PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN COMBINATION WITH CHEMOTHERAPY IN CHINESE PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
PROTOCOL NUMBER:	YO41137
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	Not applicable
NCT NUMBER:	NCT04024462
TEST PRODUCT:	Fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
MEDICAL MONITOR:	[redacted], M.D. [redacted], *Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
28-Jul-2020 07:34:07	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	14 January 2019

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol YO41137 has been amended to allow immunohistochemistry (IHC) 2+ tumor samples to be sent for in situ hybridization (ISH) testing at the central laboratory for HER2 status if ISH cannot be performed locally. Changes to the protocol, along with a rationale for each change, are summarized below:

- It has been clarified that the 9-week period between neoadjuvant treatment and adjuvant treatment begins when the final dose of neoadjuvant treatment is administered (Figure 2).
- It has been corrected that trastuzumab will be supplied for use as a freeze-dried preparation at a nominal content of 440 mg per vial (not 150 mg per vial) (Section 4.3.1.2).
- It has been amended that if ISH testing cannot be performed locally, sites will have the option to send samples with a local IHC score of 2+ for direct ISH testing by the central laboratory (Section 4.5.3 and Figure 3). This is expected to increase recruitment rate, as patients with borderline IHC+2 tumor tissues who were not being screened locally can now be screened centrally.
- It has been clarified that patients who did not receive any HER2-targeted therapy will not be required to give pharmacokinetic or anti-drug antibody blood samples during follow-up (Section 4.6.4 and Appendix 3).
- Text has been modified to account for the fact that special situations (i.e., accidental overdoses and medication errors are not required to be reported within 24 hours (Sections 5.4.5.11 and 5.5). Note that serious adverse events associated with special situations are still required to be reported within 24 hours.
- Language has been added to indicate that the study will comply with applicable laws of the country (Section 8.1).
- A new section has been added to describe the implementation of a system to manage the quality of the study (Section 9.3).
- Language has been revised to clarify that data posting will not be limited to two clinical trial registries and to clarify that redacted Clinical Study Reports will be made available upon request (Section 9.6).
- It has been clarified that tissue samples should not be prepared as fresh frozen tissue during this study (Appendix 9).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN COMBINATION WITH CHEMOTHERAPY IN CHINESE PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
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SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, MULTICENTER, OPEN-LABEL, TWO-ARM STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, AND SAFETY OF SUBCUTANEOUS ADMINISTRATION OF THE FIXED-DOSE COMBINATION OF PERTUZUMAB AND TRASTUZUMAB IN COMBINATION WITH CHEMOTHERAPY IN CHINESE PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER**
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TEST PRODUCT:	Fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous administration (RO7198574)
PHASE:	Phase III
INDICATION:	HER2-positive Early Breast Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the pharmacokinetics, efficacy, and safety of the fixed-dose combination (FDC) of pertuzumab and trastuzumab for SC administration compared with the Perjeta IV and Herceptin IV formulations in Chinese patients with HER2-positive early breast cancer (EBC).

Specific objectives and corresponding endpoints for the study are outlined below.

Co-Primary Objectives	Corresponding Endpoint
• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} of pertuzumab SC within the FDC compared with Perjeta IV	• Serum pertuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)
• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} of trastuzumab SC within the FDC compared with Herceptin IV	• Serum trastuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• tpCR, defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/isypN0), according to local pathologist assessment • iDFS, defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: – Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion) – Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast) – Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer) – Contralateral invasive breast cancer – Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible) Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as PD or relapse. • iDFS, including second primary non-breast cancer, defined in the same way as iDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) • EFS, defined as the time from enrollment to the first occurrence of one of the following events: – Breast cancer progression (PD) – Breast cancer recurrence (as defined for iDFS endpoint) – Death from any cause Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as PD or relapse. • EFS, including second primary non-breast cancer is defined in the same way as EFS, but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) • DRFI, defined as the time between randomization and the date of distant breast cancer recurrence • OS, defined as the time from randomization to death from any cause

