumab emtansine (T-DM1)
Protocol number:	MEDOPP293
EU CT #:	<u>2023-508738-32-00</u>
Protocol title:	Chemotherapy-Free pCR-Guided Strategy with Subcutaneous Pertuzumab-Trastuzumab and T-DM1 in HER2-Positive Early Breast Cancer (PHERGain-2)
Type of study:	Multicenter, open-label, phase II trial
Target disease:	Previously untreated and histologically confirmed HER2-Positive (HER2[+]) early-stage breast cancer
Subjects:	<p>Patients ≥ 18 years of age with previously untreated HER2[+] (immunohistochemistry [IHC] score 3+) invasive carcinoma according to the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) criteria, tumor size ≥ 5mm and ≤ 25mm using ultrasound and mammography, up to ≤ 30mm by breast magnetic resonance imaging (MRI), and node-negative status by clinical exam, MRI, and ultrasound.</p> <p>Patients with metastatic disease are not eligible.</p> <p>In patients with suspected axillary node involvement, a negative fine needle aspiration biopsy (FNAB) will be mandatory.</p> <p>Patients must have not been previously treated with chemotherapy, anti-HER2 therapy, radiation therapy, or endocrine therapy (ET) for invasive breast cancer.</p>
Number of patients:	393
Screening criteria:	<p>Inclusion criteria</p> <p>Patients will be included in the study only if they meet ALL of the following criteria:</p> <ol style="list-style-type: none"> 1. Written informed consent prior to beginning specific protocol procedures. 2. Female or male patients ≥ 18 years of age. 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 4. Histologically proven invasive carcinoma of the breast. 5. Tumor size must be ≥ 5mm and ≤ 25mm using ultrasound and mammography (tumor size between ≥ 5mm and ≤ 30mm by MRI is also accepted given the precision of the technique). <i>Note: Although tumors between ≥ 5mm and ≤ 10mm</i>

are not considered target lesions by RECIST v1.1, we will consider these lesions as targets to follow up.

6. Patients must have node-negative breast cancer by clinical exam, MRI and ultrasound according to the American Joint Committee on Cancer (AJCC) 8th edition.
7. Centrally confirmed HER2[+] status with IHC score 3+.
8. Known estrogen receptor (ER) and progesterone receptor (PgR) status prior to study entry that should be performed by immunohistochemical methods according to the local institution standard protocol.
9. Patients with multifocal or multicentric breast cancer are eligible; only patients with a total number of lesions ≤ 2 are eligible and if all lesions sampled meet the inclusion criteria #5, #6, and #7. *Note: If two lesions are in such proximity that it is suspected to be the same lesion, it would not be necessary to biopsy both.*
10. Normal left ventricular function and diastolic function (left ventricular ejection fraction [LVEF] $\geq 55\%$) as assessed by echocardiogram or multiple-gated acquisition scan (MUGA) documented within ≤ 28 days prior to first dose of study treatment.
11. Adequate bone marrow, liver, and renal function:
 - a. Hematological: White blood cell (WBC) count $> 3.0 \times 10^9/L$, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, platelet count $\geq 100.0 \times 10^9/L$, and hemoglobin ≥ 10.0 g/dL (≥ 6.2 mmol/L).
 - b. Hepatic: total bilirubin \leq institutional upper limit of normal (ULN) (except for Gilbert's syndrome); alkaline phosphatase (ALP) ≤ 2.5 times ULN; aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.5 times ULN.
 - c. Renal: serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min/1.73 m² for patients with creatinine levels above institutional normal.
 - d. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN.
12. Patient must be accessible for treatment and follow-up.
13. Willingness and ability to provide blood samples at baseline, C3D1 before treatment infusion, pre-surgery and then after surgery: every 6 months for the first 5 years, and every year thereafter until the EoS.
14. Willingness and ability to provide tumor tissue samples at baseline and at surgery.
15. Women of childbearing potential and men with partners of childbearing potential must be willing to use one highly effective form of nonhormonal contraception or two

effective forms of nonhormonal contraception by the patient and/or partner and to continue its use for the duration of study treatment and for seven months after the last dose of study treatment.

Note: Acceptable forms of effective contraception should include two of the following:

- i. Placement of non-hormonal intrauterine device (IUD)
- ii. Condom with spermicidal foam/gel/film/cream/suppository
- iii. Diaphragm or cervical/vault caps with spermicidal foam/film/cream/suppository

The above contraception is not a requirement in the case the male patient, or male partner of a female patient, is surgically sterilized, the female patient is post-menopausal or the patient remains abstinent and truly abstains from sexual activity (refrains from heterosexual intercourse).

16. Negative serum pregnancy test for premenopausal women including women who have had a tubal ligation and for women less than 12 months after the onset of menopause.

Exclusion criteria:

Any patient meeting ANY of the following criteria will be excluded from the study:

1. Any previous treatment, including chemotherapy, anti-HER2 therapy, radiation therapy, or ET for invasive breast cancer (except for breast carcinoma in situ of the contralateral breast cancer, in the last five years before treatment initiation in this study).
2. HER2 disease with IHC score 0, 1+ or 2+ and *in situ* hybridization (ISH) positive result.
3. Evidence of metastatic disease.

Note: All patients must be willing to undergo chest and pelvis computed tomography (CT)/MRI scan before enrolment to prove no evidence of metastatic disease. Bone scan will be performed at screening only if there is suspicion of bone metastases. If a bone scan cannot be performed at screening, an alternative is PET/CT using ¹⁸F-labeled sodium fluoride (¹⁸F-fluoride PET/CT).

4. Patients with bilateral breast cancer.
5. Known hypersensitivity reaction to any investigational or therapeutic compound or their incorporated substances.

6. History of other malignancy within the last five years prior to first dose of study drug administration, except for curatively treated basal and squamous cell carcinoma of the skin and/or in situ cervical carcinoma.
7. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) despite adequate antihypertensive treatment.
8. Serious cardiac illness or medical conditions including, but not confined to, the following:
 - History of NCI CTCAE v.5.0 Grade \geq 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class \geq II.
 - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate \geq 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz II] or third-degree AV-block).
 - Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication.
 - Angina pectoris requiring anti-angina medication.
 - Clinically significant valvular heart disease.
 - Evidence of transmural infarction on electrocardiogram (ECG).
 - Evidence of myocardial infarction within the last 12 months prior to study entry.
9. History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome.
10. Active uncontrolled infection at the time of enrollment.
11. Current known infection with human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.
12. Patients with pulmonary disease requiring continuous oxygen therapy.
13. Grade \geq 2 neuropathy as per National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI–CTCAE) version (v)5.0.
14. Previous history of bleeding diathesis.

	<p>15. Patient is currently receiving chronic treatment with corticosteroids, or another immunosuppressive agent (standard premedication for chemotherapy and local applications are allowed).</p> <p>16. Major surgical procedure or significant traumatic injury within 14 days prior to study entry or anticipation of need for major surgery within the course of the study treatment.</p> <p>17. Any other concurrent severe and/or uncontrolled medical condition that would contraindicate patient participation in the clinical study.</p> <p>18. History of having received any investigational treatment within 28 days prior to study entry.</p> <p>19. Pregnant or breast-feeding women or patients not willing to apply highly effective contraception as defined in the protocol.</p>
<p>Study objectives:</p>	<p>Primary efficacy objective</p> <p>To assess 3-year recurrence-free interval (3y-RFI) in all patients with previously untreated HER2[+] (IHC score 3+) node-negative early-stage breast cancer.</p> <p>Primary safety objective</p> <p>To assess global health status decline rate at 1 year from start of neoadjuvant treatment.</p> <p>Secondary objectives</p> <ul style="list-style-type: none"> ● To assess pathological complete response (pCR). ● To compare the rate of pCR by hormone receptor (HR) status and tumor stage. ● To evaluate residual cancer burden (RCB). ● To evaluate rate of breast-conserving surgery (BCS). ● To evaluate objective response rate. ● To evaluate the correlation between final MRI results and breast conserving surgery (BCS), pCR, and RCB at surgery. ● To analyze the rate of RFI at 5 years. ● To analyze the rate of event-free survival (EFS) at 3 and 5 years. ● To analyze the rate of relapse-free survival (RFS) at 3 and 5 years. ● To analyze the rate of distant relapse-free survival (DRFS) at 3 and 5 years.

	<ul style="list-style-type: none"> ● To analyze the rate of disease-free survival (DFS) at 3 and 5 years. ● To analyze the rate of invasive disease-free survival (iDFS) at 3 and 5 years. ● To analyze overall survival (OS) at 3 and 5 years. ● To analyze the rate of breast cancer-specific survival (BCSS) at 3 years and 5 years. ● To assess the cardiac toxicity profile after 1 year of adjuvant treatment according to the NCI-CTCAE v.5.0. ● To assess the general toxicity profile according to CTCAE v.5.0. ● To evaluate health-related quality of life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC)-QLC-C30 and QLQ-BR23 questionnaires. ● To evaluate the ratio of patients who have needed chemotherapy. <p>Exploratory objectives</p> <p>Exploratory objectives can include (but are not limited to):</p> <ul style="list-style-type: none"> ● To evaluate predictive and/or prognostic and/or pharmacodynamic biomarkers associated with disease activity status, patient outcome or response to study treatments on archival and/or liquid biopsy samples. ● To determine the association of treatment efficacy and/or safety outcomes with radiological imaging biomarkers.
<p>Endpoints:</p>	<p>Primary efficacy endpoint</p> <p>3y-RFI defined as time from start of treatment in adjuvant setting until recurrence, new invasive disease, or death from breast cancer in the overall population. Recurrence will be defined in accordance with the standardized efficacy endpoints (STEEP) criteria.</p> <p>Primary safety endpoint</p> <p>Global health status decline rate at 1 year from start of neoadjuvant treatment, defined as the rate of patients with a ≥10% global health status decline at 1 year from start of neoadjuvant treatment as assessed by the Global Health Status/QoL EORTC-QLC-C30 scale and its breast cancer module QLQ-BR23.</p> <p>Secondary endpoints</p>

- pCR rates (pCR_{BREAST+LYMPH NODES} -ypT0/Tis ypN0- and pCR_{BREAST} -ypT0/Tis-) in the overall study population.
- pCR rates (pCR_{BREAST+LYMPH NODES} -ypT0/Tis ypN0- and pCR_{BREAST} -ypT0/Tis-) according to HR status (positive, negative), and tumor stage (T1, T2).
- RCB score in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
- Rate of BCS in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
- MRI-guided objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1 in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
- Correlation of MRI-guided objective response rate by RECIST v.1.1 with BCS, pCR, and RCB in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
- 5-year RFI in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year EFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year RFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year DRFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year DFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year iDFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year OS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- 3-year and 5-year BCSS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
- Adverse events of cardiotoxicity after 1 year of adjuvant treatment according to the NCI-CTCAE v.5.0.

	<ul style="list-style-type: none"> • Toxicity and safety profile at 3 and 5 years as per NCI-CTCAE v.5.0 in the overall study population and in each study arm (A, B, C). • Patient Reported Outcomes (PROs) HRQoL assessment as per EORTC-QLC-C30 and QLQ-BR23 questionnaires in the overall study population and in each study arm (A, B, C). • Ratio of patients of cohort C who will receive adjuvant chemotherapy before T-DM1. <p>Exploratory endpoints</p> <p>Exploratory endpoints can include (but are not limited to):</p> <ul style="list-style-type: none"> • Association of clinical outcomes, safety and/or tolerability profile with mutation profiling, copy number variability, gene expression, multiplex assays, proteomic analyses, digital pathology, immunohistochemistry, taxonomic or functional analyses performed on tissue and/or liquid biopsy samples. • Association of treatment efficacy and/or safety outcomes in all patients with radiological imaging biomarkers.
<p>Study treatment:</p>	<p>Investigational Medicinal Products (IMPs) will be PH FDC SC and T-DM1.</p> <p>Breast staging at screening will be performed with mammography, breast ultrasound, and breast MRI. Nodal staging at baseline will be performed with MRI and axillary ultrasound ± FNAB if suspected lymph node involvement.</p> <p>After signing the informed consent form (ICF) and confirmed eligibility, patients will receive PH FDC SC (± ET depending on HR status) on day 1 of each 21-day cycle for 8 cycles. There will be an initial loading dose of 1,200mg pertuzumab, 600mg trastuzumab, and 30,000 units hyaluronidase in the first cycle, followed by a dose of 600mg pertuzumab, 600mg trastuzumab and 20,000 units hyaluronidase as maintenance dose for the remaining cycles.</p> <p>HR-positive patients will also receive ET continuously during neoadjuvant and adjuvant regimen (mandatory), and the type of ET will be selected according to local practice. For post-menopausal women letrozole (2.5 mg/day orally) is highly recommended, whereas for pre-/peri-menopausal women is highly recommended ovarian function suppression therapy combined with either tamoxifen (20 mg/day orally) or letrozole (2.5 mg/day orally). For men tamoxifen is highly recommended.</p> <p>After completing neoadjuvant therapy, a final breast MRI will be performed prior to surgery and after completion of Neoadjuvant treatment. All local MRI will be centrally</p>

	<p>reviewed, and results will be considered prior to surgery. Surgery will be performed not sooner than 2 weeks but no more than 4 weeks after completion of the last cycle of PH FDC SC. Sentinel node biopsy will be mandatory; subsequent axillary dissection will be performed according to local guidelines. Surgery will require free margins for any infiltrating or ductal carcinoma in situ (DCIS) lesion. Radiotherapy will be mandatory for patients with breast preservation and will be administered concomitantly with PH FDC SC (if patient achieves a pCR) or T-DM1 (if patient has a residual disease [RD]).</p> <p>Adjuvant systemic therapy will be started within 4 weeks from surgery and patients will be assigned to one of the three following cohorts depending on pathological report:</p> <ul style="list-style-type: none"> • Cohort A (pCR in breast and axilla [yp.T0/is, ypN0]): patients will receive PH FDC SC (\pm ET as per HR status) on day 1 of each 21-day cycle for 10 additional cycles. • Cohort B (residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi): patients will receive T-DM1 (\pm ET as per HR status) for 10 cycles. • Cohort C (pathological progression to nodes [ypN1-N3]): patients will receive T-DM1 (\pm ET as per HR status) for 10 cycles. As per physician's choice and according to ESMO or NCCN 2021 guidelines, patients may receive chemotherapy before adjuvant T-DM1. <p>HR-positive patients will receive ET continuously up to at least 5 years in combination with adjuvant PH FDC SC or T-DM1, apart from the cycles involving the use of chemotherapy in cohort C. The extension of ET after completing the first five years will be based on local practice.</p> <p>Patients with MRI-confirmed progression to PH FDC SC during the neoadjuvant treatment will continue in the study. Alternative neoadjuvant treatment will be administered as per investigator's choice, and assignment of adjuvant treatment will be based on the above-mentioned criteria. Despite alternative treatment, the number of PH FDC SC cycles in the neoadjuvant treatment period will remain unchanged (8 cycles). Patients without confirmed progression who by physician's choice are switched to chemotherapy during neoadjuvant treatment, will discontinue the study and not be included in the final analysis.</p> <p>Patients completing the study treatment period/discontinuing treatment will enter a post-treatment follow-up period during which survival and new anti-cancer therapy information will be collected, until end of study (EoS) or study termination, whichever occurs first.</p>
<p>Safety and efficacy assessments:</p>	<p>Patient visits</p> <p>Visits are organized in programmed cycles of 21 days (if there are no treatment delays due to the occurrence of adverse events [AEs]). All visits must occur within \pm 3 working days from the scheduled date, unless otherwise noted in the schedule of assessments.</p>

	<p>Efficacy assessments</p> <p>Axillary ultrasound/MRI ± fine needle aspiration (FNA) will be performed at screening visit. Mammography is required at screening visit too, before surgery, 6 months after the last RT session for patients who received adjuvant radiation therapy, and during follow-up, but will not be used for the objective response assessment.</p> <p>Breast MRI is required at baseline, and at the end of neoadjuvant therapy within 2 weeks prior to surgery. Imaging follow-up will be done according to standard local practice. Response evaluation with MRI will be assessed using the RECIST v.1.1.</p> <p>Medical images derived from tumor assessments (except bone scans) will be stored for exploratory analyses at MEDSIR’s central imaging repository.</p> <p>PROs HRQoL questionnaires will be collected from start of neoadjuvant treatment until the end of adjuvant treatment. It will be collected at baseline, at each neoadjuvant treatment visit and at the end of treatment. Then in each follow-up visit too.</p> <p>Patients will be followed up every 3 months for the first two years, every 6 months for the 3 next years, and yearly thereafter.</p> <p>Safety assessments</p> <p>The occurrence and maximum grade of side effects observed throughout the study will be listed and tabulated according to type and dose level. Any AEs that the investigator reports as unrelated to the drug will also be reported. In this study, side effects will be assessed according to the NCI–CTCAE version 5.0.</p>
<p>Sample size and statistical methods:</p>	<p>Primary efficacy analysis</p> <p>The 3y-RFI will be analyzed on full analysis set and will include all the patients who had surgical excision of the primary tumor. The statistic test for this primary analysis is assumed to be 95% confidence interval (95% CI) based on Kaplan-Meier estimator. The analysis will test the null hypothesis that the true 3y-RFI rate is equal or lower than 94%. The alternative hypothesis is that the true distribution of 3y-RFI in these patients had a rate greater than 98%. This analysis will be declared positive if the lower boundary for the 95% CI is higher than null hypothesis (H0: RFI≤94%). With the expectation a 20% dropout rate, a sample size of 393 patients is necessary to attain 80% power at nominal level of two-sided alpha of 0.05.</p> <p>Primary safety analysis</p>

	<p>The global health status decline rate at 1 year from start of neoadjuvant treatment as assessed by the Global Health Status/QoL EORTC-QLC-C30 scale. We will include all the patients, with baseline, and at least one follow-up QoL evaluations. The statistic test for this safety analysis is assumed to be 95% confidence interval based on Kaplan-Meier estimator. The confidence intervals will be considered descriptive.</p>
Study calendar:	<p>We expect an accrual time of 18 months and an additional 68 months for follow-up from end of accrual until EoS.</p>

VI. TABLE OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESIs	Adverse events of special interest
AI	Aromatase inhibitor
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	Aspartat transaminase
BCS	Breast conserving surgery
BCSS	Breast cancer-specific survival
BSA	Body surface area
CHF	Congestive heart failure
CMF	Cyclophosphamide, methotrexate, and fluorouracil
CRF	Case report form
ctDNA	Circulating tumor DNA
DCIS	Ductal carcinoma in situ
DRFS	Distant relapse-free survival
DFS	Disease-free survival
EBCTCG	Early breast cancer trialists' collaborative group
ECHO	Echocardiography
ECOG	Eastern cooperative oncology group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European medicines agency
EORTC	European Organisation for Research and Treatment of Cancer
EoS	End of study
ER	Estrogen receptor
ET	Endocrine therapy
FDA	Food and drug administration
FFPE	Formalin fixed paraffin-embedded blocks
FNAB	Fine needle aspiration biopsy
FPI	First patient in
G-CSF	Granulocyte-colony stimulating factors
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
HR	Hormone receptor
ICF	Informed consent form
iDFS	Invasive disease-free survival
IHC	Immunohistochemistry
ILD	Interstitial lung disease

IMP	Investigational medicinal product
ISH	In situ hybridization
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
LHRH	Luteinizing-hormone-releasing hormone
LPI	Last patient in
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MMRM	Mixed effect model repeat measurement
MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition
NCCN	National comprehensive cancer network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OFS	Ovarian function suppression
OS	Overall survival
pCR	Pathological complete response
PD	Progressive disease
PgR	Progesterone receptor
PH FDC SC	Pertuzumab and trastuzumab, fixed-dose combination in a subcutaneous injection
PRO	Patient reported outcome
QoL	Quality of life
RCB	Residual cancer burden
RECIST	Response Evaluation Criteria in Solid Tumors
RFI	Recurrence-free interval
RFS	Relapse-free survival
SC	Subcutaneous
SC FDC	Subcutaneous fixed dose combination
SERMs	Selective estrogen receptor modulators
SLNB	Sentinel lymph node biopsy
SWFI	Sterile water for injection
TBCRC	Translational breast cancer research consortium
TILs	Tumor-infiltrating lymphocytes
ULN	Upper limit of normal
UPN	Unique patient number
WBC	White blood cell