Secondary Safety Objective	Corresponding Endpoints
• To evaluate the safety of the SC FDC of pertuzumab and trastuzumab compared with Perjeta IV and Herceptin IV	• Incidence and severity of adverse events and SAEs, with severity determined according to NCI CTCAE v4 • Laboratory test abnormalities according to NCI CTCAE v4 <u>Primary cardiac endpoints</u> • Incidence of a symptomatic ejection fraction decrease ("Heart failure") of NYHA Class III or IV and a drop in LVEF of at least 10-percentage points from baseline and to below 50% • Cardiac death, defined as one of the following: – Definite cardiac death, defined as death due to heart failure, myocardial infarction, or documented primary arrhythmia – Probable cardiac death, defined as sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology <u>Secondary cardiac endpoint</u> • Incidence of an asymptomatic or mildly symptomatic left ventricular systolic dysfunction ("Ejection fraction decreased") of NYHA Class II, defined as an LVEF decrease of $\geq$10-percentage points below the baseline measurement to an absolute LVEF value of $<$50%, confirmed by a second assessment within approximately 3 weeks confirming a decrease of $\geq$10-percentage points below the baseline measurement and to an absolute LVEF value of $<$50%
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the pharmacokinetics of pertuzumab and trastuzumab following administration of the SC FDC	• Serum pertuzumab concentrations or PK parameters • Serum trastuzumab concentrations or PK parameters
• To compare the pharmacokinetics (including PK parameters such as AUC and C_{max}) following administration of the SC FDC versus Perjeta IV and Herceptin IV (in combination with chemotherapy)	• Serum pertuzumab concentrations or PK parameters during Cycle 7 (pre-dose Cycle 8) • Serum trastuzumab concentrations or PK parameters during Cycle 7 (pre-dose Cycle 8)
• To assess the trastuzumab and pertuzumab PK profile and observed C_{trough} at Cycle 7 (pre-dose Cycle 8)	• Serum pertuzumab concentrations during Cycle 7 (pre-dose Cycle 8) • Serum trastuzumab concentrations during Cycle 7 (pre-dose Cycle 8)
• To compare the pertuzumab exposure in Cycle 5 between Perjeta IV 840 mg and FDC (pertuzumab SC 1200 mg)	• Serum pertuzumab concentrations during Cycle 5

Exploratory Pharmacokinetic Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate potential relationships between pertuzumab and/or trastuzumab exposure and the efficacy and safety of the SC FDC via a pertuzumab and/or trastuzumab exposure-response analysis	• Relationship between serum concentration or PK parameters for pertuzumab and/or trastuzumab efficacy endpoints • Relationship between serum concentration or PK parameters for pertuzumab and/or trastuzumab safety endpoints
• To assess the impact of a potential PK DDI between pertuzumab and trastuzumab following administration of the SC FDC	• Serum concentrations or PK parameters for pertuzumab given in combination with trastuzumab compared with pertuzumab given alone (based on historical data) • Serum concentrations or PK parameters for trastuzumab given in combination with pertuzumab compared with trastuzumab given alone (based on historical data)
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• bpCR, defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx) • Clinical response, defined as CR, PR, SD, or PD, prior to surgery. Tumor response will be assessed prior to each new cycle of therapy by clinical examination, mammography, and/or other methods of evaluation as per routine clinical practice. Response will be assessed by the investigator as per routine clinical practice.
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20 with the SC FDC compared with Perjeta IV and Herceptin IV	• Incidence of pertuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of trastuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of rHuPH20 ADAs during the study relative to the prevalence of ADAs at baseline
• To evaluate potential effects of ADAs	• Relationship between pertuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between trastuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between rHuPH20 ADA status and efficacy, safety, or PK endpoints

Exploratory Biomarker Objectives	Corresponding Endpoint
• To explore potential association of tissue-based biomarkers or biomarker profiles to pCR • To assess blood-based biomarkers at baseline and longitudinally to explore changes over time and potential relationship to pCR and long-term efficacy endpoints	• Presence or absence of biomarker(s) and/or biomarker profiles with respect to levels of certain biomarkers and relation to efficacy endpoints

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events ;OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

Study Design

Description of Study

This is a Phase III, two-arm, open-label, multicenter, randomized study to investigate the pharmacokinetics, efficacy, and safety of the FDC (pertuzumab and trastuzumab for SC administration) in combination with chemotherapy in Chinese patients with HER2-positive EBC in the neoadjuvant/adjuvant setting.

The study will enroll patients with HER2-positive breast cancer consistent with the indication for treatment with neoadjuvant Perjeta and Herceptin and chemotherapy in routine clinical practice and as recommended in local guidelines.

Approximately 200 patients with HER2-positive, operable or locally advanced/inflammatory breast cancer with a tumor size of > 2 cm or node-positive will be randomized to one of the following treatment arms in a 1:1 ratio:

- **Arm A** (Perjeta IV + Herceptin IV): Patients will receive 8 cycles of neoadjuvant chemotherapy: 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles. Perjeta + Herceptin will be given IV for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of Perjeta IV and Herceptin IV for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.
- **Arm B** (FDC of pertuzumab and trastuzumab for SC administration): Patients will receive 8 cycles of neoadjuvant chemotherapy: 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. FDC will be given SC for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of the FDC for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.

Once eligibility is confirmed, the patient will be randomized to one of the two treatment arms using a permuted blocks randomization procedure and stratified according to the following factors:

- Hormonal receptor status (based on central assessment):
  - Estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive
  - ER-negative and PgR-negative
- Clinical stage at presentation:
  - Stage II–IIIA
  - Stage IIIB–IIIC

A patient may only be randomized once in this trial. Patients randomized into the study will not be replaced. Patients who choose to withdraw after screening, but before randomization, will be replaced.

Number of Patients

Approximately 200 Chinese patients with centrally confirmed HER2-positive, Stage II–IIIC breast cancer with a tumor size of >2 cm, or node-positive disease (clinically or on imaging and node positivity confirmed with cytology and/or histopathology) will be randomized in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1
- Female and male patients with Stage II–IIIC (T2–T4 plus any N, or any T plus N1–3, M0), locally advanced, inflammatory, or early-stage, unilateral, and histologically confirmed invasive breast cancer

  Patients with inflammatory breast cancer must be able to have a core-needle biopsy
- Primary tumor >2 cm in diameter, or node-positive disease (clinically or on imaging, and node positivity confirmed with cytology and/or histopathology)
- HER2-positive breast cancer confirmed by a central laboratory prior to study enrollment.

  HER2-positive status will be determined based on pretreatment breast biopsy material and defined as 3+ by immunohistochemistry (IHC) and/or positive by *HER2* amplification by in situ hybridization (ISH) with a ratio of ≥ 2 for the number of *HER2* gene copies to the number of signals for chromosome 17 copies.

  Patients with multifocal tumors (more than one tumor confined to the same quadrant as the primary tumor) are eligible provided at least one focus is sampled and centrally confirmed as HER2 positive.
- Hormone receptor status of the primary tumor, centrally confirmed

  Hormone receptor-positive status can be determined by either known ER-positive and/or known PgR-positive status. Hormone receptor-negative status must be determined by both known ER-negative and known PgR-negative status.
- Patient agreement to undergo mastectomy or breast conserving surgery after neoadjuvant therapy
- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor tissue for central confirmation of HER2, hormone receptor status, and *PIK3CA* mutational analyses
- Baseline LVEF $\geq 55\%$ measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For women of childbearing potential (WOCBP) who are sexually active: agreement to remain abstinent (refrain from heterosexual intercourse) or use one highly effective non-hormonal contraceptive method with a failure rate of $<1\%$ per year, or two effective non-hormonal contraceptive methods during the treatment period and for 7 months after the last dose of HER2-targeted therapy, and agreement to refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of highly effective non-hormonal contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception (see Section 5.1.3).

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom in combination with a spermicidal foam, gel, film, cream, or suppository, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom with a spermicidal product during the treatment period and for 7 months after the last dose of HER2-targeted therapy to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception (see section 5.1.3).
- A negative serum pregnancy test must be available prior to randomization for WOCBP (premenopausal women and women $<$ 12 months after the onset of menopause), unless they have undergone surgical sterilization (removal of ovaries and/or uterus)
- No major surgical procedure unrelated to breast cancer within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment

Exclusion Criteria

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

- Stage IV (metastatic) breast cancer
- Patients with a history of invasive breast cancer
- Patients with a history of concurrent or previously treated non-breast malignancies except for appropriately treated 1) non-melanoma skin cancer and/or 2) in situ carcinomas, including cervix, colon, and skin