VII. TABLE OF CONTENTS

1	STUDY BACKGROUND AND RATIONALE.....	24
1.1	INTRODUCTION.....	24
1.2	ADVANCES IN TREATMENT OF BREAST CANCER.....	25
1.2.1	<i>Importance of assays and protocols to guide therapy</i>	<i>26</i>
1.3	DEFINITION AND PROGNOSTIC IMPACT OF PATHOLOGICAL COMPLETE RESPONSE	26
1.4	RATIONALE FOR CHEMOTHERAPY-FREE TREATMENT STRATEGY FOR HER2[+] BREAST CANCER	27
1.5	STUDY RATIONALE	27
1.5.1	<i>Clinical data.....</i>	<i>27</i>
1.5.2	<i>Rationale.....</i>	<i>28</i>
2	STUDY OBJECTIVES AND ENDPOINTS	29
2.1	PRIMARY EFFICACY OBJECTIVE.....	29
2.1.1	<i>Primary efficacy endpoint.....</i>	<i>29</i>
2.2	PRIMARY SAFETY OBJECTIVE	29
2.2.1	<i>Primary safety endpoint.....</i>	<i>29</i>
2.3	SECONDARY OBJECTIVES	29
2.3.1	<i>Secondary endpoint</i>	<i>29</i>
2.4	EXPLORATORY OBJECTIVES	31
2.4.1	<i>Exploratory endpoint.....</i>	<i>31</i>
3	STUDY OVERVIEW.....	31
3.1	DESCRIPTION OF THE STUDY	31
3.1.1	<i>Central pathology review for HER2 status.....</i>	<i>33</i>
3.2	STUDY DESIGN	33
3.3	SCREENING PHASE	34
3.4	TREATMENT PHASE.....	34
3.5	TREATMENT FOLLOW-UP	35
3.6	END OF TREATMENT VISITS AND END OF STUDY.....	36
4	PATIENT SELECTION	37
4.1	STUDY TARGET POPULATION.....	37
4.2	INCLUSION CRITERIA	37
4.3	EXCLUSION CRITERIA.....	39
5	STUDY DRUG INFORMATION	41
5.1	FORMULATION, PACKAGING, AND HANDLING.....	41
5.1.1	<i>PH FDC SC.....</i>	<i>41</i>

5.1.2	<i>T-DM1 / Trastuzumab emtansine</i>	42
5.1.3	<i>Endocrine Therapy</i>	43
5.1.4	<i>Chemotherapy</i>	43
5.2	DRUG SUPPLY, STORAGE, AND DRUG ACCOUNTABILITY	43
5.3	TREATMENT COMPLIANCE.....	44
5.4	DOSAGE AND ADMINISTRATION	44
5.4.1	<i>PH FDC SC</i>	44
5.4.2	<i>T-DM1</i>	45
5.4.3	<i>ET</i>	46
5.5	TREATMENT MODIFICATIONS AND DISCONTINUATION	46
5.5.1	<i>Modification of the amount of study drug due to changes in patient’s weight</i>	49
5.5.2	<i>Treatment discontinuation due to cardiac toxicities</i>	49
5.5.3	<i>T-DM1 dose modification for thrombocytopenia</i>	51
5.5.4	<i>T-DM1 dose modification for hepatotoxicity</i>	52
5.5.5	<i>T-DM1 dose modification for neurotoxicity</i>	53
5.5.6	<i>Dose modification for infusion-related reactions</i>	53
5.5.7	<i>Dose Modification for Pulmonary Toxicity</i>	54
5.6	MEDICATION ERRORS AND OVERDOSE	55
5.7	GENERAL CONCOMITANT MEDICATION AND ADDITIONAL ASSISTANCE GUIDELINES	55
5.8	PROHIBITED THERAPIES AND MEDICATION.....	56
6	ASSESSMENTS AND STUDY PROCEDURES	56
6.1	PATIENT ENTRY PROCEDURES.....	56
6.1.1	<i>Informed consent</i>	56
6.1.2	<i>Patient allocation</i>	57
6.2	VISIT SCHEDULE	58
6.3	STUDY ASSESSMENTS.....	58
6.3.1	<i>Demographic data and medical history</i>	58
6.3.2	<i>Breast cancer surgery</i>	59
6.3.3	<i>Central testing of HER2 status by IHC</i>	59
6.3.4	<i>Imaging assessment</i>	60
6.4	SAFETY AND TOLERABILITY ASSESSMENTS.....	60
6.4.1	<i>Laboratory assessments</i>	60
6.4.2	<i>Pregnancy and assessment of fertility</i>	61
6.4.3	<i>Cardiac function monitoring</i>	62
6.4.4	<i>Physical examination</i>	62
6.4.5	<i>Vital signs</i>	63

6.4.6	<i>ECOG performance status</i>	63
6.5	HEALTH-RELATED QUALITY OF LIFE ASSESSMENTS	63
6.6	TRANSLATIONAL RESEARCH	64
6.6.1	<i>Tumor tissue samples</i>	65
6.6.2	<i>Blood samples</i>	65
6.7	EFFICACY ASSESSMENTS.....	66
6.7.1	<i>Breast cancer surgery</i>	66
6.7.2	<i>Breast tumor imaging assessment</i>	67
6.7.3	<i>Response assessment</i>	67
6.7.4	<i>pCR assessment</i>	67
6.7.5	<i>Follow-up and confirmation of disease recurrence</i>	68
6.7.6	<i>RFI, RFS, EFS, iDFS, DRFS, DFS, BCSS, and OS definitions</i>	70
6.8	PATIENT DISCONTINUATION	73
6.9	STUDY AND SITE DISCONTINUATION	73
7	SAFETY DEFINITIONS AND REPORTING REQUIREMENTS	74
7.1	AES DEFINITION	74
7.1.1	<i>SAEs definitions</i>	75
7.1.1.1	Definition of life threatening	76
7.1.1.2	Definition of hospitalization	76
7.1.1.3	Definition of clinically/medically significant event	76
7.1.2	<i>AESIs</i>	77
7.2	ADVERSE EVENT REPORTING AND OTHER SAFETY RELATED ISSUES REPORTING	78
7.2.1	<i>SAE reporting and timeframe</i>	78
7.2.2	<i>Expedited reporting to Health Authorities, Investigators, IRBs, and IECs</i>	79
7.2.3	<i>Other safety-related reports</i>	79
7.2.4	<i>Pregnancy reporting</i>	80
8	STATISTICAL CONSIDERATIONS	80
8.1	STUDY DESIGN AND SAMPLE SIZE	80
8.2	ANALYSIS SETS	82
8.3	PRIMARY ENDPOINT OF EFFICACY	83
8.4	PRIMARY ENDPOINT OF SAFETY	83
8.5	JUSTIFICATION OF NULL AND ALTERNATIVE HYPOTHESES	84
8.6	JUSTIFICATION OF DROP-OUT RATE ASSUMPTION.....	84
8.7	SAMPLE SIZE CALCULATION	84
8.8	SECONDARY EFFICACY ENDPOINTS	85
8.9	ANALYSIS OF BASELINE AND DEMOGRAPHIC VARIABLES	86

8.10	ANALYSIS OF SECONDARY ENDPOINTS.....	86
8.11	SUBGROUP ANALYSIS	86
8.12	SECONDARY SAFETY RESULTS	87
8.13	SCHEDULE FOR PRIMARY AND SECONDARY ANALYSES	89
8.14	MISSING DATA MANAGEMENT	89
8.15	SCIENTIFIC COMMITTEE REVIEW	90
9	ETHICAL CONSIDERATIONS.....	90
9.1	REGULATORY AND ETHICS COMPLIANCE.....	90
9.2	IRBs/IECs.....	90
9.3	INFORMED CONSENT.....	91
9.4	DATA PROTECTION	91
10	SOURCE DOCUMENTATION, STUDY MONITORING AND QUALITY ASSURANCE.....	92
10.1	SOURCE DATA DOCUMENTATION.....	92
10.2	STUDY MONITORING AND SOURCE DATA VERIFICATION	93
10.3	RETENTION OF RECORDS.....	93
10.4	DATA QUALITY ASSURANCE	94
11	DATA MANAGEMENT.....	94
11.1	DATA ENTRY AND MANAGEMENT	94
11.2	DATA CLARIFICATION	95
11.3	DATA CODING PROCEDURES	95
12	STUDY MANAGEMENT	95
12.1	DISCONTINUATION OF THE STUDY.....	95
12.2	CHANGES TO THE PROTOCOL	95
12.3	PUBLICATION POLICY PROTECTION OF TRADE SECRETS	95
12.4	DISSEMINATION OF CLINICAL STUDY DATA.....	96
13	REFERENCES	97
14	APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS AND PROCEDURES	101

1 STUDY BACKGROUND AND RATIONALE

1.1 Introduction

Breast cancer is the most diagnosed cancer and the second leading cause of cancer-related death in women (Azamjah et al., 2019).

Breast cancer is a very heterogeneous disease with multiple clinical presentations and tumor characteristics. The progress in gene expression profiling studies has enabled breast cancer specialists to classify breast tumors into several distinct biological and intrinsic subtypes with prognostic and therapeutic implications. In 2000, Perou et al., provided a new molecular classification of breast cancer that is still widely accepted, which considers the expression of hormonal receptors (HR) - estrogen receptors (ERs), and progesterone receptors (PgRs) - and human epidermal growth factor receptor 2 (HER2) expression (Perou et al., 2000).

Proteins from the HER family play an important role in cancer proliferation and progression. The HER family includes four structurally related transmembrane receptors: HER1 (also known as epidermal growth factor receptor [EGFR]), HER2 (also called ERBB2), HER3, and HER4. The HER2 gene, in particular, is amplified in approximately 15-20% of all cases of breast cancer and codifies for a transmembrane protein with tyrosine kinase activity (Baselga and Albanell, 2001). Whilst there are no known ligands that bind to HER2, its extracellular domain interacts with other HER family members, resulting in the formation of receptor homodimers or heterodimers that stimulate signal transduction. In additions, it has been shown that, upon HER2 inhibition, levels of other members of the HER family increase to compensate, generating resistance to some anti-HER2 therapies.

As compared with HER2-negative (HER2[-]) tumors, HER2[+] breast cancers are more aggressive and demonstrate a unique epidemiological, clinical, and prognostic differences with poor response to standard chemotherapy regimens (Li et al., 2017). The HER2 gene amplification in the breast cancer is closely related to tumor-cell multiplication and invasion, resulting in focal progression and distant metastases (Yarden, 2001).

Therefore, given its prevalence and worse prognosis factor, the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines recommend that HER2 status must be determined in all patients with invasive breast cancer (Wolff et al., 2018). Testing criteria define HER2-positive (HER2[+]) status when there is evidence of protein overexpression by IHC or gene amplification by *in situ* hybridization (ISH).

Although HER2-positivity is still considered a negative prognostic and predictive risk factor for survival, the appearance of trastuzumab is improving patients' survival. However, much controversy exists in the use of trastuzumab, including treatment duration and sequence of adjuvant treatment, and current clinical trials are trying to find the best way to use it to improve the current treatments (Engel and Kaklamani, 2007). Trastuzumab is a humanized anti-HER2

monoclonal antibody that was originally approved in combination with taxanes for the first-line treatment of patients with HER2[+] MBC (Slamon et al., 2001). Soon afterwards, the approval of trastuzumab was expanded to the neoadjuvant setting in combination with chemotherapy (Wang and Xu, 2019).

1.2 Advances in treatment of breast cancer

Thanks to mammograms that allow an early detection, the majority of breast cancers in the more developed parts of world are diagnosed in an early stage of the disease. Early stage breast cancers can be completely resected by surgery. Still, the disease may come back even after complete resection, which has prompted the development of adjuvant therapies. Surgery followed by adjuvant treatment has been the gold standard for breast cancer treatment for a long time. More recently, neoadjuvant treatment (treatment prior to surgery) has also been recognized as an important strategy in biomarker and target evaluation. It is clinically indicated for patients with large tumor size, high nodal involvement, an inflammatory component, or for those wish to preserve remnant breast tissue (Miller et al., 2014).

The growing understanding of early breast cancer as a systemic disease has firmly established the role of chemotherapy, which has progressed and changed in the past years substantially improving outcomes for the early breast cancer patients (Gupta and Joshi, 2019). However, despite ongoing research looking into newer and improved chemotherapeutic agents and their combinations, current standard combination of anthracyclines and taxanes still provide the best outcome to date (Henderson et al., 2003).

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was established in 1985 to coordinate individual-patient-level meta-analysis of all randomized trials of adjuvant treatments (Gray et al., 2019). Results from a meta-analysis they ran showed reduction in contra-lateral new primary breast cancer risk in 0–4 years following dose intense chemotherapy, with no specific patient or tumor characteristics that could predict higher or lesser benefit from dose intense chemotherapy. Proportional benefit is noted to be independent of hormone receptor (HR), nodal status or other tumor characteristics, therefore dose intense chemotherapy is beneficial to most women with early breast cancer who are offered chemotherapy (Gupta and Joshi, 2019).

In an analysis conducted by the EBCTCG which compared an anthracycline-based regimen with a CMF (cyclophosphamide, methotrexate, and fluorouracil) regimen – that was used more commonly in breast cancer starting from 1970 – demonstrated an increased efficacy of anthracycline as adjuvant chemotherapy and a greater degree of risk reduction in overall breast cancer related morbidity and mortality of anthracycline based regimen (Miller et al., 2014).

A second development which supposed another big game changer in breast cancer adjuvant chemotherapy was the introduction of taxane. After the efficacy of taxane was shown in advanced

breast cancer, several trials have incorporated docetaxel into the adjuvant setting. It is important to highlight that not only the selection of chemotherapy agents but also the method of delivery is critical in the development of chemotherapy, as shown in the CALGB 9741 study.

As for adjuvant endocrine treatment (ET), there are two main categories of hormone therapy agents:

- i) Selective estrogen receptor modulators (SERMs), which include tamoxifen, raloxifene and toremifene. SERMs competitively bind to estrogen receptors to interfere with DNA synthesis by recruiting co-repressors, and inhibit cell cycle progression.
- ii) Aromatase inhibitors (AIs), which work by inhibiting an enzyme called 'aromatase' that converts circulating testosterone to estradiol (E2), and androstenedione to estrone, by aromatization. Exemestane, anastrozole and letrozole are three main drugs of this category.

AIs only work when the primary source of estrogen is terminated – either by the menopausal state, oophorectomy, or estrogen deprivation therapy using luteinizing-hormone-releasing hormone (LHRH) agonists.

1.2.1 Importance of assays and protocols to guide therapy

Despite the advances in treatments in early stage breast cancer which are seeing very high rates of disease survival, it is also clear that the absolute benefits of chemotherapy (and other types of treatment) are not the same across all patients. Many factors need to be taken into account when deciding on the type of adjuvant therapy in individual patients (Chao et al., 2003).

Biologic characteristics of tumors can be critical in adjuvant treatment decision making. Several comprehensive genomic profiling tools to characterize and predict the prognosis of individual patients have been developed. Such genomic profiling tools not only provide sub-typing of breast cancers, but also can predict their response to adjuvant therapy.

In the rising of treatment options, it is important to find better (easy, inexpensive and non-invasive) mechanisms to identify patients that will benefit from a specific treatment, such as imaging techniques.

1.3 Definition and prognostic impact of pathological complete response

Pathological complete response (pCR) in breast cancer commonly refers to the absence of invasive/in situ cancer in the breast and axillary lymph nodes (von Minckwitz et al., 2012; Pennisi et al., 2016). Achieving pCR following neoadjuvant chemotherapy is a desirable outcome, as it frequently leads to improved survival. This is especially relevant now with the introduction of targeted therapies for HER2[+] breast cancer tumors, and the more frequent use of anthracycline

and taxanes versus CMF (Biswas et al., 2019). And, because of that, many efforts have been made in an attempt to find predictors of pCR to preoperative chemotherapy.

1.4 Rationale for chemotherapy-free treatment strategy for HER2[+] breast cancer

The positive effects of HER2 blockade, without chemotherapy, as neoadjuvant strategy for early stage HER2[+] breast cancer has been seen in several clinical trials. The NeoSphere trial that evaluated the combination of trastuzumab and pertuzumab, showed a pCR rate of 17% in the breast; and pCR was higher in patients with HR[-] tumors (29.1% vs. 5.9%), a result in line with several previous studies with anti-HER2 therapy in this setting (Gianni et al., 2012).

Likewise, the Translational Breast Cancer Research Consortium (TBCRC) 006 trial evaluated the efficacy of neoadjuvant trastuzumab and lapatinib (with or without hormonal therapy according to HR status) for 12 weeks in 66 patients with HER2[+] breast cancer (Rimawi et al. 2013). Overall, the rate of pCR in the breast of this nonchemotherapy-containing regimen was 27% (22% in the breast and axilla). In the ER[+] group, the pCR rate in the breast was 21% (18% in the breast and axilla), whereas in the ER[-] group, it was 36% (28% in the breast and axilla).

In the PerELISA neoadjuvant study, a meaningful pCR rate of 20% was achieved with the combination of letrozole, pertuzumab and trastuzumab in a sub-group of patients defined as molecular responders (Ki67 drop off >20% from baseline after 2 weeks of letrozole monotherapy) (Guarneri et al., 2019).

In the PAMELA study, 151 stage I-III HER2[+] breast cancer patients were treated with lapatinib plus trastuzumab (in addition to letrozole if HR[+]) for 18 weeks. At the time of surgery, 46 patients (30%) had pCR in the breast (Llombart-Cussac et al., 2017).

In the ADAPT study, early stage HER2[+]/HR[+] breast cancer patients were randomly assigned to 12 weeks of T-DM1 with or without ET or to trastuzumab with ET. pCR was observed in 41.0% of patients treated with T-DM1, 41.5% of patients treated with T-DM1 and ET, and 15.1% with trastuzumab and ET (Harbeck et al., 2017).

All these data seem to point at the possibility of using dual HER2 blockade to eliminate the need for chemotherapy in a subset of HER2[+] patients.

1.5 Study rationale

1.5.1 Clinical data

Analysis of the NeoSphere clinical trial, a phase II trial where patients were given neoadjuvant pertuzumab, trastuzumab and docetaxel, showed a significantly improved pCR compared with those given only trastuzumab and docetaxel after surgery. These results, together with results

from the TRYPHAENA study, made possible the rapid approval of pertuzumab in the neoadjuvant setting in 2013 (Gianni et al., 2016).

Another clinical trial, the phase III study KRISTINE, evaluated the efficacy and safety of T-DM1 (trastuzumab emtansine) with pertuzumab versus chemotherapy, trastuzumab and pertuzumab. The study, which comprised a neoadjuvant treatment period followed by surgery and an adjuvant treatment period, showed that significantly more patients receiving neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab achieved a pathological complete response than those receiving trastuzumab emtansine plus pertuzumab. However, neoadjuvant trastuzumab emtansine plus pertuzumab was associated with fewer grade 3–4 adverse events than systemic chemotherapy-based treatment (Hurvitz et al., 2018).

Initial results from ongoing clinical trials such as the phase III APHINITY trial have also showed pertuzumab significantly improves the rates of invasive disease-free survival (iDFS) among patients with HER2[+], operable breast cancer when added to trastuzumab and chemotherapy (von Minckwitz et al., 2017).

1.5.2 Rationale

A number of clinical trials (including NeoSphere and KRISTINE) have shown the promising effects and the significant antitumor activity of the dual HER2 blockade with trastuzumab and pertuzumab (Gianni et al., 2016; Hurvitz et al., 2018). However, the side-effects of the current treatments compromise patients' quality of life (QoL).

Non-invasive imaging tools could guide the response to therapy. MRI might help to recognize patients with an increased probability of pCR and better outcome with a chemotherapy-free treatment strategy based on the dual HER2 blockade with trastuzumab and pertuzumab. Given the side-effects and the impact of chemotherapy in QoL, it is important to replace traditional systemic chemotherapy with targeted treatments.

This open-label single-arm phase II study will assess a chemotherapy-free alternative for HER2[+] EBC patients guided by MRI. Treatment will consist in the combination of trastuzumab and pertuzumab (PH FDC SC) ± ET according to HR status, as exclusive neoadjuvant treatment, and either PH FDC SC (± ET) or T-DM1 (± ET) as adjuvant treatment after surgery, depending on pCR. Trastuzumab and pertuzumab will be administered as a subcutaneous fixed-dose combination PH FDC SC, since results from the phase III FeDeriCa study (NCT03493854) demonstrated non-inferior levels of drugs in the blood and comparable efficacy and safety compared to standard intravenous infusions. This offers a benefit in patients' quality of life, as this fixed-dose subcutaneous combination has the potential to provide a quicker and less invasive method of administration (Tan et al., 2020).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary efficacy objective	2.1.1 Primary efficacy endpoint
To assess 3-year recurrence-free interval (3y-RFI) in all patients with previously untreated HER2[+] (IHC score 3+) node-negative early-stage breast cancer.	3y-RFI defined as time from start of treatment in adjuvant setting until recurrence, new invasive disease, or death from breast cancer in the overall population. Recurrence will be defined in accordance with the standardized efficacy endpoints (STEEP) criteria.
2.2 Primary safety objective	2.2.1 Primary safety endpoint
To assess global health status decline rate at 1 year from start of neoadjuvant treatment.	Global health status decline rate at 1 year from start of neoadjuvant treatment, defined as the rate of patients with a $\geq 10\%$ global health status decline at 1 year from start of neoadjuvant treatment as assessed by the Global Health Status/QoL EORTC-QLC-C30 scale and its breast cancer module QLQ-BR23.
2.3 Secondary objectives	2.3.1 Secondary endpoint
To assess pathological complete response (pCR).	pCR rates concerning breast and lymph nodes (<u>pCR_{BREAST+LYMPH_NODE}</u>) and pCR concerning breast only (<u>pCR_{BREAST}</u>) in the overall population.
To compare the rate of pCR by hormone receptor (HR) status and tumor stage.	pCR rates concerning breast and lymph nodes (<u>pCR_{BREAST+LYMPH_NODE}</u>) and pCR concerning breast only (<u>pCR_{BREAST}</u>) according to HR status (positive, negative) and tumor stage (T1, T2).
To evaluate residual cancer burden (RCB).	RCB score in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
To evaluate rate of breast-conserving surgery (BCS).	Rate of BCS in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
To evaluate objective response rate.	MRI-guided objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) version (v.)1.1 in the overall study

	population and according to HR status (positive, negative), and tumor stage (T1, T2).
To evaluate the correlation between final MRI results and breast conserving surgery (BCS), pCR, and RCB at surgery.	Correlation of MRI-guided objective response rate by RECIST v.1.1 with BCS, pCR, and RCB in the overall study population and according to HR status (positive, negative), and tumor stage (T1, T2).
To analyze the rate of RFI at 5 years.	5-year RFI in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To analyze the rate of event-free survival (EFS) at 3 years and 5 years.	3-year and 5-year EFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To analyze the rate of relapse-free survival (RFS) at 3 years and 5 years.	3-year and 5-year RFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To analyze the rate of distant relapse-free survival (DRFS) at 3 years and 5 years	3-year and 5-year DRFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To analyze the rate of disease-free survival (DFS) at 3 years and 5 years.	3-year and 5-year DFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To analyze the rate of invasive disease-free survival (iDFS) at 3 years and 5 years	3-year and 5-year iDFS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To analyze overall survival (OS) at 3 years and 5 years.	3-year and 5-year OS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).

To analyze the rate of breast cancer-specific survival (BCSS) at 3 years and 5 years.	3-year and 5-year BCSS in the overall study population and according to study arm (A, B, C), HR status (positive, negative), and tumor stage (T1, T2).
To assess the cardiac toxicity profile after 1 year of adjuvant treatment according to the NCI-CTCAE v.5.0.	Adverse events of cardiotoxicity after 1 year of adjuvant treatment according to the NCI-CTCAE v.5.0.
To assess the general toxicity profile according to CTCAE v.5.0.	Toxicity and safety profile at 3 and 5 years as per NCI-CTCAE v.5.0.
To evaluate health-related quality of life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC)-QLC-C30 and QLQ-BR23 questionnaires.	Patient Reported Outcomes (PROs) HRQoL assessment as per EORTC-QLC-C30 and QLQ-BR23 questionnaires.
To evaluate the ratio of patients who have needed chemotherapy.	Ratio of patients of cohort C who will receive adjuvant chemotherapy before T-DM1.
2.4 Exploratory objectives	2.4.1 Exploratory endpoint
To evaluate predictive and/or prognostic and/or pharmacodynamic biomarkers associated with disease activity status, patient outcome or response to study treatments on archival and/or liquid biopsy samples.	Association of clinical outcomes, safety and/or tolerability profile with mutation profiling, copy number variability, gene expression, multiplex assays, proteomic analyses, digital pathology, immunohistochemistry, taxonomic or functional analyses performed on tissue and/or liquid biopsy samples.
To determine the association of treatment efficacy and/or safety outcomes with radiological imaging biomarkers.	Association of treatment efficacy and/or safety outcomes in all patients with radiological imaging biomarkers.

3 STUDY OVERVIEW

3.1 Description of the study

This is a multicenter, open-label, phase II clinical trial to evaluate the efficacy of PH FDC SC followed by either continuation with PH FDC SC or T-DM1 based on individual pCR after pre-operative treatment, as adjuvant treatment in node-negative HER2[+] (IHC score 3+) early breast cancer patients. ET will be administered based on HR status as per local practices.

Patients aged ≥ 18 years with previously untreated HER2[+] invasive early breast cancer and tumor size between ≥ 5 mm and ≤ 25 mm using ultrasound and mammography, up to ≤ 30 mm by breast magnetic resonance imaging (MRI), and node-negative status are eligible to participate in the study. Patients with metastatic disease are not eligible. In patients with suspected axillary node involvement, a negative fine needle aspiration biopsy (FNAB) will be mandatory. Evidence of histologically confirmed invasive carcinoma of the breast with HER2[+] is mandatory (IHC score 3+), as well as MRI imaging to confirm size of the tumor.

Breast staging at baseline will be performed with mammography, breast ultrasound, and breast MRI. Nodal staging at screening will be performed with MRI and axillary ultrasound \pm FNAB if suspected lymph node involvement. The tumor site must be marked with a radiopaque marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

After signing informed consent form (ICF) and confirmed eligibility, patients will receive PH FDC SC (\pm ET as per local practices depending on HR status) on day 1 of each 21-day cycle for 8 cycles.

After completing neoadjuvant therapy, a final breast MRI will be performed within 2 weeks prior to surgery. All local MRI will be centrally reviewed, and results will be considered prior to surgery.

Surgery will be performed not sooner than 2 weeks but no more than 4 weeks after completion of the last cycle of PH FDC SC. Surgery will require free margins for any infiltrating or ductal carcinoma in situ (DCIS) lesion. Radiotherapy will be mandatory for patients with breast preservation and will be administered concomitantly with PH FDC SC (if patient achieves a pCR) or T-DM1 (if patient has a residual disease [RD]).

Adjuvant systemic therapy will be started within 4 weeks from surgery and will depend on pathological report. During adjuvant treatment patients will receive study treatment for a maximum of 10 cycles; treatment will be discontinued prior to 10 cycles in the event of disease recurrence, unacceptable toxicity, or study termination by the Sponsor. Following discontinuation or completion of study treatment, patients will continue to be followed for efficacy and safety objectives until the end of the study.

Patients will be assigned to one of the three following cohorts depending on pathological report:

- **Cohort A** (pCR in breast and axilla [yp.T0/is, ypN0]): patients will receive PH FDC SC (\pm ET as per HR status) on day 1 of each 21-day cycle for 10 additional cycles.
- **Cohort B** (residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi): patients will receive T-DM1 (\pm ET as per HR status) for 10 cycles.
- **Cohort C** (pathological progression to nodes [ypN1-N3]): patients will receive T-DM1 (\pm ET as per HR status) for 10 cycles. As per physician's choice and according to ESMO or NCCN 2021 guidelines, patients may receive chemotherapy before adjuvant T-DM1.

In HR-positive patients will receive ET continuously up to at least 5 years in combination with adjuvant PH FDC SC or T-DM1, apart from the cycles involving the use of chemotherapy in cohort C. The extension of ET after completing the first five years will be based on local practices.

Patients with MRI-confirmed progression to PH FDC SC during the neoadjuvant treatment will continue in the study. Progression will be determined by MRI after physician's suspicion of lack of response or tumor growth in routine assessments. Alternative neoadjuvant treatment will be administered in these patients as per investigator's choice without an increase in the total amount of PH FDC SC cycles, and assignment of adjuvant treatment will be based on the above-mentioned criteria. Patients without confirmed progression who by physician's choice are switched to chemotherapy during neoadjuvant treatment, will discontinue the study and not be included in the final analysis.

Patients will be followed up after surgery (including during and after adjuvant treatment).

Patients completing the study treatment period/discontinuing treatment will enter a post-treatment follow-up period during which survival and new anti-cancer therapy information will be collected, until end of study (EoS) or study termination, whichever occurs first.

To enable long-term follow-up for survival and safety information, the last follow-up assessment is scheduled to occur 5 years after the first patient has completed surgery.

3.1.1 Central pathology review for HER2 status

All patients will undergo baseline tumor tissue acquisition prior to enrollment. Assessment of ER and PgR status will be performed at local pathology laboratory. A central confirmation of HER2-positivity will be mandatory. Eligible patients will have HER2 status centrally evaluated approximately within 7-10 working days before patients are eligible to enter the study.

Only patients who are HER2[+] by IHC score 3+ will be eligible, as defined in **Section 6.3.3** of this protocol.

3.2 Study design

Figure 1 summarizes the study design for the PHERGain-2 trial.

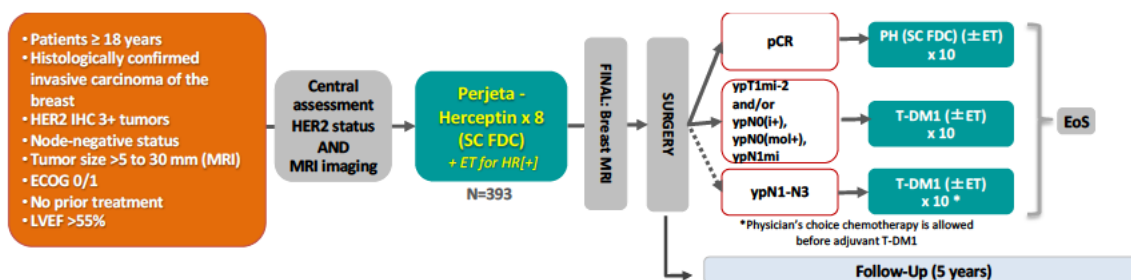


Figure 1. PHERGain-2 study design.

3.3 Screening phase

During this phase, subject eligibility is determined, including the documentation of baseline characteristics. Only patients with previously untreated HER2[+] (IHC score 3+) invasive EBC and tumor size between ≥ 5 mm and ≤ 25 mm using ultrasound and mammography, up to ≤ 30 mm by breast magnetic resonance imaging (MRI), and node-negative status are eligible to participate in the study.

This phase of the study will begin once the ICF is signed by the patient.

3.4 Treatment phase

When a patient is identified and all the study screening criteria have been met, a breast MRI will be performed up to a maximum of 28 days +/- 7 days before starting the study treatment.

Patients will receive PH FDC SC (\pm ET depending on HR status) for 8 cycles of 21 days each. There will be an initial loading dose of 1,200mg pertuzumab, 600mg trastuzumab, and 30,000 units hyaluronidase in the first cycle, followed by a dose of 600mg pertuzumab, 600mg trastuzumab and 20,000 units hyaluronidase as maintenance dose for the remaining cycles. More details on administration doses can be found in **Sections 5.1.1 and 5.5**. ET for patients with HR-positive status will be administered according to local practices. For post-menopausal women is highly recommended letrozole (2.5 mg/day orally), whereas for pre-/peri-menopausal women is highly recommended ovarian function suppression combined with either tamoxifen (20 mg/day orally) or letrozole (2.5 mg/day orally). For men tamoxifen is highly recommended.

After completing neoadjuvant therapy, a final breast MRI will be performed within 2 weeks before surgery. All local MRI will be centrally reviewed, and results will be considered prior to surgery. Surgery will be performed not sooner than 2 weeks but no more than 4 weeks after completion of the last cycle of PH FDC SC. Sentinel node biopsy will be mandatory; and subsequent axillary dissection will be performed according to local guidelines. Surgery will require free margins for

any infiltrating or ductal carcinoma in situ (DCIS) lesion. Radiotherapy will be mandatory for patients with breast preservation and will be administered with adjuvant treatment.

Adjuvant systemic therapy will be started within 4 weeks from surgery depending on pathological report:

- **Cohort A** (pCR in breast and axilla [yp.T0/is, ypN0]): patients will receive PH FDC SC (\pm ET as per HR status) on day 1 of each 21-day cycle for 10 additional cycles.
- **Cohort B** (residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi): patients will receive T-DM1 (\pm ET as per HR status) for 10 cycles.
- **Cohort C** (pathological progression to nodes [ypN1-N3]): patients will receive T-DM1 (\pm ET as per HR status) for 10 cycles. As per physician's choice and according to ESMO or NCCN 2021 guidelines, patients may receive chemotherapy before adjuvant T-DM1.

Patients with confirmed MRI-progression during PH FDC SC neoadjuvant treatment will continue in the study. Alternative neoadjuvant treatment will be administered in these patients as per investigator's choice, without an increase in the total number of PH FDC SC cycles, and assignment of adjuvant treatment will be based on the above-mentioned criteria. Patients without confirmed progression who by physician's choice are switched to chemotherapy during neoadjuvant treatment, will discontinue the study and not be included in the final analysis.

HR-positive patients will receive ET continuously up to at least 5 years in combination with adjuvant PH FDC SC or T-DM1, apart from the cycles involving the use of chemotherapy in cohort C. The extension of ET after completing the first five years will be based on local practice.

Patients will be followed up after surgery (including during and after adjuvant treatment).

3.5 Treatment follow-up

Patients will be followed up after surgery (including during and after adjuvant treatment).

The follow-up will consist on:

- Imaging follow-up according to standard clinical practice.
- Clinical exam (including quality of life [QoL] assessment) every 3 months after surgery for the first two years, every 6 months for the 3 next years, and yearly thereafter. When only QoL assessment is required, telephone contact is also acceptable.
- Blood test including liver, renal, and bone marrow functions every 6 months for the first 5 years.
- Safety assessments that will consist of monitoring and recording protocol-defined AEs, SAEs and non-serious adverse events of special interest (AESIs); measurement of

protocol-specified hematology, clinical chemistry, measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The schedule of follow-up visits and tests for this study is the minimum required; investigators may see their patients more frequently according to their routine practice.

The end of treatment [EoT] visit will be scheduled for all patients at 28 days (\pm 7 days) after the last dose of study treatment.

All patients must be followed up for 5 years from when the last patient has completed surgery, even if the assigned treatment is discontinued permanently. After surgery, the follow-up period of 60 months will include visits every 3 months for the first 2 years, every 6 months for the 3 next years, and every year after the 5th year. The visits must be performed at the completion of the corresponding period (e.g. after completion of 3 months, 6 months, etc.) from surgery. Patients who discontinue treatment without surgery will require follow-up visits every 6 months (+ 14 days) from the last dose of investigational drug.

In cases of disease recurrence, diagnosed at any time during the study, patients will be out of the study schedule and will be followed up once a year (starting 1 year after first relapse) until the end of the study.

After the study treatment completion/early termination visit, AEs should be followed as outlined in **Section 7.2**.

Safety assessments will include the incidence, nature, and severity of AEs and laboratory abnormalities graded per the NCI-CTCAE v.5.0. Laboratory safety assessments will include the regular monitoring of hematology, blood chemistry, coagulation, and pregnancy test. Cardiac monitoring is also required for patients taking PH FDC SC, therefore LVEF will be assessed prior to treatment initiation and at regular intervals during treatment to ensure that LVEF is within normal limits. A schedule of assessments is provided in **Appendix 1**. All grade \geq 3 AEs related to IMP will be followed up by the investigator until the event or its sequelae resolve or stabilize at the level acceptable to the investigator, and the Sponsor concurs with that assessment.

Patients completing the study treatment period/discontinuing treatment will enter a post-treatment follow-up period during which survival and new anti-cancer therapy information will be collected, until EoS or study termination, whichever occurs first.

3.6 End of Treatment visits and End of Study

EoT visit will be 28 days (\pm 7days) after the last dose of study treatment or withdrawal from study treatment.

Afterwards, follow-up contacts will continue up to the end of the study (EoS). The EoS is defined as the last patient last visit (LPLV) at the end of the follow-up period. This will occur at 5 years after the last patient surgery unless premature termination of the study. This will be the last data collection point, which can be a clinic visit or a telephone call.

After surgery, the follow-up period of 60 months will include visits every 3 months for the first 2 years, every 6 months for the 3 next years, and every year after the 5th year. The visits must be performed at the completion of the corresponding period (e.g. after completion of 3 months, 6 months, etc.) from surgery.

At EoS, survival status and new anticancer therapy information will be collected.

4 PATIENT SELECTION

The following eligibility criteria can be used in the screening of patients for whom the protocol treatment is deemed suitable. In order to determine whether this protocol is suitable for a given patient, all medical and non-medical criteria should be taken into consideration.

4.1 Study target population

Patients ≥ 18 years of age with previously untreated HER2[+] (IHC score 3+) invasive carcinoma according to the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) criteria.

Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Tumor size between ≥ 5 mm and ≤ 25 mm using ultrasound and mammography, up to ≤ 30 mm by breast magnetic resonance imaging (MRI), and node-negative status by clinical exam, MRI and ultrasound.

In patients with suspected axillary node involvement, a negative fine needle aspiration biopsy (FNAB) will be mandatory.

4.2 Inclusion criteria

Patient eligibility will be reviewed and documented by a suitable member of the investigator's study team before the patients are enrolled in the study. Patients must meet ALL the following inclusion criteria to be enrolled in the study:

1. Written informed consent prior to beginning specific protocol procedures.
2. Female or male patients ≥ 18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

4. Histologically proven invasive carcinoma of the breast.
5. Tumor size must be between $\geq 5\text{mm}$ and $\leq 25\text{mm}$ using ultrasound and mammography (tumor size between $\geq 5\text{mm}$ and $\leq 30\text{mm}$ by MRI is also accepted given the precision of the technique). *Note: Although tumors between $\geq 5\text{mm}$ and $\leq 10\text{mm}$ are not considered target lesions by RECIST v1.1, we will consider these lesions as targets to follow up.*
6. Patients must have node-negative breast cancer by clinical exam, MRI and ultrasound according to the American Joint Committee on Cancer (AJCC) 8th edition.
7. Centrally confirmed HER2[+] status with IHC score 3+.
8. Known estrogen receptor (ER) and progesterone receptor (PgR) status prior to study entry that should be performed by immunohistochemical methods according to the local institution standard protocol.
9. Patients with multifocal or multicentric breast cancer are eligible; only patients with a total number of lesions ≤ 2 are eligible and if all lesions sampled meet the inclusion criteria #5, #6, and #7. *Note: If two lesions are in such proximity that it is suspected to be the same lesion, it would not be necessary to biopsy both.*
10. Normal left ventricular function and diastolic function (left ventricular ejection fraction [LVEF] $\geq 55\%$) as assessed by echocardiogram or multiple-gated acquisition scan (MUGA) documented within ≤ 28 days prior to first dose of study treatment.
11. Adequate bone marrow, liver, and renal function:
 - a. Hematological: White blood cell (WBC) count $> 3.0 \times 10^9/\text{L}$, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$, platelet count $\geq 100.0 \times 10^9/\text{L}$, and hemoglobin $\geq 10.0 \text{ g/dL}$ ($\geq 6.2 \text{ mmol/L}$).
 - b. Hepatic: total bilirubin \leq institutional upper limit of normal (ULN) (except for Gilbert's syndrome); alkaline phosphatase (ALP) ≤ 2.5 times ULN; aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.5 times ULN.
 - c. Renal: serum creatinine $\leq 1.5 \times \text{ULN}$ or creatinine clearance $\geq 50 \text{ mL/min/1.73 m}^2$ for patients with creatinine levels above institutional normal.
 - d. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times \text{ULN}$.
12. Patient must be accessible for treatment and follow-up.

13. Willingness and ability to provide blood samples at baseline, C3D1 before treatment infusion, pre-surgery, and then after surgery: every 6 months for the first 5 years, and every year thereafter until the EoS.
14. Willingness and ability to provide tumor tissue samples at baseline and at surgery.
15. Women of childbearing potential and men with partners of childbearing potential must be willing to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception by the patient and/or partner and to continue its use for the duration of study treatment and for seven months after the last dose of study treatment.

Note: Acceptable forms of effective contraception should include two of the following:

- iv. Placement of non-hormonal intrauterine device (IUD)
- v. Condom with spermicidal foam/gel/film/cream/suppository
- vi. Diaphragm or cervical/vault caps with spermicidal foam/film/cream/suppository

The above contraception is not a requirement in the case the male patient, or male partner of a female patient, is surgically sterilized, the female patient is post-menopausal or the patient remains abstinent and truly abstains from sexual activity (refrains from heterosexual intercourse).