  A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than 5 years.
- Patients who have received any previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy (selective estrogen receptor modulators, aromatase inhibitors, and antitumor vaccines) for treatment or prevention of breast cancer, or radiation therapy for treatment of cancer
- Patients who have a past history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) if they have received any systemic therapy for its treatment or radiation therapy to the ipsilateral breast

  Patients are allowed to enter the study if treated with surgery alone.
- Patients with high-risk for breast cancer who have received chemopreventative drugs in the past are not allowed to enter the study
- Patients with multicentric (multiple tumors involving more than one quadrant) breast cancer, unless all tumors are HER2-positive
- Patients with bilateral breast cancer
- Patients who have undergone an excisional biopsy of primary tumor and/or axillary lymph nodes
- Axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy

  Patients with clinically negative axilla (by physical examination and radiographic imaging) may undergo a core or needle biopsy procedure prior to neoadjuvant systemic therapy if in keeping with local practice
- Sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy
- Treatment with any investigational drug within 28 days prior to randomization

- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE (v4) Grade ≥ 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 ≥ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second degree AV-block Type 2 [Mobitz 2] or third-degree AV-block)
  - Serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality
  - Angina pectoris requiring anti-anginal medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on ECG
  - Evidence of myocardial infarction within 12 months prior to randomization
  - Poorly controlled hypertension (e.g., systolic > 180 mm Hg or diastolic > 100 mmHg)
- Inadequate bone marrow function, defined as:
  - Absolute neutrophil count $< 1.5 \times 10^9$/L
  - Platelet count $< 100 \times 10^9$/L
  - Hemoglobin < 9 g/dL
- Impaired liver function, defined as:
  - Serum (total) bilirubin $> 1.25 \times$ upper limit of normal (ULN)

    In case of Gilbert's syndrome: a total bilirubin of $2 \times$ ULN is permitted.
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $> 1.25 \times$ ULN
  - Albumin < 25 g/L
- Inadequate renal function with serum creatinine $> 1.5 \times$ ULN
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the last dose of HER2-targeted therapy

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
- Concurrent, serious, uncontrolled infections, or known infection with HIV
- Known hypersensitivity to study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, colon, skin, and/or non-melanoma skin carcinoma
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe 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

End of Study

The end of the study is expected to occur approximately 4.5 years after the last patient is randomized to the study. The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient (or when all patients have died or the trial is terminated by the Sponsor, whichever is earliest).

Length of Study

The total length of the study, from screening of the first patient to the end of the study is expected to be approximately 5.5 years.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are Perjeta® IV, Herceptin® IV, and the SC FDC of pertuzumab and trastuzumab.

Test Product (Investigational Drug)

For patients randomized to receive the FDC SC, the FDC is given as a fixed non–weight-based dose. A loading dose of 1200 mg SC pertuzumab and 600 mg SC trastuzumab is then followed by 600 mg SC pertuzumab and 600 mg SC trastuzumab Q3W. Chemotherapy should be given after the FDC.

After surgery, patients continue to receive the FDC in the adjuvant setting until a total of 18 cycles of the FDC have been administered during the study. Adjuvant FDC treatment should not start until at least 2 weeks after surgery. If the interval between the first dose of adjuvant FDC and the last dose of neoadjuvant FDC is $\geq$6 weeks, a reloading dose of FDC (1200 mg of pertuzumab and 600 mg of trastuzumab) is required. Subsequent maintenance FDC doses (600 mg pertuzumab and 600 mg trastuzumab) will then be given Q3W, starting 3 weeks later. The interval between the last dose of neoadjuvant FDC and the first dose of adjuvant FDC should be $\leq$9 weeks.

Comparator

For patients randomized to receive the IV formulations of Perjeta and Herceptin, Perjeta is given as a fixed non–weight-based dose of 840-mg IV loading dose and then 420-mg IV Q3W. Herceptin is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. The order of administration of Perjeta and Herceptin is according to investigator preference. Chemotherapy should be given after Perjeta and Herceptin.

After surgery, patients continue to receive Perjeta and Herceptin in the adjuvant setting until a total of 18 cycles of Perjeta and Herceptin have been administered during the study (neoadjuvant and adjuvant). Adjuvant Perjeta and Herceptin treatment should not start until 2 weeks after surgery. If the interval between the first dose of adjuvant Perjeta and Herceptin and the last dose of neoadjuvant Perjeta and Herceptin exceeds 6 weeks, a reloading dose of 840 mg of Perjeta and 8 mg/kg of Herceptin is required. The interval between the last dose of neoadjuvant Perjeta and Herceptin and the first dose of adjuvant Perjeta and Herceptin should be $\leq$9 weeks.

Non-Investigational Medicinal Products

Doxorubicin, cyclophosphamide, docetaxel, G-CSF, and adjuvant hormone therapy are administered in accordance with local prescribing information and these drugs are not regarded as IMPs. These drugs will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

Statistical Methods

Primary Analysis

The co-primary endpoints of this study are observed pertuzumab and trastuzumab trough concentration (C_{trough}) at Cycle 7 (i.e., the measured pre-dose concentration value at Cycle 8), following 3 cycles of Perjeta IV and Herceptin IV or FDC (pertuzumab and trastuzumab SC). Pertuzumab and trastuzumab C_{trough} will be analyzed at the time of the primary analysis, which will occur after the last patient has completed (all) neoadjuvant therapy and has undergone surgery.

The non-inferiority of the SC and IV dose of pertuzumab and trastuzumab will be assessed by a one-sided testing procedure. The C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose

will be estimated together with the two-sided 90% CI based on the log-transformed trough concentration values. The null hypothesis will be rejected and non-inferiority will be concluded if the lower bound of the 90% CI of the GMR is ≥ 0.8.

A hierarchical testing procedure for the co-primary endpoints will be used to adjust for multiple comparison.

Determination of Sample Size

Sample size calculations are based on the coefficient of variation (CV)% for the C_{trough} of trastuzumab observed from previous studies in MBC and EBC patients after Q3W treatment. With a CV of 60% assumed, a minimum of 80 patients per arm (i.e., a total of 160 patients) is needed to demonstrate C_{trough} non-inferiority with a power of 80% if the true means of the two formulations do not differ (GMR = 1). The sample size is increased to 200 (i.e., 100 patients per arm), as it is expected 80% of patients would be PK evaluable.

Interim and Final Analyses

No formal, statistical interim analyses are planned prior to the primary analysis.

The final analysis will occur 3 years after the last patient's last treatment.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	doxorubicin (Adriamycin®) plus cyclophosphamide
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse events of special interest
ALND	axillary lymph node dissection
ARDS	acute respiratory distress syndrome
ARR	administration-related reaction
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
AV	atrioventricular
BSA	body surface area
BCS	Breast Conserving Surgery
bpCR	breast pathologic complete response
CBE	clinical breast examination
CHF	congestive heart failure
CISH	chromogenic in situ hybridization
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CR	complete response
CSCO	Chinese Society of Clinical Oncology
CT	computed tomography (scan)
C_{trough}	steady-state concentration at the end of a dosing interval (i.e., just prior to next drug administration)
CV	coefficient of variation
DCIS	ductal carcinoma in situ
dd	dose-dense
ddAC	dose-dense doxorubicin (Adriamycin®) plus cyclophosphamide
DDI	drug-drug interaction
DFS	disease-free survival
DRFI	distant recurrence-free inverval
EBC	early breast cancer
EC	Ethics Committee
ECG	electrocardiogram

Abbreviation	Definition
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ER	estrogen receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDC	fixed-dose combination of pertuzumab and trastuzumab for SC administration
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescent in situ hybridization
GBG	German Breast Group
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GMR	geometric mean ratio
HCP	healthcare provider
GnRH	gonadotropin-releasing hormone
H	Herceptin (trastuzumab)
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HIPAA	Health Insurance Portability and Accountability Act
HMV	healthy male volunteer
HR	hazard ratio
ICH	International Council for Harmonization
iDFS	invasive disease-free survival
iDCC	independent Data Cooridinating Center
IMP	investigational medicinal product
IHC	immunohistochemistry
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISH	in situ hybridization
ISR	injection-site reaction