16. Negative serum pregnancy test for premenopausal women including women who have had a tubal ligation and for women less than 12 months after the onset of menopause.

4.3 Exclusion criteria

Any patient meeting ANY of the following criteria will be excluded from the study:

1. Any previous treatment, including chemotherapy, anti-HER2 therapy, radiation therapy, or ET for invasive breast cancer (except for breast carcinoma in situ of the contralateral breast cancer, in the last five years before treatment initiation in this study).
2. HER2 disease with IHC score 0, 1+ or 2+ and *in situ* hybridization (ISH) positive result.
3. Evidence of metastatic disease.

Note: All patients must be willing to undergo chest and pelvis computed tomography (CT) or MRI before enrolment to prove no evidence of metastatic disease. Bone scan will be performed at screening only if there is suspicion of bone metastases. If a bone scan cannot be performed at screening, an alternative is PET/CT using ¹⁸F-labeled sodium fluoride (¹⁸F-fluoride PET/CT).

4. Patients with bilateral breast cancer.
5. Known hypersensitivity reaction to any investigational or therapeutic compound or their incorporated substances.

6. History of other malignancy within the last five years prior to first dose of study drug administration, except for curatively treated basal and squamous cell carcinoma of the skin and/or in situ cervical carcinoma.
7. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) despite adequate antihypertensive treatment.
8. Serious cardiac illness or medical conditions including, but not confined to, the following:
 - History of NCI CTCAE v.5.0 Grade \geq 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) Class \geq II.
 - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate \geq 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second-degree AV-block Type 2 [Mobitz II] or third-degree AV-block).
 - Serious cardiac arrhythmia or severe conduction abnormality not controlled by adequate medication.
 - Angina pectoris requiring anti-angina medication.
 - Clinically significant valvular heart disease.
 - Evidence of transmural infarction on electrocardiogram (ECG).
 - Evidence of myocardial infarction within the last 12 months prior to study entry.
9. History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction [LVSD], left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome.
10. Active uncontrolled infection at the time of enrollment.
11. Current known infection with human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.
12. Patients with pulmonary disease requiring continuous oxygen therapy.
13. Grade \geq 2 neuropathy as per National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI–CTCAE) version (v)5.0.
14. Previous history of bleeding diathesis.

15. Patient is currently receiving chronic treatment with corticosteroids, or another immunosuppressive agent (standard premedication for chemotherapy and local applications are allowed).
16. Major surgical procedure or significant traumatic injury within 14 days prior to study entry or anticipation of need for major surgery within the course of the study treatment.
17. Any other concurrent severe and/or uncontrolled medical condition that would contraindicate patient participation in the clinical study.
18. History of having received any investigational treatment within 28 days prior to study entry.
19. Pregnant or breast-feeding women or patients not willing to apply highly effective contraception as defined in the protocol.

5 STUDY DRUG INFORMATION

PH FDC SC (Pertuzumab and trastuzumab for subcutaneous administration), and T-DM1 IV (Kadcyla® / ado-trastuzumab emtansine) will be the IMPs, and will be provided by Roche.

Complete description of the IMPs will be documented in the Summary of Product Characteristics (SmPCs) for T-DM1 and in the Investigator's Brochure (IB) for PH FDC SC, located in the Site/Investigator's file. Summarized information is reported in this section, but the SmPC and IB are the source documents for the study drugs.

5.1 Formulation, packaging, and handling

Study drug packaging will bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labeling of the study drug will be in accordance with Sponsor standards and local regulations.

The study drug must be stored according to the details on the Product Information. The drug label indicates the storage temperature. Upon arrival of investigational products at the site, site personnel should check them for damage, verify proper identity, quantity, integrity of seals, and temperature conditions and report any deviations or product complaints upon discovery.

5.1.1 PH FDC SC

PH FDC SC will be administered subcutaneously injected in the thigh only, and as a fixed non-weight-based dose combination on the day 1 of each cycle. The initial dose (loading dose) of PH FDC SC (pertuzumab, trastuzumab, and hyaluronidase-zzxf,) will be 1,200mg pertuzumab, 600mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously over

approximately 8 minutes. The initial dose will be followed next cycles by a dose (maintenance dose) of 600mg pertuzumab, 600mg trastuzumab and 20,000 units hyaluronidase administered subcutaneously every 3 weeks (on the day 1 of each cycle) for over approximately 5 minutes. No dose adjustments for PH FDC SC are required for patient body weight.

The combination will be in the form of a solution in a single-dose vial with

- 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase/15mL (80 mg, 40 mg, and 2,000 units/mL) for the initial dose.
- 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase/10 mL (60 mg, 60 mg, and 2,000 units/mL) for the maintenance doses.

Instructions on delayed dosing and re-administration of loading dose can be found on **Section 5.5**.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vial if particulates or discoloration is present. Do not shake. Discard any unused portion remaining in the vial.

For both the initial and maintenance dose, each corresponding PH FDC SC vial is ready-to-use for one subcutaneous injection and should not be diluted.

5.1.2 T-DM1 / Trastuzumab emtansine

Trastuzumab emtansine is provided as a single-use, lyophilized formulation in a colorless 20 mL Type I glass vial containing 160 mg of T-DM1, closed by means of a FluroTec coated stopper and an overseal with flip-off cap. Upon receipt of T-DM1, vials should be refrigerated at 2–8°C (36–46°F) until use and must not be frozen nor shaken. Trastuzumab emtansine must be stored in the original carton (as the expiry date will only be indicated on the carton). Do not use the product beyond the expiration date provided by the manufacturer. The reconstituted product contains no preservative and is intended for single use only. Any remaining medication should be discarded. The lyophilized product should be reconstituted using sterile water for injection (SWFI). Using a new syringe, 8 mL SWFI should be added to the vial and the vial swirled gently until the product is completely dissolved. The vial should not be shaken. The resulting product contains 20 mg/mL T-DM1, 10 mM sodium succinate, pH 5.0, 60 mg/mL sucrose, and 0.02% (w/v) polysorbate 20. Each 20 mL vial contains enough T-DM1 to allow delivery of 160 mg T-DM1. The reconstituted product contains no preservative and is intended for single use only. The vial should be inspected to ensure the reconstituted product is a clear colorless solution and is free of particulates before proceeding. Drug from any vial that appears abnormal upon inspection should not be administered to patients.

5.1.3 Endocrine Therapy

HR-positive patients will also receive ET continuously during neoadjuvant and adjuvant regimen (mandatory), and the type of ET will be selected according to local practices. For post-menopausal women is highly recommended letrozole (2.5 mg/day orally), whereas for pre-/peri-menopausal women is highly recommended ovarian function suppression therapy combined with either tamoxifen (20 mg/day orally) or letrozole (2.5 mg/day orally). For men tamoxifen is highly recommended.

For further details about neoadjuvant and adjuvant endocrine treatment see **Section 5.4.3**, as well as the local prescribing information for any ET and/or recognized clinical practice guidelines.

5.1.4 Chemotherapy

Chemotherapy as per investigator's choice and according to ESMO or NCCN 2021 guidelines (standard approved taxane-based chemotherapy regimens) will be supplied by the investigational sites and will apply to patients with residual disease in Cohort C of adjuvant treatment.

In addition, if disease progression is confirmed with MRI during neoadjuvant treatment, alternative neoadjuvant treatment will be administered in these patients as per investigator's choice along with PH FDC SC. The total number of cycles in the neoadjuvant treatment will remain unchanged and not increase despite addition of chemotherapy.

In order to minimize the risk of cardiac events, it is recommended to avoid anthracycline-containing chemotherapy.

5.2 Drug supply, storage, and drug accountability

All IMPs required for completion of this study will be provided by F. Hoffmann-La Roche Ltd. The study site will acknowledge receipt of IMPs supplied by Roche by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP (annex 13) requirements for labeling. Label text will be translated into local language.

The patient emergency contact details will not be on the label but can be found in the informed consent and the "Patient Dispensing Card". For emergency purposes the patient must be in possession of the emergency contact details at all times.

IMPs will be disposed of at the study site according to the study site's institutional standard operating procedure with the appropriate documentation. The site must obtain written

authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded throughout the course of the study.

The investigational sites will be supplied with study drug according to the sites' needs. The Investigator is responsible for safe and proper handling and storage of the study drug at the investigational site (IMPs must be stored according to their SmPC and IB) and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol. IMP must be kept in a locked temperature-controlled area, which can be accessed only by the pharmacist, the Investigator, or designee. Returned medication should be stored separately from medication that needs to be dispensed. Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of investigational products. These may include thermometers for both the room and refrigerator storage. Any temperature excursions must be reported immediately to the Sponsor and documented. Once a deviation is identified, the IMP must be quarantined and not used until the Sponsor provides documentation of permission.

To ensure adequate records, IMPs will be accounted for as instructed by the Sponsor.

5.3 Treatment compliance

Patients will receive treatment under physician supervision. Personnel will check the administration volume and total administered dose. The administered dose of each treatment will be recorded in the source data and the appropriate case report form (CRF).

5.4 Dosage and administration

5.4.1 PH FDC SC

All patients will receive the same dose of PH FDC SC, and no adjustments will be required for patient body weight. An initial fixed-dose of PH FDC SC of 1,200mg pertuzumab, 600mg trastuzumab, and 30,000 units hyaluronidase will be administered subcutaneously over approximately 8 minutes. After the initial dose on cycle one, the following doses (maintenance doses) in the next cycles will be of 600mg pertuzumab, 600mg trastuzumab and 20,000 units hyaluronidase administered subcutaneously every 3 weeks (day 1 of each cycle) for over approximately 5 minutes.

The combination will be in the form of a solution and in a single-dose labelled vial, ready-to-use for one subcutaneous injection. It should not be diluted.

PH FDC SC should only be administered subcutaneously. The subcutaneous injection site should be alternated between the left and right thigh only. New injections should be given at least 1 inch (2.5 cm) from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. Do not split the dose between two syringes or between two sites of administration. During the treatment course with PH FDC SC, other medications for subcutaneous administration should preferably be injected at different sites.

A syringe, a transfer needle, and an injection needle are needed to withdraw the solution from the vial and inject it subcutaneously. PH FDC SC may be injected using 25G-27G (3/8"-5/8") hypodermic injection needles.

After the first injection, patients will be observed for 30 minutes from the end of the injection for injection-related symptoms. The injection should be slowed or interrupted if the patient experiences injection-related symptoms. If the first injection is well tolerated, patients will be observed for 15 minutes after subsequent injections.

5.4.2 T-DM1

Patients in Cohorts B and C of this study will receive adjuvant T-DM1 3.6 milligrams per kilogram (mg/kg) via IV infusion. The initial doses will be administered over 90 minutes on Day 1 of cycle 1. If infusions are well tolerated, subsequent doses may be administered as 30-minute infusions.

If chemotherapy is required for patients in Cohort C, it will be administered before T-DM1.

Patients should be observed closely for hypersensitivity. Serious, allergic/anaphylactic-like reactions have been observed in clinical trials with treatment of T-DM1. Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients will be observed closely for infusion-related/hypersensitivity during and after each T-DM1 infusion for a minimum of 90 minutes after the first infusion and for a minimum of 30 minutes after subsequent infusions in the absence of infusion-related AEs.

5.4.2.1. Risk of extravasation

It exists the possibility of extravasation, and reactions secondary to extravasation could be observed. These reactions are usually mild and comprised of erythema, tenderness, skin irritation, pain or swelling at the infusion site. Close monitoring of the infusion site for possible subcutaneous infiltration during drug administration is recommended.

As a general recommendation, in the event of extravasation, the following advice should be considered:

- Stop the infusion immediately.
- Do not remove the needle or cannula.
- Aspirate with the same needle as much infiltrated drug as possible from the subcutaneous site.
- Apply ice to area for 15 to 20 minutes every four to six hours for the first 72hours.
- Paint the skin over the extravasated site with 100% dimethylsulfoxide (DMSO) (or hyaluronidase) four times daily for two weeks.

Watch the area closely during the following days in order to determine whether a surgical excision and skin graft is necessary.

5.4.3 ET

HR positive patients will receive ET neoadjuvant and adjuvant therapy.

For postmenopausal women is highly recommended letrozole 2.5 mg tablet orally once daily beginning on Day 1 and continuing through Day 21 of a 21-day cycle as neoadjuvant therapy.

For pre/peri-menopausal women is highly recommended ovarian function suppression combined with either letrozole 2.5 mg tablet or tamoxifen 20 mg tablet orally once daily beginning on Day 1 and continuing through Day 21 of a 21-day cycle as neoadjuvant therapy.

Fore male patients is highly recommended tamoxifen 20 mg tablet orally once daily beginning on Day 1 and continuing through Day 21 of a 21-day cycle as neoadjuvant therapy.

All patients with HR[+] tumors will be treated with adjuvant ET for at least 5 years.

Adjuvant ET will be administered as per local practice and according to recognized clinical practice guidelines.

5.5 Treatment modifications and discontinuation

Safety and tolerability of all patients will be closely monitored throughout study treatment and the follow-up period using the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5. Patients will be assessed in order to detect any side effects before administering new study treatment during each treatment visit. Treatment will only be administered if clinical evaluation and local laboratory test results are acceptable.

Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever occurs first, which includes all study assessments appropriate to monitor the event.

Treatment administration may be delayed up to 42 days from the last planned study treatment dose to assess or treat AEs (such as cardiac AEs, myelosuppression, or other events) and to allow AE recovery.

For PH FDC SC, the following recommendations must be accomplished:

- No dose reduction is allowed for PH FDC SC.
- If the patient develops hepatic toxicity (increased AST, ALT of Grade 2 or higher), do not administer PH FDC SC until AST and ALT levels recover to Grade ≤ 1 . Treatment may be delayed for a maximum of 42 days from the last planned study treatment dose. If AST and ALT levels do not recover to Grade ≤ 1 within the 42-day window, discontinue PH FDC SC.

Note: If there is suspicion or evidence that the increase in AST and ALT is not due to PH FDC SC treatment, consult the steering committee before permanently discontinuing PH FDC SC.

- If the patient misses a dose of the PH FDC SC for any cycle and the time between doses is ≥ 6 weeks, a reloading dose of the PH FDC SC (1200mg pertuzumab and 600mg trastuzumab) should be given. Subsequent maintenance PH FDC SC doses (600mg pertuzumab and 600mg trastuzumab) will then be given every 3 weeks, starting 3 weeks later. In the neoadjuvant period, if the time between doses is > 9 weeks then the patient will discontinue study treatment and enter follow-up.
- If the interval between the first dose of adjuvant PH FDC SC and the last dose of neoadjuvant PH FDC SC is ≥ 6 weeks, a reloading dose (1200mg of pertuzumab and 600mg of trastuzumab) is required. Subsequent maintenance doses (600mg pertuzumab and 600mg trastuzumab) will then be given every 3 weeks, starting 3 weeks later. The interval between the last dose of neoadjuvant PH FDC SC and the first dose of adjuvant PH FDC SC must be 4 to 49 weeks, depending on patient recovery and investigator assessment.

For T-DM1, dose delays and reductions are designed to maximize treatment for those patients who respond to or present clinical benefit from treatment while ensuring patient's safety. Trastuzumab emtansine dose should not be re-escalated after a dose reduction is made.

- If significant treatment-related toxicities (other than infusion reactions, thrombocytopenia, hepatotoxicity, neurotoxicity, and cardiotoxicity) have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days from the last planned study treatment dose.
- If dosing resumes after AE recovery, the patient may receive T-DM1 either at the same dose level as before or at one lower dose level (see **Table 1**).

Table 1. Dose reduction for T-DM1.

Dose Level	Every 3 weeks schedule
0	3.6 mg/kg
-1	3.0 mg/kg
-2	2.4 mg/kg
Indication for further dose reduction	Off study treatment

Dose modification guidelines for T-DM1 are summarized in **Table 2**, with further details provided in the next sections.

Adverse reaction	Severity	Treatment modification
Thrombocytopenia	Grade 2-3 on day of scheduled treatment (25,000 to <75,000/mm ³)	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥75,000/mm ³), and then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
	Grade 4 at any time <25,000/mm ³	Do not administer trastuzumab emtansine until platelet count recovers to ≤ Grade 1 (≥75,000/mm ³), and then reduce one dose level.
Increased Alanine Transaminase (ALT)	Grade 2-3 (>3.0 to ≤20×ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until ALT recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (>20×ULN at any time)	Discontinue trastuzumab emtansine
Increased Aspartate Transaminase (AST)	Grade 2 (>3.0 to ≤5×ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1, and then treat at the same dose level
	Grade 3 (>5 to ≤20×ULN on day of scheduled treatment)	Do not administer trastuzumab emtansine until AST recovers to Grade ≤ 1, and then reduce one dose level
	Grade 4 (>20×ULN at any time)	Discontinue trastuzumab emtansine
Hyperbilirubinemia	TBILI >1.0 to ≤ 2.0×ULN on day of scheduled treatment	Do not administer trastuzumab emtansine until total bilirubin recovers to ≤1.0×ULN, and then reduce one dose level
	TBILI >2×ULN at any time	Discontinue trastuzumab emtansine
Drug Induced Liver Injury (DILI)	Serum transaminases >3×ULN and concomitant total bilirubin >2×ULN	Permanently discontinue trastuzumab emtansine in the absence of another likely cause for the elevation of liver enzymes and bilirubin, e.g. liver metastasis or concomitant medication
Nodular Regenerative Hyperplasia (NRH)	All Grades	Permanently discontinue trastuzumab emtansine
Peripheral Neuropathy	Grade 3-4	Do not administer trastuzumab emtansine until resolution ≤ Grade 2

Left Ventricular Dysfunction	LVEF < 45%	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 45% is confirmed, discontinue trastuzumab emtansine.
	LVEF 45% to < 50% and decrease is ≥ 10% points from baseline*	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF remains < 50% and has not recovered to < 10% points from baseline, discontinue trastuzumab emtansine.
	LVEF 45% to < 50% and decrease is < 10% points from baseline*	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.
	LVEF ≥ 50%	Continue treatment with trastuzumab emtansine
Heart failure	Symptomatic CHF, Grade 3-4 LVSD or Grade 3-4 heart failure, or Grade 2 heart failure accompanied by LVEF <45%	Discontinue trastuzumab emtansine
Pulmonary toxicity	Interstitial lung disease (ILD) or pneumonitis	Permanently discontinue trastuzumab emtansine
Radiotherapy-Related Pneumonitis	Grade 2	Discontinue trastuzumab emtansine if not resolving with standard treatment
	Grade 3-4	Discontinue trastuzumab emtansine

Table 2. Dose modification guidelines for patients with EBC taking T-DM1.

5.5.1 Modification of the amount of study drug due to changes in patient’s weight

PH FDC SC is administered at a fixed dose irrespective of the patient ‘s body weight.

The amount of T-DM1 is calculated according to the patient’s weight on Day 1 of (or up to 3 days before) each cycle. Height should be recorded at baseline, weight at baseline and thereafter at every scheduled visit, and the BSA calculated accordingly. The amount to be administered must be recalculated if the patient’s body weight has changed by > 10% (increased or decreased) from the weight recorded at Day 1 of Cycle 9. Re- calculation based upon smaller changes in body weight or BSA are at investigators’ discretion.

5.5.2 Treatment discontinuation due to cardiac toxicities

Anti-HER2 therapies are associated with cardiac toxicity, as well as treatment with T-DM1. All patients must have a baseline LVEF > 55% assessed by ECHO (preferred method) or MUGA scan. Results of ECHO/MUGA performed prior to commencement and immediately after completion of preoperative therapy will be collected in the eCRF.

The same method should be used throughout the study for each patient, and preferably performed and assessed by the same assessor. LVEF will be monitored regularly (every 12 weeks approximately) according to the schedule of study assessments and procedures (see **Appendix 1** and **Section 6.4.3** for further details).

For PH FDC SC, withhold treatment for at least 3 weeks for an LVEF decrease to < 50% with a fall of $\geq 10\%$ -points below pre-treatment value. Resume the treatment after 3 weeks if LVEF has recovered to either $\geq 50\%$ or $<10\%$ points below pre-treatment value.

For T-DM1, if grade 3-4 LVSD or grade 3-4 of heart failure is observed, as well as grade 2 heart failure accompanied by LVEF < 45%, discontinue study treatment and will be reported as a SAE.

Refer to **Figure 2** for the algorithm for continuation and discontinuation of study treatment on the basis of asymptomatic LVEF assessment.

Symptomatic left ventricular systolic dysfunction (LVSD)/CHF:

Study treatment will be discontinued in any patient who develops clinical signs and symptoms suggesting symptomatic LVSD/CHF with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA scan. Symptomatic LVSD/CHF should be treated and monitored according to standard medical practice.

Asymptomatic LVEF decline:

Patient must be managed according to algorithm shown in **Figure 2**.

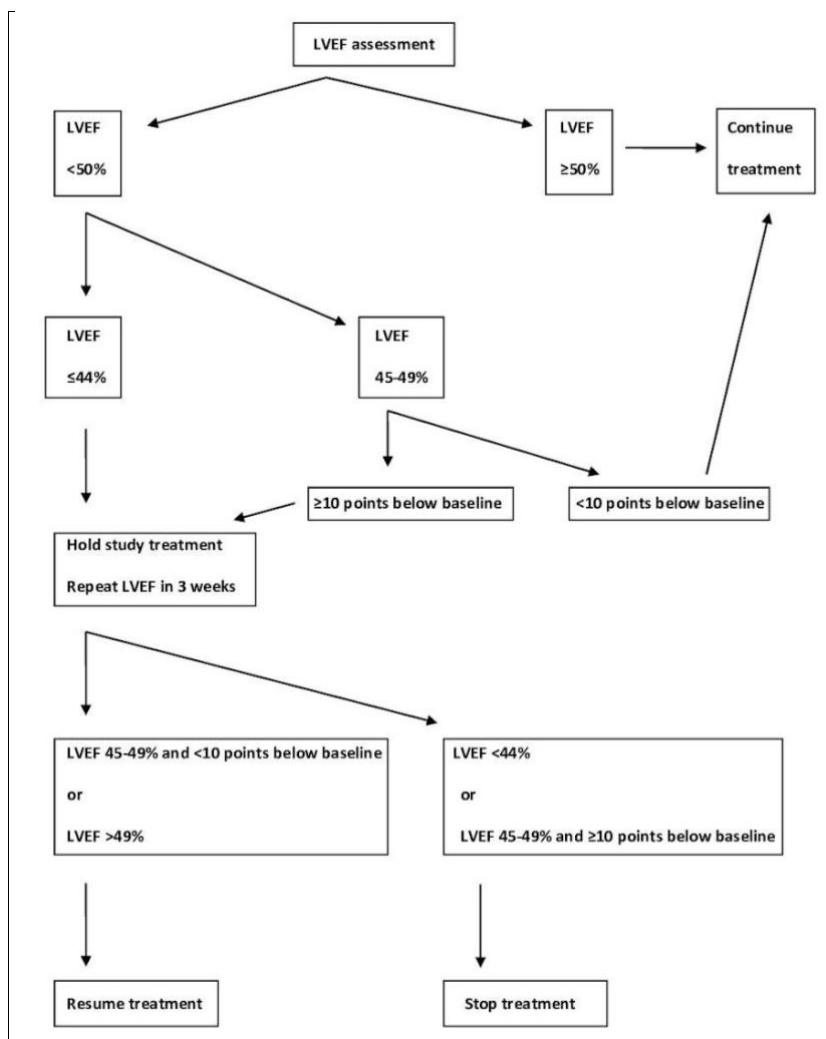


Figure 2. Study algorithm for continuation and discontinuation of anti-HER2 therapy based on asymptomatic drop in LVEF.

5.5.3 T-DM1 dose modification for thrombocytopenia

Thrombocytopenia, or decreased platelet counts, has been reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events ($\geq 50 \times 10^9/L$), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 ($\geq 75 \times 10^9/L$), by the next scheduled dose.

Patients with thrombocytopenia and on anticoagulant treatment have to be monitored closely during treatment with trastuzumab emtansine. Platelet counts should be obtained no less frequently than weekly to evaluate recovery whenever any of the events listed below occurs, at least prior to each trastuzumab emtansine dose.

Monitoring follow-up of thrombocytopenia episodes:

- If platelet counts do not recover to Grade ≤ 1 within 42 days from the last planned study treatment dose, the patient will be discontinued from study treatment. No re-escalation of the T-DM1 dose is allowed.
Note: although complete blood counts with platelets are required within 72 hours prior to study treatment administration at each cycle, the investigator may monitor platelet counts (or any other laboratory test) more frequently as clinically indicated.
- In the event of decreased platelet count to Grade 3 ($< 50 \times 10^9/L$), do not administer T-DM1 until platelet counts recover to Grade 1 ($\geq 75 \times 10^9/L$), then treat at the same dose level. If a patient requires 2 delays due to thrombocytopenia, consider reducing dose by one level.
- Patients receiving T-DM1 who experience a first Grade 4 thrombocytopenia event may, after adequate recovery to a platelet count of Grade ≤ 1 or baseline, continue treatment with one dose level reduction (i.e., from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg) in subsequent cycles. If event occurs with 2.4 mg/kg dose, discontinue study treatment.

Use of erythropoiesis stimulating agents will be allowed as consistent with prescribing guidelines. Transfusion of red blood cells and/or platelets will be allowed according to and at the discretion of the treating physician.

5.5.4 T-DM1 dose modification for hepatotoxicity

The finding of an increased serum ALT or AST ($> 3 \times \text{ULN}$) in combination with either an increased serum TBILI ($> 2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report the occurrence of either of those findings as an AE (or SAE) to the Sponsor within 24 hours, and the most appropriate diagnosis or abnormal laboratory values should be recorded on the AE eCRF.

Concurrent elevations of ALT/AST and bilirubin meeting Hy's Law laboratory criteria: Regardless of dose level, T-DM1 must be permanently discontinued in patients with ALT and/or AST $> 3 \times \text{ULN}$ and concurrent increase of total bilirubin to $> 2 \times \text{ULN}$.

Nodular regenerative hyperplasia (NRH): T-DM1 must be permanently discontinued in patients who are diagnosed with NRH. NRH, whether or not accompanied by liver laboratory abnormalities, should be reported to the Sponsor as a SAE.

Transaminase elevations or bilirubin elevations requiring dose adjustment: Patients who experience a \geq Grade 3 elevation of liver function should be checked twice weekly for the recovery of transaminases and/or total bilirubin. If a patient's transaminases and/or total bilirubin do not

recover within 42 days from the patient's last dose of study treatment received (with treatment withheld during this period), the patient will be discontinued from study treatment.

No re-escalation of the T-DM1 dose is allowed.

5.5.5 T-DM1 dose modification for neurotoxicity

Patients receiving T-DM1 who experience Grade 3 or 4 peripheral neuropathy that does not resolve to Grade ≤ 2 or baseline within 42 days after the last dose received will be discontinued from study treatment.

5.5.6 Dose modification for infusion-related reactions

Administration of monoclonal antibodies, including trastuzumab and pertuzumab, or different chemotherapeutic agents, may cause administration-related reactions. AEs such as chills and/or fever, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, skin rashes, headache, nausea, or vomiting have been observed. For this reason, study treatment must be administered by staff trained to monitor for and respond to medical emergencies in a setting with emergency equipment.

Patients who experience administration-related reactions may be managed by:

- Slowing or stopping the treatment administration.
- Supportive care with oxygen, β -agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion.

Patients who experience infusion reaction symptoms may be premedicated with paracetamol and antihistamines for subsequent injections or may be treated using desensitization protocols according to institutional practices.

Patients with preexisting pulmonary compromise who are treated with trastuzumab may be at increased risk of severe or serious administration-related reactions. Therefore, careful consideration must be made before enrolling patients with chronic pulmonary disease into the study.

Discontinue the injection of PH FDC SC immediately if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis)

T-DM1 treatment should be interrupted in patients with severe infusion-related reactions. T-DM1 should be permanently discontinued in the event of life-threatening infusion-related reactions. Infusion of T-DM1 should be interrupted for patients who develop dyspnea or clinically significant hypotension. The infusion should be slowed to $\leq 50\%$ or interrupted for patients who experience

any other infusion-related symptoms. When the patient's symptoms have completely resolved, the infusion may be continued at $\leq 50\%$ of the rate prior to the reaction and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate during the next cycle.

Patients who experience T-DM1 infusion-related temperature elevations to $> 38.5^{\circ}\text{C}$ and/or other infusion-related symptoms may be treated symptomatically with acetaminophen and/or diphenhydramine hydrochloride. Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive care, such as oxygen, beta-agonists, antihistamines, or antipyretics, at the investigator's discretion. Antihistamines and antipyretics may be used before subsequent infusions of T-DM1 at the investigator's discretion. Medication with corticosteroids may be used after cycle 2. Patients should be monitored until complete resolution of symptoms. In the event of a true hypersensitivity reaction (i.e., if the severity of reaction increases with subsequent infusions), T-DM1 treatment must be permanently discontinued. Patients who experience a Grade ≥ 3 hypersensitivity reaction or acute respiratory distress syndrome (ARDS) will be discontinued from the study. Patients who experience a severe delayed infusion reaction will be discontinued from study treatment.

5.5.7 Dose Modification for Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis (including severe, life-threatening cases) and some leading to ARDS or fatal outcome have been reported with intravenous trastuzumab (and therefore it is important to consider these adverse reactions when taking PH FDC SC) as well as T-DM1.

Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. Patients with dyspnea at rest as a result of complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Treatment includes administration of steroids and oxygen, as well as study drug discontinuation.

Discontinue PH FDC SC for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Monitor patients until symptoms completely resolve.

Upon diagnosis of drug-related ILD/pneumonitis, T-DM1 treatment has to be permanently discontinued.

5.6 Medication errors and overdose

Medication errors in this study may arise when the drug is administered at the wrong time or when the wrong dose strength is taken. Patient medication errors should be recorded on the relevant section in the CRF. In the event of an error in the administration of the medication, the Sponsor should be informed immediately.

Medication errors must be reported irrespective of the presence of an associated clinical AE/SAE, and will be considered AE/SAEs themselves and recorded in the AE page in the following situations:

- **Administration of an incorrect dose** – Any dose that deviates from the expected protocol-defined dose. This includes the administration of a loading dose of PHESGO when a maintenance dose is expected or vice versa, or the administration of a dose of T-DM1 other than 3.6 mg/kg when 3.6 mg/kg is the intended dose. Note that the protocol allows investigators discretion in recalculating the dose if the patient's weight does not change by more than $\pm 10\%$.
- **Administration of the wrong drug or a drug intended for another patient** – This includes any case where a study drug is given to the incorrect patient, or an unintended medication is administered in place of the investigational product.
- **Errors in the route of administration** – Any deviation from the protocol-specified route of administration, such as intravenous administration instead of subcutaneous or vice versa.

5.7 General concomitant medication and additional assistance guidelines

Concomitant treatment and prior medication are defined as non-investigational medicinal product (non-IMP). Concomitant treatment includes any prescribed medication or phytotherapy between the 28 days prior to the administration of the first treatment dose and the last safety visit during treatment period. All concomitant medications (within 7 days prior to study entry) and prior treatments for breast cancer must be reported in the electronic CRF (eCRF). After this time, information will only be collected on any anti-cancer drugs taken by the patient until EoS.

Information on concomitant medication will include start date, end date, brand or generic name, route of administration, dose, and treatment indication. The following concomitant treatments are permitted during the study:

- Preoperative ET (tamoxifen and letrozole), and adjuvant ET according to local practices.
- Erythropoiesis-stimulating agents (ESA) are allowed (such as Procrit®, Aranesp®, Epopgen®) for the supportive treatment of anemia. Blood transfusions are permitted during the study.

- The prophylactic use of granulocyte-colony stimulating factors (G-CSF; GM-CSF) is allowed during the first treatment cycle, and can be used for cases of neutropenia arising during treatment, as primary and secondary treatment, in accordance with the National Comprehensive Cancer Network (NCCN) guidelines.
- The use of medication for the treatment of diarrhea, nausea, or vomiting is permitted.
- Any medications deemed necessary to ensure patient safety and well-being may be administered at the discretion of the investigator with the exception of prohibited therapies contained in **Section 5.8**.

5.8 Prohibited therapies and medication

The following therapies and medication should be avoided:

- Other investigational therapies, except for those used for this study.
- Any oral, injected, or implanted hormonal methods of contraception.
- Anticancer therapy other than the study treatments including chemotherapy, biologic, endocrine (except for patients with HR positive tumors who should receive continuous ET therapy according to local practices; section 5.4.3), or radiation therapy (except for adjuvant radiotherapy).
- Therapeutic doses of warfarin sodium or any other anticoagulants are not permitted. The use of prophylactic doses of low-molecular weight heparin is allowed.
- High doses of systemic steroids (> 20 mg of dexamethasone a day [or equivalent] for > seven consecutive days) and other immunosuppressive agents should be avoided. Standard premedication for chemotherapy and local applications are allowed.

Potent CYP3A4 inhibitors, such as ketoconazole and erythromycin, should be avoided during the study treatment period with trastuzumab emtansine. Excessive alcohol intake should be avoided (occasional to moderate use is permitted).

No other clinically significant interactions were observed. SmPC of PH FDC SC, T-DM1, tamoxifen, and letrozole must be reviewed for additional information.

6 ASSESSMENTS AND STUDY PROCEDURES

6.1 Patient entry procedures

6.1.1 Informed consent

Written informed consent from the patient (or the patient's legally authorized representative) must be signed and dated before his or her participation in the study and before performing any study

specific procedure. Since some of the procedures required by this study protocol form part of regular medical care, if patient have had some of them before signing the study ICF, they do not need to be repeated as long as they fall within the specified time frames. Patients will be informed as to the nature of the study drug and will receive pertinent written information regarding the study objectives, possible benefits, and potential AEs. They will also receive information on the follow-up procedures and possible risks they will be exposed to. The informed consent form will also inform patients about how biological samples will be obtained and collected and its legal implications. A copy of the signed ICF must be provided to the patient or the patient's legally authorized representative. Patients have the right to voluntarily withdraw from the study at any time for any reason, and this will not affect any future medical treatment the patient will receive.

6.1.2 Patient allocation

The following steps must be taken before registering patients to this study:

1. Completion of patient eligibility checklist, once checked all selection criteria after receiving results of centralized confirmation of HER2[+] and results of central review of baseline MRI.
2. Registration of patient in the Sponsor study database.

Mandatory tumor samples from the primary tumor (biopsy) will be collected for eligibility testing (central confirmation of HER2[+] status), and mandatory baseline MRI will be performed for eligibility testing (central confirmation of baseline MRI validity).

Confirmation of patient allocation using Sponsor study database:

Each patient will be identified with a unique patient number (UPN) obtained from eCRF that will be used to identify the subject for all study procedures. All data will be recorded with this identification number on the appropriate CRFs. Each subject will be assigned only one UPN. UPNs must not be re-used for different subjects. Any subject who is screened multiple times will retain the original UPN assigned at the initial screening visit.

Confirmation of patient's eligibility for study participation will be recorded on the eCRF. The investigator is responsible for safeguarding patient information (i.e., age, name, address, telephone number, social security number, and study identification number), ensuring access to this information by Health Authorities if necessary. These records will remain confidential for the period stipulated by current legislation.

One re-screening is allowed for patients that were screening failure. Patients have to re-consent Informed Consent Form (ICF) before any study procedure is done. At re-screening, study

assessments and procedures can be omitted if were performed during the initial screening period within the specified time frames.

6.2 Visit schedule

All screening tests and evaluations must be completed within the protocol scheduled time windows and reviewed to confirm that patients meet all eligibility criteria within 28 days prior to the first administration of study medication (dosing). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Visits are organized in programmed cycles of 21 days from the date of the administration of the previous cycle (if there are no treatment delays due to the occurrence of AEs). All visits must occur within ± 3 working days from the scheduled date, unless otherwise noted in the schedule of assessments.

Assessments scheduled for day 1 (before treatment) of all cycles, including screening, must be performed within 72 hours prior to study treatment administration, unless otherwise indicated in the schedule of assessments, to confirm to the patient if treatment can be followed up. If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (i.e., within a period of ± 3 working days).

After surgery, patients will be followed up every 3 months for the first two years, every 6 months for the 3 next years, and yearly thereafter. The visits must be performed at the completion of the corresponding period (e.g. after completion of 3 months, 6 months, etc.) from surgery. Patients who discontinue treatment without surgery will require follow-up visits every 6 months (+ 14 days) from the last dose of investigational drug.

All follow-up visits must occur within + 14 working days from the scheduled date. If treatment visits and follow-up visits overlap in time within + 14 working days, the study assessments and procedures common to both visits should be performed just once.

The summary of study assessments is included in **Appendix 1**.

6.3 Study Assessments

6.3.1 Demographic data and medical history

Demographic data include age, sex, and self-reported race/ethnicity. Medical history comprises clinically significant diseases, surgical interventions, history of cancer (including prior

antineoplastic treatments and procedures) as well as any medications (i.e., prescribed drugs, over-the-counter drugs, medicinal plants, homeopathic remedies, or food supplements) used by the patient in the 28 days prior to screening visit.

6.3.2 Breast cancer surgery

Definitive breast surgery will be performed not sooner than 2 weeks but no more than 4 weeks after completion of neoadjuvant treatment (so the MRI result can be used to plan the surgery accordingly). Sentinel node biopsy will be mandatory; subsequent axillary dissection will be performed according to local guidelines. Surgery will require free margins for any infiltrating or DCIS lesion.

Tumor samples from breast cancer surgery will be collected for translational purposes.

Options for surgical management of the primary tumor include breast-conserving surgery, mastectomy plus reconstruction, and mastectomy alone at the discretion of the surgeon. Patients with involved or close surgical margins after breast conserving surgery will undergo re-excision or mastectomy to obtain negative margins. It is important to place a marker (i.e., surgical clip, carbon) into the tumor at biopsy in order to ensure surgical resection of the correct site.

Sentinel lymph node biopsy will be performed after preoperative surgery in all patients except if there is confirmed axillary progression. All patients should undergo level I and level II axillary dissections if the sentinel node(s) are reported positive for malignancy. One-step nucleic acid amplification (OSNA) method for intraoperative analysis and staging of sentinel lymph nodes (by measuring cytokeratin19 mRNA copy numbers in homogenized sentinel lymph nodes) is not allowed in order to calculate the RCB score.

Feasibility and type of surgery as indicated by surgeon prior to study treatment will be recorded at baseline for each patient enrolled. After the neoadjuvant treatment period, the investigator will report if patient undergoes breast surgery, and the type of surgery performed.

6.3.3 Central testing of HER2 status by IHC

Central laboratory confirmation of HER2[+] status is required prior to treatment start. The outcome of this assessment will be communicated to the investigator.

A patient's HER2 status will be considered positive if the central laboratory reports a staining intensity 3+ (on a scale of 0 to 3+) by means of IHC analysis. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or a partial block must be obtained. If sites are unable to send a tissue block due to local regulations, at least 8 unstained slides sections of tissue FFPE block at 5 µm

thickness should be sent for HER2 testing, and in addition up to 30 slides sections of tissue FFPE block at 5 µm thickness for exploratory biomarker research.

6.3.4 Imaging assessment

Mammography is required at screening, before surgery, 6 months after the last RT session for patients who received adjuvant radiation therapy, and during follow-up, but will not be used for the objective response assessment. During follow-up mammography will be performed every 12 months up to 3 years after surgery. In patients without progression and who have not undergone surgery, mammography will be performed every 12 months up to 3 years from the last dose of investigational product. In patients who have not undergone surgery due to disease progression mammography is not necessary.

Breast and axillary ultrasound ± FNA will be performed at screening visit.

Breast MRI is required at screening (prior to inclusion) and within 2 weeks prior to surgery, so the result can be used to plan the surgery accordingly. Response evaluation with MRI will be assessed using the RECIST criteria version 1.1.

Bone scan, CT, MRI, and/or PET-FDG scans may be performed as clinically indicated according to the investigator.

6.4 Safety and tolerability assessments

6.4.1 Laboratory assessments

Laboratory tests will be performed as per local standard of care and clinical indication before treatment administration. For Cycle 1 day 1 (C1D1), blood samples extracted up to 72 hours before the cycle can be used. These values are recommended to be included: hematological test (hemoglobin, hematocrit, red blood cell count, platelet count, WBC with differential count [ANC, lymphocytes, monocytes, eosinophils and basophils]), coagulation, chemistry with renal function analysis (serum creatinine, creatinine clearance according to the Cockcroft-Gault formula), liver function (AST, ALT, ALP, gamma-glutamyl transferase [GGT], total and direct bilirubin), glucose, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.

Laboratory tests will be performed on the first day of each cycle. After surgery, blood test including liver, renal, and bone marrow functions every six months for the first five years.

6.4.2 Pregnancy and assessment of fertility

Only female patients of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the trial and within one week prior to start of study medication (with result available prior to dosing) and thereafter a urine pregnancy test every 4 cycles (serum pregnancy test only for confirmation), and before surgery (serum pregnancy test only for confirmation).