Abbreviation	Definition
ITT	intent-to-treat (population)
IUD	intrauterine device
IxRS	interactive voice or web-based response system
LCIS	lobular carcinoma in situ
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAPK	mitogen-activated protein kinase
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NYHA	New York Heart Association
OS	overall survival
pCR	pathological complete response
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
popPK	population PK
PR	partial response
PVC	polyvinyl chloride
QW	once a week
Q2W	every 2 weeks
Q3W	every 3 weeks
RBR	Research Biosample Repository
rHuPH20	recombinant human PH20 hylauronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SID	single-use injection device

Abbreviation	Definition
SISH	silver in situ hybridization
SLNB	sentinel lymph node biopsy
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TCH	docetaxel (Taxotere®), cyclophosphamide, and trastuzumab (Herceptin®)
tpCR	total pathological complete response
TTE	time-to-event
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE BREAST CANCER

Globally, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer in women (Bray et al. 2018). In China, breast cancer is the most common cancer in women and the eighth leading cause of cancer death in both sexes combined (Wold Health Organization 2018). Approximately 20% of breast cancers strongly overexpress human epidermal growth factor receptor 2 (HER2). This is usually the result of amplification of the gene encoding *HER2*, which is found on chromosome 17 (Wolff et al. 2007). HER2 belongs to the family of human epidermal growth factor receptors (HER) (which also includes HER1 [also known as epidermal growth factor receptor (EGFR)], HER3, and HER4) that mediate normal cell growth, survival, and differentiation (for details, see the Herceptin and Perjeta Investigator's Brochures). These receptors may be activated by external ligands and by dimerization with other HER family members. HER2 activity is mediated by homodimerization (with other HER2 receptors) or heterodimerization (with other HER family receptors), leading to activation of multiple intracellular signaling pathways, including the phosphoinositide 3-kinase (PI3K)/Akt and RAS/Raf/mitogen-activated protein kinase (MAPK) pathways (Olaylioye et al. 2000). In the case of HER2, activation may also be achieved by proteolytic cleavage of the extracellular domain (shedding) to leave an activated truncated internal domain. HER2 is also known to play a role in the normal development of myocardial tissue and in the repair of damaged myocardium (Sawyer et al. 2002; Timolati et al. 2006; Zhao et al. 2006).

Primary breast cancers with HER2 amplification and overexpression were found to have a poor prognosis, including a greater risk of relapse and shortened survival, compared with tumors without this abnormality (Slamon et al. 1987, 1989; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001). Breast cancers that overexpress HER2 have been shown to be susceptible to treatment with the anti-HER2 monoclonal antibody, trastuzumab (Herceptin®), as well as other HER2-targeted agents, including pertuzumab (rhuMAb 2C4; Perjeta®), trastuzumab emtansine (T-DM1; Kadcyla®), lapatinib (Tykerb®; Tyverb®), and neratinib (Nerlynx®).

The combination of Perjeta with Herceptin and chemotherapy has become standard of care for treating HER2-positive early and metastatic breast cancer globally (Coates et al. 2015; Cardoso et al. 2014; Gradisher et al. 2016).

F. Hoffman-La Roche (hereafter referred to as Roche) has developed a new product combining pertuzumab and trastuzumab in one fixed-dose combination for SC injection (hereafter referred to as "the FDC"). The FDC is a ready-to-use formulation of pertuzumab and trastuzumab co-formulated with recombinant human PH20 hylauronidase (rHuPH20) developed to improve dispersion of large volumes of drugs when administered subcutaneously (i.e., it functions as a permeation enhancer).

In this Phase III neoadjuvant/adjuvant study, the FDC will be compared to Perjeta and Herceptin IV formulations in patients with HER2-positive early breast cancer (EBC).

Neoadjuvant and Adjuvant Therapy of Early Breast Cancer and Patholgoical Complete Response in Breast Cancer