After surgery, the urine pregnancy test (serum pregnancy test only for confirmation) will be done every 3 months until 7 months post discontinuation of either treatment and at completion of adjuvant treatment (in the EoT visit). In case an additional pregnancy test is indicated during the trial by investigator, a urine (serum pregnancy test only for confirmation) test should be performed.

Post-menopausal status is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a post-menopausal status in those patients younger than 50 years old.

Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use a highly effective, non-hormonal form of contraception (such as surgical sterilization), or two effective forms of non-hormonal contraception or true abstinence during the treatment period and for at least seven months after discontinuation of study treatment. The following highly effective non-hormonal methods of contraception are acceptable:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [i.e., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment. Tubal ligation will not be considered a highly effective non-hormonal methods of contraception and will not be acceptable.
- Male sterilization (at least six months prior to screening). For subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Or two of the following effective forms of contraception:
 - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
 - Condom with spermicidal foam/gel/film/cream/suppository.
 - Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

In case of pregnancy during study treatment or within seven months after the last dose of PH FDC SC and/or T-DM1, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form as specified in **Section 7.2.4**.

Male patients will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within seven months after the last dose of PH FDC SC.

6.4.3 Cardiac function monitoring

Cardiac function monitoring consists of LVEF measurement, standard 12-lead ECG, and cardiac signs or symptoms collection. All patients must have a standard 12-lead ECG and an LVEF measurement of at least 55% by ECHO (preferably) or MUGA scan. The same method should be used throughout the study for each patient, and preferably performed and assessed by the same assessor.

At screening, LVEF must be done within 28 days prior to neoadjuvant treatment by ECHO or MUGA scan. During study treatment, cardiac assessments - using the same method as performed at screening - should be repeated every 12 weeks as close to the assigned week as possible but prior to the next infusion: before cycle 5 during period 1, before cycles 1, 5, and 9 during period 2 (e.g.: between days 15-21 of the previous cycle to allow evaluation of the results before the indicated cycle).

Following discontinuation of treatment, cardiac assessments should be performed every 6 months up until 24 months from the last administration of either treatment.

Any patient who develops clinical signs or symptoms of cardiac failure should undergo an LVEF assessment and a standard 12-lead ECG. See **Figure 2** for study algorithm for continuation and discontinuation of anti-HER2 therapy based on interval LVEF assessments.

6.4.4 Physical examination

Physical exams should include, as part of tumor assessment, evaluation of the breast and regional lymph nodes. Measurement with calipers is recommended, although it will not be used for the objective response assessment.

A complete physical examination should also include an examination of head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, digestive, genitourinary, and neurological systems. Changes to abnormalities identified during the screening period should be recorded at all subsequent physical examinations. New or worsening abnormalities should be recorded as AEs, if applicable.

Physical examination will be performed on screening and prior to surgery, as well as on the first day of each cycle (neoadjuvant and adjuvant treatment).

After surgery, the clinical examination will be done together with a quality of life assessment, every 3 months for the first two years after surgery, every 6 months for the next 3 years, and every year after the 5th year.

6.4.5 Vital signs

These will include the measurement of height (only during screening), weight, respiratory rate, heart rate, blood pressure, and body temperature. Abnormal or significant changes in vital signs from screening should be recorded as AEs, if appropriate.

Vital signs will be measured on screening and prior to surgery, as well as on the first day of each cycle (neoadjuvant and adjuvant treatment).

6.4.6 ECOG performance status

Performance status will be determined using the ECOG performance status scale (see **Table 3**). Wherever possible, the patient’s performance status should always be assessed by the same personnel throughout the study.

Grade	Scale
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, i.e., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Table 3. ECOG performance status scale. (http://www.ecog.org/general/perf_stat.html).

6.5 Health-related quality of life assessments

Health-related quality of life will be determined using the EORTC QLQ-C30 and the breast cancer module QLQ-BR23 questionnaires.

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status/quality of life scale, and six single items. Each of the multi-item scales includes a different set of items (no item occurs

in more than one scale). All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. The scales evaluated are: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties.

The QLQ-BR23 breast cancer module is meant for use among patients varying in disease stage and treatment modality. The module comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy, and hormonal treatment), body image, sexual functioning, and future perspective. The breast cancer module incorporates five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning. In addition, single items assess sexual enjoyment, hair loss, and future perspective. The scoring approach for the QLQ-BR23 is identical in principle to that for the function and symptom scales/single items of the QLQ-C30. The scales evaluated are: body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss.

The quality of life assessments will be done together with a clinical exam before starting neoadjuvant treatment, on day 1 at each neoadjuvant treatment cycle, within two weeks prior to surgery, after surgery prior to start of adjuvant treatment and every 3 months for the first two years after surgery, every 6 months for the next 3 years, and every year after the 5th year. For patients who progress to neoadjuvant anti-HER2 treatment and receive alternative neoadjuvant treatment, quality assessment must also be done prior to start alternative treatment.

6.6 Translational research

Translational research will be performed with exploratory purposes outside of the scope of this clinical study protocol.

During the study, tissue and blood samples will be collected, processed, and stored for subsequent analysis in independent sub-studies.

Overall, tumor tissues and blood samples obtained during the study will be used to identify dynamic biomarkers that may be predictive of response to the study treatment and/or prognostic for breast cancer response. Since the identification of new markers that correlate with disease activity and the efficacy or safety of treatment is rapidly developing, the definitive list of analyses remains to be determined, but may include determination of markers of tumor genesis pathways or mechanisms of response to anti-HER2 therapies.

Medical images derived from tumor assessments (except bone scans) will be stored for exploratory analyses at MEDSIR's central imaging repository.

Some exploratory analyses may include, but are not limited to the following:

- The comparison of pCR between the different intrinsic tumor subtypes as determined by PAM50 genetic test.
- The assessment the predictive value of circulating tumor DNA (ctDNA) dynamics using next generation sequencing (NGS) gene panel.
- The analysis of differential expression in plasma microRNA levels at different time points.
- The monitoring of HER2 messenger RNA (mRNA) levels.
- Genomic analysis through NGS gene panel.
- Transcriptomic analysis using microRNA Whole Transcriptome Assay.
- The evaluation of the predictive value of tumor-infiltrating lymphocytes (TILs).
- The correlation of molecular analysis results with early relapse rates.
- Evaluation of imaging biomarkers potentially predicting for response to IMPs.

6.6.1 Tumor tissue samples

Mandatory tumor samples from the primary tumor (biopsy) will be collected for eligibility testing (local confirmation for ER and PgR status; central confirmation of HER2[+] status with IHC score 3+) and the exploratory assessment of predictive biomarkers to the study treatment, intrinsic molecular subtyping (Parker et al., 2009), and additional exploratory endpoints. Two FFPE tissue blocks/slide sections should be obtained no more than 8 weeks prior to informed consent.

Mandatory tumor samples will be also collected at definitive surgery for biomarker assessment.

A separate study manual will be provided which details tumor tissue sample preparation, processing, storage, and shipment.

6.6.2 Blood samples

Approximately 20 mL of blood (2 *STRECK tubes of 10mL*) for DNA analysis will be obtained at baseline, C3D1 before treatment infusion, pre-surgery (2 weeks before surgery). In addition, blood samples will be collected at each follow-up visit during adjuvant treatment: every 6 months for the next 5 years, and every year thereafter until the EoS.

A separate study manual will be provided with details blood sample collection, processing, storage, and shipment.

6.7 Efficacy assessments

6.7.1 Breast cancer surgery

Definitive breast surgery will be performed not sooner than 2 weeks but no more than 4 weeks after completion of neoadjuvant treatment. Tumor samples from breast cancer surgery will be collected for translational purposes. Options for surgical management of the primary tumor include breast-conserving surgery, mastectomy plus reconstruction, and mastectomy alone at the discretion of the surgeon. Patients with involved or close surgical margins after breast conserving surgery will undergo re-excision or mastectomy to obtain negative margins. It is important to place a marker (i.e., surgical clip, carbon) into the tumor at biopsy in order to ensure surgical resection of the correct site. Surgical staging of the axilla should also be performed by:

- Complete axillary dissection and pathological examination of the level I and II lymph nodes is recommended if there is axillary involvement at the time of diagnosis. However, patients with axillary involvement at the time of diagnosis may be restaged after preoperative therapy; complete axillary dissection must be performed if axilla is still clinically positive; sentinel lymph node biopsy (SLNB) could be performed if axilla is clinically negative and considering the following recommendations:
 - Marking biopsied lymph nodes before starting study treatment.
 - Using dual tracer.
 - Removing more than two sentinel nodes.
 - Axillary dissection will be performed with any pathological positive lymph node including micrometastatic disease and isolated tumor cells.
- SNLB will be performed in patients with T1 and T2 breast cancers without axillary involvement at the time of diagnosis. SNLB can be performed before or after preoperative systemic therapy. All patients should undergo level I and level II axillary dissections if the sentinel node(s) are reported positive for malignancy. If patient had a sentinel node biopsy before preoperative systemic treatment which was negative, axillary dissection will be not performed after treatment completion, and such patient will be considered to be pN0 for pCR definitions.

One-step nucleic acid amplification (OSNA) method for intraoperative analysis and staging of sentinel lymph nodes (by measuring cytokeratin19 mRNA copy numbers in homogenized sentinel lymph nodes) is not allowed in order to calculate the RCB score.

Feasibility and type of surgery as indicated by surgeon prior to study treatment will be recorded at screening for each patient enrolled. After the neoadjuvant treatment period, the investigator will report if patient undergoes breast surgery, and the type of surgery performed.

6.7.2 Breast tumor imaging assessment

Mammography is required at screening visit (screening mammography does not need to be repeated if patient has had a mammography performed within 6 weeks prior to enrollment), before surgery, 6 months after the last RT session for patients who received adjuvant radiation therapy, and during follow-up, but will not be used for the objective response assessment. Breast and axillary ultrasound \pm FNA will be performed at screening visit. Breast MRI is required at screening (prior to inclusion) and prior to surgery. Physicians may perform additional breast MRI scans during neoadjuvant treatment if they find it necessary and/or to confirm disease progression. Response evaluation with MRI will be assessed using the RECIST criteria version 1.1.

6.7.3 Response assessment

The response assessment of the tumor is defined as best overall response, in terms of complete CR, PR, SD, and progressive disease (PD) according to the following list:

- CR: Complete disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to < 10 millimeter (mm).
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Additionally, non-target lesions cannot fulfil progressive disease criteria.
- 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.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameters while on study; or unequivocal progression of existing non-target lesions. The development of new, previously undetected lesions is also considered progression.

ORR is defined as the number of patients with CR and PR divided by the number of patients in the analysis set. Tumor response will be defined as best response, based on local investigator's assessment according to RECIST criteria guidelines v.1.1.

6.7.4 pCR assessment

- pCR_{BREAST+LYMPH NODES} defined as no invasive residual disease in the breast and lymph nodes (ypT0/isN0 in the current AJCC staging system).

- pCR_{BREAST} defined as no invasive residuals in the breast only (ypT0/is in the current AJCC staging system).

- pCR assessment according to the RCB score. Microscopic and macroscopic pathological components, namely size of tumor bed (millimeters), average percent overall tumor cellularity

(invasive and in situ), average percent of the cancer within the tumor bed that is in situ, size of largest axillary metastasis (mm), and number of involved nodes are assessed and RCB categories are assigned to each case following calculation of the numerical RCB index score (Symmans et al., 2007).

6.7.5 Follow-up and confirmation of disease recurrence

The diagnosis of a breast cancer recurrence or second primary tumor should be confirmed histologically whenever possible. Some patients may have a suspicious recurrence that leads to death quite quickly without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such cases. The earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological or cytological evidence.

Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. Patients who have a diagnosis of in situ breast disease or second (non-breast) malignancies should be maintained on a regular follow-up schedule wherever possible in order to fully capture any subsequent recurrent disease events.

The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events on follow-up are detailed in the **Table 4**.

Event	Definition
Local invasive recurrence Ipsilateral breast after previous lumpectomy	<p>Ipsilateral breast after previous lumpectomy</p> <ul style="list-style-type: none"> - Defined as evidence of invasive tumor (except DCIS and LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis. - Confirmed by positive histology or cytology <p>Ipsilateral after previous mastectomy</p> <ul style="list-style-type: none"> - Defined as evidence of invasive tumor in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle, and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence. - Confirmed by positive histology or cytology
Regional recurrence	<ul style="list-style-type: none"> - Defined as the development of tumor in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes or supraclavicular lymph nodes as well as extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumor in the opposite breast. - Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT or MRI if no biopsy was performed).

Distant recurrence	<p>Defined as evidence of tumor in all areas, with the exception of those described in a) and b) above. Confirmed by the following criteria:</p> <ul style="list-style-type: none"> - Skin, subcutaneous tissue, and lymph nodes (other than local or regional): Positive cytology, aspirate or biopsy, OR Radiological (CT scan, MRI, PET, or ultrasound) evidence of metastatic disease - Bone: X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR Bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), OR Biopsy proof of bone metastases or cytology. - Bone marrow: Positive cytology or histology or MRI scan - Lung: Radiologic evidence of multiple pulmonary nodules consistent with pulmonary metastases Positive cytology or histology (practically rarely performed with the exception of solitary nodules). <i>NOTE: For solitary lung lesions, cytological or histological confirmation should be obtained in case of diagnostic doubt. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy.</i> - Liver: Radiologic evidence consistent with liver metastases, OR Liver biopsy or fine needle aspiration <i>NOTE: If radiological findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained if possible to document stability or progression.</i> - Central nervous system: Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR Biopsy or cytology (e.g., for a diagnosis of meningeal involvement). However, meningeal involvement may also be diagnosed by CT scan or MRI and depending from the general status of the patient additional investigations (including cytology of the cerebrospinal fluid).
Contralateral invasive breast cancer	<ul style="list-style-type: none"> - Confirmed by positive cytology or histology
Second primary malignancy (breast or other cancer)	<ul style="list-style-type: none"> - Any positive diagnosis of a second (non-breast) primary cancer other than basal or squamous cell carcinoma of the skin, or CIS of the cervix will be considered an event in the analysis of the iDFS including second primary non-breast cancer endpoint; however, they will not be included in the iDFS primary endpoint. - LCIS and DCIS of the breast and myelodysplastic syndrome are not considered progression events. The diagnosis of a second primary cancer must be confirmed histologically. - All second primary malignancies are to be reported whenever they occur during the study. <p><i>NOTE: Patients diagnosed with a second primary malignancy not requiring systemic therapy (i.e., chemotherapy, hormonal therapy, targeted therapy, etc) and with no evidence of breast cancer</i></p>

	<i>recurrence will remain on study and should continue with study drug treatment according to the protocol and schedule of assessment, if considered by the investigator to be in the patient's best interest, whenever possible.</i>
Death without recurrence	Any death occurring without prior breast cancer recurrence or second (non- breast) malignancy is considered an event for the following endpoints: IDFS including second primary non-breast cancer, DFS, and OS.
Other noteworthy events	The following events should be recorded on the follow-up eCRF: - Ipsilateral and contralateral LCIS - Ipsilateral and contralateral DCIS <i>NOTE: These events are not considered recurrent disease, but must be recorded.</i>

Table 4. Definitions and procedures to confirm disease recurrence and death.

6.7.6 RFI, RFS, EFS, iDFS, DRFS, DFS, BCSS, and OS definitions

a) RFI is defined as time from start of treatment in adjuvant setting until recurrence, new invasive disease, or death from breast cancer. An RFI event will be defined according with the STEEP criteria:

- Ipsilateral invasive breast tumor recurrence: Invasive breast cancer involving the same breast parenchyma as the original primary.
- Local/regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to breast cancer.
- RFI specifically excludes ipsilateral or contralateral ductal carcinoma in situ, invasive contralateral breast cancer, second primary invasive cancers, and deaths not related with breast cancer.

b) RFS is defined as the time from start of treatment in adjuvant setting until recurrence, new invasive recurrence, or death from any cause. An RFS event will be defined according with the STEEP criteria:

- Ipsilateral invasive breast tumor recurrence: Invasive breast cancer involving the same breast parenchyma as the original primary.
- Local/regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.

- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.

- Death from any cause.

- RFS specifically excludes ipsilateral or contralateral ductal carcinoma in situ, invasive contralateral breast cancer, and second primary invasive cancers.

c) EFS is defined as the time until the first date of treatment to disease progression, including local progression that precludes surgery; disease recurrence—local, regional, distant, ipsilateral noninvasive, or contralateral (invasive or noninvasive)—or death from any cause.

d) EFS2 as an alternative to EFS is defined as the time until the first date of treatment to disease progression, including local progression before surgery; disease recurrence—local, regional, distant, ipsilateral noninvasive, or contralateral (invasive or noninvasive)—or death from any cause.

e) iDFS is defined as the time from the start of treatment in adjuvant setting until recurrence, new invasive breast cancer disease, or death by any cause. An iDFS event will be defined according to the updated recommendations for STEEP criteria (Tolaney et al., 2021) :

- Ipsilateral invasive breast tumor recurrence: Invasive breast cancer involving the same breast parenchyma as the original primary.

- Local/regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.

- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.

- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.

- Contralateral invasive breast cancer.

- iDFS specifically excludes ipsilateral or contralateral ductal carcinoma in situ, squamous or basal cell skin cancers, and new in situ carcinomas of any site, and second primary non-breast invasive cancers.

f) iDFS2 as an alternative definition of iDFS is defined as the time from start of treatment in adjuvant setting until recurrence, new invasive disease, or death by any cause. An iDFS event will be defined according with the STEEP criteria (Hudis et al., 2007):

- Ipsilateral invasive breast tumor recurrence: Invasive breast cancer involving the same breast parenchyma as the original primary.

- Local/regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- Second primary non-breast invasive cancer. Second non-breast primary cancers should not include squamous or basal cell skin cancers, or new in situ carcinomas of any site.
- iDFS2 specifically excludes ipsilateral or contralateral ductal carcinoma in situ, squamous or basal cell skin cancers, and new in situ carcinomas of any site.

g) DRFS is defined as the time from start of treatment in adjuvant setting until distant recurrence or death by any cause. A DRFS event will be defined according with the STEEP criteria:

- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- DRFS specifically excludes ipsilateral, local or regional invasive breast cancer recurrence, ipsilateral or contralateral ductal carcinoma in situ, invasive contralateral breast cancer, and second primary non-breast invasive cancer.

h) DFS is defined as the time from start of treatment in adjuvant setting until recurrence, new invasive disease, new ductal carcinoma in situ, or death by any cause. A DFS event will be defined according with the STEEP criteria:

- Ipsilateral invasive breast tumor recurrence: Invasive breast cancer involving the same breast parenchyma as the original primary.
- Local/regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- Second primary non-breast invasive cancer. Second non-breast primary cancers should not include squamous or basal cell skin cancers, or new in situ carcinomas of any site.

- New diagnosis of an ipsilateral or contralateral ductal carcinoma in situ.
- DFS specifically excludes squamous or basal cell skin cancers, and new in situ carcinomas of any site.
- i) OS is defined as the time from the first date of treatment until death by any cause.
- j) BCSS is defined as the time from the first date of treatment until death due to breast cancer.

6.8 Patient discontinuation

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs, and treatment failure after a prescribed procedure, protocol violation, administrative reasons, or for other reasons. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients without confirmed progression who by physician's choice are switched to chemotherapy during neoadjuvant treatment, will discontinue the study and not be included in the final analysis.

Should a patient decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible. Although the patient has no obligation to provide the reasons for his/her voluntary withdrawal, the investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal.

A complete final evaluation at the time of the patient's discontinuation from the study should be made. The principal specific reason for the removal of a patient from the study must be clearly stated in his/her medical records and will be recorded on the CRF.

In the case that the patient decides to prematurely discontinue study treatment, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the CRF.

6.9 Study and site discontinuation

The Sponsor reserves the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or seriousness of AEs in this or other studies indicates a potential health risk to patients.
- Patient enrollment is unsatisfactory.

- Data recording is inaccurate or incomplete.
- Excessively slow recruitment.
- Poor protocol adherence.
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP).

7 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and recording protocol-defined AEs, SAEs and non-serious adverse events of special interest (AESIs); measurement of protocol-specified hematology, clinical chemistry, measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee are responsible for reporting relevant SAEs to the CA competent authorities (CAs), other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, European Clinical Trials Regulation (EU Regulation Nr. 536/2014), and/or local regulatory requirements.