Neoadjuvant therapy is given prior to surgery and was originally developed for patients with large or inoperable tumors to enable definitive surgery to be performed. Studies comparing adjuvant with neoadjuvant systemic therapy for breast cancer have shown no difference in the rates of death, disease progression, or disease recurrence relative to the timing of the systemic therapy (Mauri et al. 2005; Bear et al. 2006). Accordingly, neoadjuvant therapy is now also recommended in selected patients with operable EBC by global guidelines (see National Comprehensive Cancer Network [NCCN], European Society for Medical Oncology [ESMO], St Gallen, and other international guidelines [Berruti et al. 2011; Harbeck et al. 2013; Senkus et al. 2013; Theriault et al. 2013], including China guidelines [China Breast Cancer Society 2017; Chinese Society of Clinical Oncology (CSCO) 2018]). Aside from the potential clinical benefits that are achieved by down-staging, neoadjuvant therapy allows direct and early observation of the response to treatment (Gralow et al. 2008). Numerous studies and meta-analyses have demonstrated that the burden of pathologically detected residual disease after neoadjuvant chemotherapy is associated with long-term prognosis. Typically, these studies showed that achieving pathological complete response (pCR) following neoadjuvant therapy is associated with a significantly decreased risk of disease recurrence and improvement in survival across the various breast cancer subtypes, including HER2-positive breast cancer (Cortazar et al. 2014; Broglio et al. 2016; Spring et al. 2016). Therefore, pCR is considered a surrogate marker for survival outcomes as newer, targeted therapies are evaluated in the neoadjuvant setting (Mazouni et al. 2007; Symmans et al. 2007).

Several studies have evaluated Perjeta- and Herceptin-based neoadjuvant regimens in patients with HER2-positive breast cancer. An overview of key neoadjuvant studies in HER2-positive EBC with Perjeta and Herceptin including pCR rates in the Perjeta + Herceptin arm only is provided in Table 1. Although these studies differ with regard to the type of chemotherapy, the number of cycles, the administration of Perjeta and Herceptin (i.e., concurrent with the beginning of chemotherapy or starting with the taxane component of regimen), overall, patients with all tumor and nodal stages of HER2-positive, EBC had a higher pCR rate with Perjeta-containing therapy than control groups without Perjeta. Based on data from two neoadjuvant Phase II studies (NEOSPHERE and TRYPHAENA), Perjeta was approved in combination with Herceptin and docetaxel as neoadjuvant therapy of HER2-positive breast cancer. The BERENICE study confirmed the tolerability and efficacy of Perjeta and Herceptin when combined with the doxorubicine-containing regimen in HER2-positive EBC, establishing the safety of Perjeta as part of a doxorubicin-containing regimen.

In the adjuvant setting, Perjeta and Herceptin-based regimens were evaluated in a single, large, Phase III randomized study BO25126 (APHINITY). The study demonstrated that treatment with Perjeta, Herceptin, and chemotherapy resulted in improvement in invasive disease-free survival (iDFS) compared with treatment with Herceptin and chemotherapy, providing confirmatory data for the benefit of Perjeta and Herceptin-based treatment in EBC setting. Based on the APHINITY results, Perjeta + Herceptin has been approved in the United States and the European Union as adjuvant treatment of patients with HER2-positive EBC at high risk of recurrence.

For details about these studies, please refer to Section 1.2.2.2.

1.2 BACKGROUND ON PERJETA, HERCEPTIN, AND RHUPH20

1.2.1 Background on Herceptin IV and Herceptin SC

Trastuzumab (Herceptin®) is a humanized monoclonal antibody directed at the HER2 receptor. Binding of trastuzumab to the sub-domain IV of the HER2 receptor inhibits ligand-independent HER2 signaling, which prevents the proteolytic cleavage of its extracellular domain and the subsequent constitutive activation of the associated downstream intracellular signaling pathways. As a result, trastuzumab has been shown, in both in vitro assays and in nonclinical animal models, to inhibit the proliferation of human tumor cells that overexpress HER2.

Herceptin (trastuzumab) is indicated for the treatment of patients with HER2-positive breast cancer in the neoadjuvant, adjuvant, and metastatic settings. The addition of Herceptin to standard chemotherapy increases time to progressive disease (PD) or the length of progression-free survival (PFS) and improves overall survival (OS) when given with chemotherapy to women with HER2-positive breast cancer (Slamon et al. 2001; Romond et al. 2005).

Herceptin can also be administered subcutaneously. Herceptin SC is approved in many countries as treatment for patients with HER2-positive EBC and MBC.

For a more detailed overview of nonclinical and clinical studies with Herceptin IV and Herceptin SC, please refer to the Herceptin Investigator's Brochure.

1.2.1.1 Nonclinical Information on Herceptin SC

For details on nonclinical studies of Herceptin SC, please refer to the Herceptin Investigator's Brochure.