7.1 AEs definition

An AE is any untoward medical occurrence in a clinical study subject/patient administered a pharmaceutical product, which does not necessarily have a causal relationship with his/her treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, regardless of whether it is considered related to the medicinal (investigational) product.

AE reports will not be derived from PRO data. However, if any patient responses suggestive of a possible AE are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an AE, it will be reported on the AE eCRF.

The causal relationship between an AE and the IMP will be defined as below:

Not related: The temporal association between the adverse event and the IMP makes a causal relationship unlikely, or the subject/patient's clinical state or the study procedure/conditions provide a sufficient explanation for the adverse event.

Related: The temporal association between the adverse event and the IMP makes a causal relationship possible and the subject/patient's clinical state or the study procedure/conditions do not provide a sufficient explanation for the adverse event.

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the IMP drugs.

The descriptions and grading scales found in the revised NCI-CTCAE v.5.0 will be utilized for all toxicity reporting. A copy of the CTCAE v.5.0 can be downloaded from the CTEP website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

The intensity (severity) of an AE will be recorded as one of the following but also CTCAE Grade will be recorded:

- Mild - Easily tolerated and does not interfere with normal daily activities, CTCAE Grade 1.
- Moderate - Causes some interference with daily activities, intervention or treatment may be needed. CTCAE Grade 2.
- Severe - Normal daily activities are substantially impaired, hospitalization and/or intervention or treatment is required, CTCAE Grade 3 or 4.
- Fatal - Death, CTCAE Grade 5.
- Not applicable (clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments, for which no CTCAE grading guidance is applicable but which are considered as AEs).

A mild, moderate or severe AE may or may not be serious (see definition below). These terms are used to describe the intensity of a specific AE. However, a severe AE (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

7.1.1 SAEs definitions

Per definition, a SAE is defined as any adverse event that either:

- results in death (i.e., the AE actually causes or leads to death),
- is life threatening (i.e., the AE, in the view of the investigator, places the subject/patient at immediate risk of death when it occurs),

- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person ability to conduct normal life functions),
- is a congenital anomaly/birth defect (in a neonate/infant born to a mother exposed to the investigational product(s)).

7.1.1.1 Definition of life threatening

An AE is life threatening if the subject/patient was at immediate risk of death from the event as it occurred, i.e. does not include an event that might have caused death if it had occurred in a more serious form. For instance, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

7.1.1.2 Definition of hospitalization

AEs requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject/patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment which would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not to be notified according to immediate reporting criteria. If anything untoward is reported during any procedure, this must be reported as an AE and either 'serious' or 'non-serious' attributed according to the usual criteria.

7.1.1.3 Definition of clinically/medically significant event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clinically/medically significant events **MUST** be reported as SAEs.

In this clinical trial and as defined in this protocol, SAEs and hospitalizations unequivocally and solely related to established tumor disease progression will NOT be treated as SAEs for reporting obligations.

SAEs, if brought to the attention of the Investigator at any time after the cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment (so, in fact serious adverse reactions), will be reported to the Sponsor.

7.1.2 AESIs

AESIs must be reported by the Investigator to the Sponsor expeditiously (see **Section 7.2**), regardless of their seriousness (i.e., no more than 24 hours after learning of the event). AESIs for this study include:

PH FDC SC:

- CHF/LVSD
- Oligohydramnios/congenital abnormalities
- Interstitial lung disease

T-DM1:

Not applicable

General AESIs:

- Potential drug-induced liver injury as assessed by laboratory criteria for Hy's law. The following laboratory abnormalities define potential Hy's law cases and must be reported as an AESI:
 - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) elevations that are $>3 \times$ upper limit of normal (ULN)
 - Concurrent elevation of total bilirubin $>2 \times$ ULN (or clinical jaundice if total bilirubin measures are not available), except in patients with documented Gilbert's syndrome. For patients with Gilbert's syndrome, elevation of direct bilirubin $>2 \times$ ULN should be used instead.
- Suspected transmission of an infectious agent by a medication, whereby any organism, virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term **ONLY** applies when contamination of a medication is suspected and **DOES NOT** apply to infections supported by the mode of action, e.g., immunosuppression.

7.2 Adverse event reporting and other safety related issues reporting

AEs will be collected from the first study-mandated procedure until the safety follow-up visit to be done 28 days (\pm 7 days) after the last day of study treatment. All study subjects/patients will be carefully monitored for the occurrence of AEs during this period.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible. Any additional events that fall outside this definition should also be reported separately.

All AEs must be recorded in the CRF.

7.2.1 SAE reporting and timeframe

Reporting requirements will comply with all EU safety reporting requirements as detailed in “Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC”.

The investigator or investigator’s team will report all protocol defined SAEs and AESIs to the Sponsor (MEDSIR) no later than 24 hours of any site study team staff becoming aware of the event as follows:

- The full details of the SAE and/or AESI should be collected and fully documented using the SAE form and sent to MEDSIR.
- Follow-up information, copies of the results of any tests, the outcome of the event plus the investigator’s opinion of IMP relationship to the SAE(s) and AESI(s), and other document when requested and applicable, will accompany the SAE form as available on the day of reporting or provided as soon as possible thereafter.
- The original SAE Report Form and the fax confirmation sheet from the Sponsor must be kept with the CRF documentation at the study site(s).

All SAE forms will be sent by the investigator or investigator’s team to the Sponsor (MEDSIR) according to the reporting instructions provided by MEDSIR at the site initiation visit and filed in the Investigator’s File.

Serious adverse events (SAEs) will be collected from the first study-mandated procedure until the safety follow-up visit to be done 28 days (\pm 7 days) after the last day of study treatment. SAEs and AESIS will be followed until resolved, a stable outcome or baseline condition is reached, subject/patient is lost to follow-up or dies.

As Sponsor, MEDSIR will be responsible for ensuring that events are reported within the mandated timeframe to the EMA and other Competent Authorities, Institutional Review Boards /Institutional Ethics Committees (IRBs/IECs) and investigator(s), as necessary and in accordance with all applicable guidelines, approved directives and regulations. All safety reporting local regulatory requirements will be followed.

7.2.2 Expedited reporting to Health Authorities, Investigators, IRBs, and IECs

To determine reporting requirements for single SAE cases, MEDSIR (as Sponsor) or its designee will assess the expectedness of these events using the following reference documents:

- Current PH FDC SC IB
- Current Trastuzumab emtansine (IV) SmPC

MEDSIR (as Sponsor) or its designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Within 7 calendar days after being notified of the event, MEDSIR (as Sponsor) or its designee will report unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities, to the investigators and IRBs/IECs. MEDSIR (as Sponsor) or its designee will report other unexpected SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/IECs by a written safety report within 15 calendar days of notification. All safety expedited reports will be reported in accordance with all regulatory reporting obligations (including timelines) and local regulatory requirements.

7.2.3 Other safety-related reports

As Sponsor, MEDSIR will assess constantly the benefit/risk rate of the trial, that means a continuous evaluation of the safety profile of the drugs under investigation will be done using all available information. MEDSIR will provide the regulatory agencies and competent authorities and the investigators with any relevant information that may affect the benefit/risk rate of the trial. An annual Development Safety Update Report (DSUR safety report) for PH FDC SC and Trastuzumab emtansine IV will be prepared and distributed by MEDSIR or its designee in accordance to all regulatory reporting obligations and local regulatory requirements.

MEDSIR or its designee will report any finding of noncompliance (as failure to follow any applicable regulation or institutional policies that govern human subjects' research) and/or serious noncompliance (as noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants) according to any reporting obligation and local regulatory requirements.

7.2.4 Pregnancy reporting

Irrespective of the treatment received by the subject/patient, any subject/patient's or subject/patient's partner pregnancy occurring during study treatment or during the 7 months following study drug discontinuation must be reported within 24 hours of investigator's knowledge of the event.

Pregnancies will be treated as SAEs and the investigator will complete a pregnancy form, and forward it to the Sponsor according to the reporting instructions provided by MEDSIR at the site initiation visit and filed in the Investigator's File.

The subject/patient will be asked to provide follow-up information on the outcome of the pregnancy, including premature termination should the case arise and on the infant until 12 months of life. Spontaneous miscarriage and congenital abnormalities will also be reported as SAEs. Follow-up queries may be sent, asking for further information, if required for a comprehensive assessment of the case.

The follow-up period will be deemed to have ended when the health status of the child has been determined at 12 months of the infant's life.

Additional follow-up information on any PH FDC SC / Trastuzumab emtansine IV -exposed pregnancy and infant will be requested at specific time points (i.e., after having received the initial report, at the end of the second trimester, two weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

In case of a report of a pregnancy or congenital abnormality following exposure to PH FDC SC and/or T-DM1, in addition, a guided questionnaire will be sent out by Roche Drug Safety.

8 STATISTICAL CONSIDERATIONS

8.1 Study design and sample size

A total of 393 patients will be enrolled in the study. Adjuvant systemic therapy will be started within 4 weeks from surgery and depending on the pathological report patients will be assigned to one of the following three cohorts:

- **Cohort A** (pCR in breast and axilla [ypT0/is, ypN0]): Patients will receive PH FDC SC ± ET for 10 additional cycles.
- **Cohort B** (residual invasive breast tumor and/or ypN0(i+), ypN0(mol+), ypN1mi): Patients will receive T-DM1 ± ET for 10 cycles
- **Cohort C** (pathological progression to nodes [ypN1-N3]): Patients will receive T-DM1 ± ET for 10 cycles, with possibility of physician's choice chemotherapy, according to ESMO or NCCN 2021 guidelines, before adjuvant T-DM1.

8.2 Analysis sets

Full analysis set (FAS) in adjuvant setting

All the patients who have surgical excision of the primary tumor.

The FAS will be the analysis set for primary efficacy endpoint. All secondary efficacy and safety endpoints in adjuvant setting will be analyzed in this set of analysis (RFS, iDFS, DRFS, DFS, OS, BCSS, and AEs reporting including toxicity).

Quality of life analysis set (QoLS) in neoadjuvant setting

Quality of life (QoL) assessment applies together with the clinical exam at baseline, on day 1 of each neoadjuvant treatment cycle, within at least 2 weeks but no more than 4 weeks prior to surgery. Data must be registered within the electronic CRF.

For patients who progress to neoadjuvant anti-HER2 treatment and receive alternative neoadjuvant treatment, QoL assessment must also be done prior to start alternative treatment. The QoLS will be the analysis set for primary safety endpoint. All QoL endpoints in neoadjuvant setting will be analyzed in this set of analysis (EORTC-QLC-C30 and QLQ-BR23 scales).

Full analysis set (FAS) in neoadjuvant setting

All patients having received at least 1 dose of treatment at the neoadjuvant setting.

All efficacy and safety endpoints in neoadjuvant setting will be analyzed in this population (pCR rates, RCB score, rate of BCS, MRI-guided response rate, EFS, and AEs reporting including toxicity).

Quality of life analysis set (QoLS) in adjuvant setting

Patients are evaluable for QoL analysis if they have surgical excision of the primary tumor and have completed their baseline evaluation for the adjuvant setting.

Quality of life (QoL) assessment applies on day 1 of the first adjuvant treatment cycle, every 3 months for the first two years after surgery, every 6 months for the next 3 years, and every year after the 5th year. Data must be registered within the electronic CRF.

All QoL endpoints analyzed specifically in adjuvant setting will be analyzed in this set of analysis (EORTC-QLC-C30 and QLQ-BR23 scales).

Per-Protocol (PP) set in adjuvant setting

All patients that accomplished selection criteria and received the protocol required study drug exposure and processing. Criteria for determining the PP group assignment would be established by the Steering Committee before the statistical analysis begins.

Per-Protocol (PP) set in neoadjuvant setting

All patients that accomplished selection criteria and received the protocol required study drug exposure and processing. Criteria for determining the PP group assignment would be established by the Steering Committee before the statistical analysis begins.

Analysis schedule:

Efficacy and subgroup analysis will be performed on the full analysis and PP sets. The FAS will be considered the primary population of analysis.

The primary safety endpoint and QoL endpoints will be analyzed in the QoLS. The other safety endpoints will be evaluated in FAS.

8.3 Primary endpoint of efficacy

The primary efficacy analysis will estimate the 3y-RFI rate. This primary efficacy analysis will be based on full analysis set and will include all the patients who had surgical excision of the primary tumor. We have planned a sensitivity analysis with per protocol approach. Patients who receive chemotherapy in the neoadjuvant phase will be included in the full analysis set. However, these subjects will be excluded from the per protocol analysis set together with non-compliant patients (see **Section 8.2**).

The primary analysis is to estimate the 95% confidence interval for the 3y-RFI rate based on Kaplan-Meier estimator. The analysis will test the null hypothesis that the true 3y-RFI rate is equal or lower than 94%. The alternative hypothesis is that the true distribution of 3y-RFI in these patients had a rate greater than 98%. This analysis will be declared positive if the lower boundary for the 95% confidence interval is higher than 94%. Additionally, we will describe the number and the rate of patients with RFI events. The confidence intervals will be calculated according to Clopper Pearson method and defined as exact binomial intervals.

8.4 Primary endpoint of safety

The primary safety analysis will estimate the Global health status decline rate at 1 year from start of neoadjuvant treatment. It is defined as the rate of patients with a $\geq 10\%$ global health status decline at 1 year from start of neoadjuvant treatment by the Global Health Status/QoL EORTC-QLC-C30 scale. This primary safety analysis will be based on quality of life analysis set (QoLS) (see **Section 8.2**). We will include all the patients with neoadjuvant treatment, with baseline, and at least one follow-up QoL evaluations (Quality of life analysis set (QoLS) in neoadjuvant setting). The statistic test for this safety analysis is assumed to be 95% confidence interval based on Kaplan-Meier estimator. The confidence intervals will be considered descriptive. Additionally, we will describe the number and the rate of patients with $\geq 10\%$ global health status decline at 1 year.

The confidence intervals will be calculated according to Clopper Pearson method and defined as exact binomial intervals.

8.5 Justification of null and alternative hypotheses

In the KRISTINE Trial, 444 patients were randomly assigned to neoadjuvant T-DM1 plus pertuzumab (n = 223) or docetaxel/carboplatin/trastuzumab plus pertuzumab (n = 221) every 3 weeks for six cycles. Three-year invasive disease-free survival was 92.0% vs 93.0%.

Initial results from ongoing clinical trials such as the phase III APHINITY trial have also showed pertuzumab significantly improves the rates of RFS among patients with HER2[+], operable breast cancer when added to trastuzumab and chemotherapy (von Minckwitz et al., 2017). The patients with Pertuzumab plus chemotherapy (N=2400) achieve a 3y-RFS rate of 95.2% and the subgroup of patients with node negative status (N=897) achieve a 3y-iDFS rate of 98.4%. However, patients recruited in KRISTINE and APHINITY trials included node positive patients, with tumor size > 2.5 cm and HER2 IHC 2+ status. Additionally, the adjuvant treatment was assigned in accordance with a pCR guided strategy. Accordingly, rejecting a 3y-RFI rate lower than 94% (which represents the null hypothesis) would be a conservative approach to assess the chemotherapy-free strategy in HER2[+] early breast cancer patients. Moreover, we defined as clinically meaningful efficacy a 3y-RFI rate greater than or equal to 98% (which represents the alternative hypothesis).

8.6 Justification of drop-out rate assumption

We have assumed a 20% drop-out rate due to the relevance of some secondary endpoints evaluated at 3 and 5 years (Rate of EFS, RFI, RFS, iDFS, DRFS, DFS, OS, and BCSS at 5 years). We have based our assumption in Results 1 of Tolaney et al. 2019. They recruited a cohort of 406 node-negative HER2[+] breast cancer patients who were treated with adjuvant paclitaxel in combination with trastuzumab. After a median follow-up of 6.5 years, they reported 119 patients (29.3%) discontinued at the end of follow-up, including 15 deaths and 30 patients discontinued due to toxicity. In the PHERGain-2 trial, deaths will be also considered as events in DFS analyses and although pertuzumab and T-DM1 should have a better toxicity profile than paclitaxel, discontinuations are also expected, mainly with T-DM1. Therefore, we exclude deaths and patients discontinued due to toxicity to calculate the drop-out rate expected in our study. In accordance, we should expect a 20% drop-out rate (74 among 406 patients equals to 18.2% ≈ 20%).

8.7 Sample size calculation

Primary analysis of efficacy:

The statistical analysis will estimate a one sample non-parametric confidence interval for the 3y-RFI rate. The statistical method assumed for sample size was the log-minus-log Kaplan-Meier

estimator. We assumed an accrual period of 18 months and an additional 42 months of follow-up for primary analysis. For secondary analyses 68 months of follow-up has been planned (maximum follow-up of 6 to 7 years). We hypothesize that excluding a 94% 3y-RFI rate while targeting an improvement of the 98% 3y-RFI rate (4% absolute increase) would be an optimal approach to evaluate the clinical efficacy of trastuzumab, pertuzumab and T-DM1 for HER2[+] early breast cancer patients. With the expectation a 20% dropout rate, a sample size of N = 393 patients is necessary to attain 80% power at nominal level of two-sided alpha of 0.05.

8.8 Secondary efficacy endpoints

The secondary efficacy variables are pCR rate, RCB score, rate of BCS, MRI-guided response (by BCS, pCR, and RCB), 3 and 5-year RFI, RFS, EFS, iDFS, DRFS, DFS, OS, BCSS, and QoL (see **Section 6.7**).

pCR_{BREAST+LYMPH NODES}: This is defined as no invasive residuals in the breast and lymph nodes (ypT0/isN0). It will be also evaluated according to HR status and tumor stage.

pCR_{BREAST}: This is defined as no invasive residuals in the breast only (ypT0/is). It will be also evaluated according to HR status and tumor stage.

RCB score: This is defined as a variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden). It is a numeric index with numerical cut points to define the four classes (RCB-0: No carcinoma in breast or axillary lymph nodes; RCB-1; RCB-2; and RCB-3). RCB will be estimated from pathologic sections of the primary breast tumor site and the axillary lymph nodes after the completion of neoadjuvant therapy.

Rate of BCS: This is defined as the proportion of patients who achieved breast conserving surgery.

Tumor response rate by MRI: This is defined as best response, in terms of complete response, partial response, stable disease, and progressive disease. ORR will be defined as the proportion of patients with best overall response of confirmed complete response or partial response. Evaluation will be based on central radiological assessment according to the RECIST criteria version 1.1.

Time-to-Event Measures Definitions

EFS: This is defined as the time from first date of treatment to disease progression, including local progression before surgery; disease recurrence—local, regional, distant, ipsilateral noninvasive, or contralateral (invasive or noninvasive)—or death from any cause.

DFS outcomes: This is defined as the time from enrolment in adjuvant setting until the first documentation of recurrence or death. We will consider five definitions in accordance with the STEEP criteria: RFI, RFS, iDFS, DRFS, and DFS (refer to **Section 6.7.6**). Patients who are

withdrawn from the study without documented recurrence or death will be censored at the date of the last assessment when the patient was known to be disease-free.

OS: This is defined as the time from the first treatment until death by any cause or the last date the patient was known to be alive. Patients who are lost to follow-up and the patients who are alive at the date of data cut-off will be censored at the date the patient was last known alive.

BCSS: This is defined as the time from the first treatment until death by breast cancer, or the last date the patient was known to be alive. Patients who are lost to follow-up, who are alive at the date of data cut-off, or death for other causes will be censored at the date the patient was last known alive, or last date of follow-up.

8.9 Analysis of baseline and demographic variables

The demographics and baseline characteristics will be summarized using descriptive statistics each analysis set.

8.10 Analysis of secondary endpoints

The number and proportion of patients with pCR, RCB, BCS and MRI response rates with the 95% Pearson-Clopper CI will be calculated. The pCR will be also evaluated according to HR status and the MRI response according pathological and breast conserving responses.

We will provide Kaplan-Meier plots for time-to-event endpoints (RFI, RFS, iDFS, EFS, DRFS, DFS, BCSS, and OS). The time-to-event endpoints will be also evaluated according to study cohort (A, B, and C) separately. We will estimate median and the 95% CI. We will provide the 3 and 5-year survival rates with corresponding 95%CI. Additionally, we will describe the number and the rate of patients with time-to-event events. The confidence intervals will be calculated according to Clopper Pearson method and defined as exact binomial intervals.

8.11 Subgroup analysis

RFI, RFS, iDFS, DRFS, DFS, global health status decline rate at 1 year after neoadjuvant treatment, EFS, QoL scores, BCSS, and OS will be analyzed in patients' subgroups categorized based on factors of potential prognostic value. The baseline factors will include but not limited to the following: (1) age, (2) HR, (3) study cohort, (4) BCS, (5) MRI response, and (6) neoadjuvant chemotherapy, (7) tumor size, (8) menopausal status, and (9) duration of hormonal therapy. The subgroup analysis will be performed on the full analysis and PP sets.

The Cox proportional hazards model will be used to test the association between prognostic factors and the time-to-event outcomes if sample size is adequate. Covariate estimates, hazard ratio and corresponding 95% CIs, applicable test statistics, and P-values will be presented. We will use the Breslow method for tie handling in survival analysis. P-values and 95% CIs for hazard ratio will be based on likelihood ratio test and profile likelihood confidence intervals. Mean and

mean change from baseline QoL scores were analyzed by mixed effect model repeat measurement (MMRM). In the MMRM analysis, change from baseline was the dependent variable. It will be adjusted for baseline values, treatment group, visit, and HR status.

The pCR will be also evaluated according to HR status and the MRI response according pathological and breast conserving responses. For binary outcomes we will use logistic regression for adjusting for multiple prognostic factors if sample size is adequate. Covariate estimates, odds ratios and corresponding 95% CIs and applicable test statistics, P-values will be presented. P-values and 95% CIs for odds ratio will be based on likelihood ratio test.

The statistical analysis plan did not include a provision for correcting for multiplicity in tests for secondary and exploratory analyses. For all tests, we will use two-sided P-values compared to a significance level of 0.05. The P-values emerging from these analyses will not be interpreted in a confirmative sense but will be considered of descriptive nature only.

8.12 Secondary safety results

Health-related quality of life outcomes

This will be evaluated with the EORTC QLQ-C30 and the QLQ-BR23 questionnaires (refer to **Section 6.5**). Quality of life outcomes will be determined in operable study cohorts at baseline, during treatment and at different post-treatment periods (refer to Section 6.5). These endpoints will be analyzed in QoL sets of analyses. We will describe visit scale scores in HRQoL questionnaires and difference against baseline as mean, standard deviation, medians, interquartile range, range, and 95%CI of mean and median.

The other secondary safety endpoints will be analyzed in neoadjuvant and adjuvant treatments in FAS.

Adverse events

The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary will be applied for the coding of AEs. NCI-CTCAE toxicity Grades will be utilized for classifying severity.

Adverse events, related adverse events, serious adverse events and related serious adverse events, adverse events with NCI-CTCAE Grades ≥ 3 , related adverse events with NCI CTCAE Grades ≥ 3 , adverse events leading to premature discontinuation, interruptions or discontinuation of study drug or dose modification will be analyzed descriptively utilizing corresponding MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs).

Deaths within 28 days after the last dose and the corresponding reasons will be summarized. Also, all deaths overall will be summarized.

Vital signs

Vital signs will be summarized by descriptive statistics at each visit. We will include change from baseline and patient listings will be provided.

Safety Laboratory

Laboratory values will be graded by NCI-CTCAE version 5 (or higher), if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline (screening). Shift tables for CTCAE grades and normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

Electrocardiogram (ECG)

ECG data will be listed overall and a separate listing for any clinically significant finding in ECG values will be provided. Change from baseline in QT intervals by cohort will be summarized for each visit as well as change from baseline in all other ECG parameters. Also, the worst change from baseline will be summarized. The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated by cohort.

Duration of treatment, duration of follow-up, and extend of exposure

The duration of follow-up in months will be summarized with descriptive statistics. The duration of treatment will be also summarized in months and number of cycles for each treatment.

The number of patients with delays, reductions and discontinuations and their reasons will be summarized with descriptive statistics.

The relative dose intensity will be summarized with descriptive statistics.

Other parameters

Eastern Cooperative Oncology Group (ECOG) status, physical examinations, body weight, exposure to study medication and will be summarized by descriptive statistics at each visit. We will include change from baseline and patient listings will be provided.

Prior and concomitant medications

Prior and concomitant medications will be summarized by therapeutical group in accordance to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification.

All safety data will be reported with patient listings.

8.13 Schedule for primary and secondary analyses

The first primary safety analysis (Global health status decline rate) will occur after last patient with one dose of neoadjuvant treatment has completed the 1-year follow-up or has been discontinued. The analysis will be considered descriptive. We will also evaluate the secondary safety, efficacy and QoL endpoints in neoadjuvant setting (pCR rates, RCB score, rate of BCS, MRI-guided response rate, EFS, AEs reporting including toxicity, and EORTC-QLC-C30 and QLQ-BR23 scales).

The first primary efficacy analysis (3y-RFI) will occur after last patients with primary tumor surgery has completed the 3.5 years of follow-up or has been discontinued. The primary analysis will be evaluated with a significance level of 0.05. We will also evaluate the secondary safety, efficacy and QoL endpoints at 3-years of follow-up in adjuvant setting (3y-RFS, 3y-iDFS, 3y-DRFS, 3y-DFS, 3y-OS, 3y-BCSS, 3y-EFS, AEs reporting including toxicity, and EORTC-QLC-C30 and QLQ-BR23 scales.)

The analyses at the end of follow-up will occur after last patients with primary tumor surgery has completed the 68 months of follow-up or has been discontinued. We will evaluate the secondary safety, efficacy and QoL endpoints at 5-years of follow-up in adjuvant setting (5y-RFI, 5y-RFS, 5y-iDFS, 5y-DRFS, 5y-DFS, 5y-OS, 5y-BCSS, 5y-EFS, AEs reporting including toxicity, and EORTC-QLC-C30 and QLQ-BR23 scales).

The primary, secondary and subgroup analyses will be reported as point estimates, 95% confidence intervals and p-values. For all secondary analysis tests, we will use two-sided p-values with a significance level of 0.05. The intervals and p-values will be considered descriptive.

8.14 Missing data management

Study variables could be missing for patients who withdrawn from the trial or for specific visits. We will report and summarize reasons for withdrawal. The analysis of time-to-event endpoints is based on a Kaplan-Meier method, therefore, not affected by patient withdrawals (as they are censored) provided that dropping out is unrelated to prognosis. Patients for whom response could not be assessed (pCR, MRI, RCB, and BCS) will be considered not to having response. Missing values in QoL endpoints will be managed based on mixed effect model repeat measurement, assuming missing at random. The other variables will be managed with simple imputations methods (last observation carried forward). The effect that any missing data might have on results will be assessed via sensitivity analysis of study sets.

8.15 Scientific committee review

A Steering Committee will be established for this study. It will be composed of the investigators, the sponsor's medical scientist and the scientific global coordinator. Further details on the steering committee and its responsibilities will be provided in a separate document.

The Steering Committee will meet on demand to review, discuss, and evaluate all of the gathered efficacy and safety data. In case of any arising safety concern, these meetings can also be called at any time at request of a participating investigator. At these meetings, the Sponsor and the participating investigators must reach a consensus on study data. The Sponsor will prepare minutes from these meetings and circulate them to each investigator for comment prior to finalization.

Study site investigators and the Sponsor will review patient data at least every six months. Each study site investigator will monitor patient's data for serious toxicities on an ongoing basis.

9 ETHICAL CONSIDERATIONS

9.1 Regulatory and ethics compliance

The study will be performed and reported in accordance with the guidelines of the International Conference on Harmonization (ICH), and the ethical principles laid down in the Declaration of Helsinki. The study will be also compliance with the European Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, as well as any other applicable local requirements.

9.2 IRBs/IECs

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, protocol amendments, informed consent forms, study subject information sheets, and advertising materials. The IRB/IEC must also be contacted in the event of any major protocol violation or any SAE.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all phases during the study.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC/CA of any protocol amendments (approval is required before implementation of substantial amendments).

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC/CA all unanticipated problems involving risk

to human patients. Some IRBs/ECs/CA may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written safety reports or other safety related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC/CA and archived in the site's study file.

9.3 Informed consent

For each study subject, written informed consent will be obtained prior to any protocol related activities. As part of this procedure, the study site Investigator or designee must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drugs in such a manner that the study subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. The subject will receive all information that is required by local regulations and ICH guidelines.

The Consent Form must be signed and dated by the patient or the patient's legally authorized representative before her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative, if applicable.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to the Sponsor for regulatory purposes.

9.4 Data protection

The Sponsor will ensure the confidentiality of patient's medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data

[95/46/EC] confirms herewith compliance to Directive 95/46/EC in all stages of Data Management.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

10 SOURCE DOCUMENTATION, STUDY MONITORING AND QUALITY ASSURANCE

10.1 Source data documentation

Source data refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (i.e., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Sponsor's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

At a minimum, source documentation must be available to substantiate subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; adequate reporting and follow-up of AEs; administration of concomitant medication; study receipt/dispensing/return records; study administration information; and date of completion and reason.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records) in order to ensure data completeness and accuracy as required by study protocol. The Investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by MEDSIR or its representative at the time of each monitoring visit.

The source documents must also be available for inspection, verification, and copying, as required by regulations, officials of the regulatory health authorities (i.e., FDA, EMEA, and others), and/or ECs/IRBs. The Investigator and study site staff must comply with applicable privacy, data protection, and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

The patient must also allow access to the patients' medical records. Each patient should be informed of this prior to the start of the study.

10.2 Study monitoring and source data verification

Study progress will be monitored by MEDSIR or its representative (i.e., a CRO) as frequently as necessary to ensure:

That the rights and well-being of human subjects are protected;

- the reported trial data are accurate, complete, and verifiable from the source documents; and
- the conduct of the trial follows the current approved protocol/amendment(s), GCP, and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be identified in a handout located in the Investigator Site File.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records, subject diaries) in order to ensure data completeness and accuracy as required by study protocol. The Investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit.

10.3 Retention of records

Investigators must retain all study records required by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The

CHMP requires retention for the maximum period of time permitted by the institution, but not less than 15 years (ICH E6, 4.9.5). It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained (ICH E6, 5.5.12).

The study site Investigator must not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The study site Investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA and/or EMA (or respective individual EU country regulatory authorities).

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

10.4 Data quality assurance

During and/or after completion of the study, quality assurance auditor (s) named by the MEDSIR or the regulatory authorities may wish to perform on-site audits. The Investigators will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

The Sponsor's representatives are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (i.e., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH E6 Good Clinical Practice (GCP) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) Quality Assurance Department. Inspection of site facilities (i.e., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (ICH E6), and applicable country regulatory requirements.

11 DATA MANAGEMENT

11.1 Data entry and management

In this study, all data will be entered onto CRFs in a timely fashion by the Investigator and/or the Investigator's dedicated site staff.

The Investigator must review data recorded in the CRF to verify their accuracy.

Reconciliation of the data will be performed by the designated CRO. At the conclusion of the study, the occurrence of any protocol violations will be identified and recorded as part of the clinical

database. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and will become available for statistical data analysis.

11.2 Data clarification

As part of the conduct of the trial, MEDSIR may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query.

11.3 Data coding procedures

Coding of AEs, medical history, and prior and concomitant medications will be performed using standard dictionaries as described in the Data Management Plan.

12 STUDY MANAGEMENT

12.1 Discontinuation of the study

MEDSIR reserves the right to discontinue the study for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all investigational drugs pertaining to the study must be returned to MEDSIR. Any actions required to assess or maintain study subject safety will continue as required, in spite of termination of the study.

12.2 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment or administrative letter that must be approved by MEDSIR, the Scientific Global Coordinator, the study site Investigator, and the IRB/IE/CA before implementation. This requirement for approval should in no way prevent any immediate action from being taken by the study site Investigator or MEDSIR in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the study site Investigator and is implemented for safety reasons, MEDSIR should be notified as soon as possible (within 24 hours if possible) and the IRB/IE/CA should be informed as necessary.

12.3 Publication policy protection of trade secrets

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the Scientific Global Coordinator and MEDSIR. However, authorized regulatory officials, the Scientific Global Coordinator or the study site Investigator, and MEDSIR personnel (or their representatives) will be allowed full access to inspect and copy the records. All clinical

investigational drug, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Scientific Global Coordinator or the study site Investigator and MEDSIR.

The Sponsor will ensure that as far as possible results of this study will be published as scientific/clinical papers in high-quality peer-reviewed journals. Preparation of such manuscripts will be made with full collaboration of principal Investigators and in accordance with the current guidelines of Good Publication Practice.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from Sponsor must be obtained prior to publication.

12.4 Dissemination of clinical study data

A description of this clinical study will be available on <http://www.clinicaltrials.gov> and <https://www.clinicaltrialsregister.eu/> as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

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14 APPENDIX 1: Schedule of study assessments and procedures

For all cohorts: A (PH FDC SC ± ET), B (T-DM1 ± ET) and C (T-DM1 ± ET and optional chemotherapy)

	SCREENING	BASELINE	TREATMENT PERIOD 1 ¹	BEFORE SURGERY	TREATMENT PERIOD 2 ¹ (after surgery up to cycle 18)		FOLLOW-UP ² (from surgery until EoS)
	Day -28 to Day -1	Day -7 to Day 1 (cycle 1)	Day 1 of each cycle (total of 8 cycles)	Day -28 to Day -1 pre-surgery (after 8 cycles)	Day 1 (Cycles 9-18)	End of Treatment or Withdrawal from Study Treatment (after 28 days ± 7 days)	
Informed consent ³	X						
Centrally confirmed HER2 status	X						
Hormone receptor status	X						
Demographics and medical history ⁴	X						
Menopausal status	X						
Chest and pelvis CT/MRI scan	X						
Bone scan or PET-FDG ⁵	X (only if there is suspicion of bone metastases)						
ECOG performance status ⁶	X	X	X	X	X	X	

	SCREENING	BASELINE	TREATMENT PERIOD 1 ¹	BEFORE SURGERY	TREATMENT PERIOD 2 ¹ (after surgery up to cycle 18)		FOLLOW-UP ² (from surgery until EoS)
	Day -28 to Day -1	Day -7 to Day 1 (cycle 1)	Day 1 of each cycle (total of 8 cycles)	Day -28 to Day -1 pre-surgery (after 8 cycles)	Day 1 (Cycles 9-18)	End of Treatment or Withdrawal from Study Treatment (after 28 days ± 7 days)	
Physical examination and vital signs ⁷		X	X	X	X	X	X (every 3 months during 1 st year / every 6 months during 2 nd and 3 rd year up to 3 years from surgery)
Height		X					
Weight		X	X		X		
Assessment of symptoms	X		X	X	X	X	
Mammography ⁸	X			X		X	X (only mammography every 12 months up to 3 years from surgery)
Breast and axillary US ± FNA	X						
Breast MRI	X ⁹		X ¹⁰	X ¹⁰			
LVEF (ECHO or MUGA scan)	X		X ¹¹ (before cycle 5)		X ¹¹ (before		X (every 6 months until 24 months from the last administration of study treatment)

	SCREENING	BASELINE	TREATMENT PERIOD 1 ¹	BEFORE SURGERY	TREATMENT PERIOD 2 ¹ (after surgery up to cycle 18)		FOLLOW-UP ² (from surgery until EoS)
	Day -28 to Day -1	Day -7 to Day 1 (cycle 1)	Day 1 of each cycle (total of 8 cycles)	Day -28 to Day -1 pre-surgery (after 8 cycles)	Day 1 (Cycles 9-18)	End of Treatment or Withdrawal from Study Treatment (after 28 days ± 7 days)	
					cycles 9, 13, 17)		
Standard 12-lead ECG	X		X ¹¹ (before cycle 5)		X ¹¹ (before cycles 9, 13, 17)		X (every 6 months until 24 months from the last administration of study treatment)
Clinical exam including QoL assessment (EORTC QLQ-C30 and QLQ-BR23 questionnaires)		X	X	X	X (only on day 1 of cycle 9)	X	X (every 3 months for the first two years partially coinciding with the adjuvant treatment period, every 6 months for the next 3 years, and then every year until EoS)
Pregnancy test	X (serum)	X (urine, serum only for confirmation)	X (every 4 cycles: C5D1, before surgery; urine; serum only for confirmation)	X (urine, serum only for confirmation)		X (urine, serum only for confirmation)	X (every 3 months up to 7 months after discontinuation of either treatment; urine, serum only for confirmation)

	SCREENING	BASELINE	TREATMENT PERIOD 1 ¹	BEFORE SURGERY	TREATMENT PERIOD 2 ¹ (after surgery up to cycle 18)		FOLLOW-UP ² (from surgery until EoS)
	Day -28 to Day -1	Day -7 to Day 1 (cycle 1)	Day 1 of each cycle (total of 8 cycles)	Day -28 to Day -1 pre-surgery (after 8 cycles)	Day 1 (Cycles 9-18)	End of Treatment or Withdrawal from Study Treatment (after 28 days \pm 7 days)	
Hematology, coagulation, and serum chemistry ¹²	X	X	X	X	X	X	X (every 6 months for the first 5 years)
Tissue samples	X		X (from surgery)				
Blood samples for exploratory study ¹³		X	X (C3D1 pre-treatment)	X (2 weeks pre-surgery)	X (every 6 months for the first 5 years, and every year thereafter)		
Concomitant medications ¹⁴		X	X	X	X	X	X
Study treatment		X		X	X		
AEs/SAEs assessment	X		X	X	X	X	
Complete survival follow-up							X

AE: Adverse event; ECG: Electrocardiogram; ECHO: Echocardiography; ECOG: Eastern Cooperative Oncology Group; FNA: Fine needle aspiration; MUGA: Multiple-gated acquisition; SAE: Serious adverse event; US: Ultrasound.

1. All treatment visits must occur within \pm 3 working days from the scheduled date. Cycles will last 21 days. All follow-up visits must occur within + 14 working days from the scheduled date. If treatment visits and follow-up visits overlap in time within + 14 working days, the study assessments, and procedures common to both visits should be performed just once.

2. *Since FU period starts after surgery, visits FU1 and FU2 will be done during adjuvant treatment.*
3. *Signed written informed consent obtained prior to any trial-specific procedure. Since some of the procedures required by this study protocol form part of regular medical care (tumor biopsy, physical examination, thorax, abdomen, pelvis, breast CT/MRI scan, mammography, breast ultrasound), if patient have had some of them previously, they do not need to be repeated as long as they fall within the specified time frames.*
4. *Complete medical history, demographics (including age, gender, and ethnic origin), and all medications taken the last 28 days prior to enrollment will be collected.*
5. *Bone scan or PET-FDG scan to rule out metastatic disease (including bone metastasis) will be performed before enrolment only if suspicion of bone metastases.*
6. *ECOG performance status will be assessed before trial drug administration and before the administration of each cycle.*
7. *Physical examination will include, as part of tumor assessment, evaluation of the breast and regional lymph nodes. In addition to an examination of head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, digestive, genitourinary, and neurological systems. Vital signs assessment will include respiratory rate, blood pressure measurements, heart rate, and body temperature.*
8. *Screening mammography does not need to be repeated if patient has had a mammography performed within 6 weeks prior to enrollment. Patients who received adjuvant radiation therapy (RT) should only undergo mammography 6 months after the last RT session.*
9. *When a patient is identified and all the study screening criteria have been met, breast MRI will be performed up to a maximum of 28 days +/- 7 days before starting the study treatment.*
10. *Breast MRI will also be performed during neoadjuvant treatment if the physician suspects there is tumor growth and progression, or lack of response to treatment and within 2 weeks prior to surgery. Medical images derived from tumor assessments (except bone scans) will be stored for exploratory analyses at MEDSIR's central imaging repository.*
11. *During study treatment, cardiac assessments - using the same method as performed at baseline - should be repeated every 12 weeks as close to the assigned week as possible but prior to the next infusion, before cycle 5 during period 1, before cycles 1, 5, and 9 during period 2 (e.g.: between days 15-21 of the previous cycle to allow evaluation of the results before the indicated cycle).*
12. *Blood test will be performed as per local standard of care and clinical indication before treatment administration. For C1D1, blood samples extracted up to 72 hours before the cycle can be used. These values are recommended to be included: hemoglobin, hematocrit, red blood cell count, platelet count, and white blood cell count with differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), coagulation, chemistry with renal function analysis (serum creatinine, creatinine clearance according to the Cockcroft-Gault formula), liver function (AST, ALT, ALP, gamma-glutamyl transferase [GGT], total and direct bilirubin), glucose, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.*
13. *Approximately 20 mL of blood (2 STRECK tubes of 10mL) for exploratory study will be obtained at baseline, after two cycles of neoadjuvant therapy (C3D1 before treatment infusion), pre-surgery (2 weeks before surgery). In addition, blood samples will be collected at each follow-up visit during adjuvant treatment (every 6 months for the next 5 years, and every year thereafter until the EoS).*
14. *Relevant concomitant medication will be recorded at screening and on an ongoing basis.*