1.2.1.2 Clinical Efficacy of Herceptin SC

Herceptin SC (formulated with rHuPH20) has been studied in several clinical trials (BP22023, BO22227 [HannaH], MO22982 [PrefHer], and BO29159 [MetaPHer]) that used conventional handheld syringes and hypodermic needles to administer the study drug, and two studies (MO28048 [SafeHER] and BO25532) that additionally assessed

the safety of assisted- and self-administered Herceptin SC and Herceptin SC single-use injection device (SID) as therapy in patients with operable HER2-positive EBC.

In the Phase Ib dose-finding study (BP22023), the dose of Herceptin SC that resulted in exposure comparable to that achieved with Herceptin IV was selected. The pharmacokinetic (PK) modeling of fixed Herceptin SC dose selection indicated that a flat and a weight-based dosing strategy would result in a comparable range of exposure. A fixed dose of 600 mg resulted in steady-state concentrations at the end of a dosing interval (C_{trough}) values that were at least as high as the every-3-week (Q3W) IV regimen (i.e., 8-mg/kg loading dose followed by 6-mg/kg maintenance dose).

In the pivotal neoadjuvant/adjuvant study BO2227 (HannaH), in which EBC patients were randomized to Herceptin SC or Herceptin IV with chemotherapy, non-inferiority of trastuzumab SC was established if the lower limit of the two-sided 90% CI of the geometric mean ratio (GMR) of C_{trough} SC/IV was 0.8 or more. The study showed that trastuzumab SC was non-inferior to trastuzumab IV in terms of C_{trough}. The GMR was 1.33 (90% CI: 1.24, 1.44), with the lower limit of the two-sided 90% CI being greater than the pre-specified non-inferiority margin. The analysis of pCR (the efficacy co-primary endpoint) demonstrated pCR rates of 40.7% (95% CI: 34.7%, 46.9%) in the Herceptin IV arm and 45.4% (95% CI: 39.2%, 51.7%) in the Herceptin SC arm, a difference of 4.7 percentage points in favor of the Herceptin SC arm. The 4.7% (95% CI: −4.0%, 13.4%) pCR difference between SC and IV crossed the pre-specified non-inferiority margin of −12.5%, demonstrating that pCR rates of Herceptin SC were non-inferior to Herceptin IV (Ismael et al. 2012). The long-term efficacy results of the BO22227 (HannaH) study (i.e., 6-year event-free survival [EFS] and OS) supported the established non-inferiority of trastuzumab SC (Jackisch et al. 2016).

For further details on the clinical efficacy of Herceptin SC, please see the Herceptin Investigator's Brochure.

1.2.1.3 Clinical Safety of Herceptin SC

Data from the Herceptin SC trials show that Herceptin SC injections were generally well tolerated. The safety profiles of Herceptin SC formulations are comparable and consistent with the known safety profile of Herceptin IV. There were no notable differences in the type and frequency of all-grade adverse events across study arms. No new adverse event or safety signals were identified either for Herceptin SC vial or SID administration. Safety and tolerability results were consistent with the known safety profile for Herceptin IV.

Herceptin SC has a similar cardiac safety profile to that of Herceptin IV. Administration-related reactions (ARRs) and hypersensitivity (such as chills and/or fever, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, respiratory distress) have been frequently reported following Herceptin IV or SC administration. These reactions were

usually mild to moderate (Grades 1 and 2) and were more common in the Herceptin SC arm in the BO22227 (HannaH) study.

A higher rate of anti-drug antibodies (ADAs) against trastuzumab was observed in the BO22227 (HannaH) study for the Herceptin SC formulation compared with Herceptin IV (18.0% [53/295] of patients in the Herceptin SC arm vs. 11.1% [33/296] of patients in the Herceptin IV arm). One patient treated with the IV formulation and 2 patients treated with the SC formulation developed neutralizing ADAs. However, the higher incidence of ADAs in the SC arm was not associated with adverse events or altered pharmacokinetics (Ismael et al. 2012).

For further details on the clinical safety of Herceptin SC, please see the Herceptin Investigator's Brochure.

1.2.2 Background on Perjeta IV

Pertuzumab (Perjeta®) is a fully humanized monoclonal antibody based on the human IgG1 framework sequences. It consists of two heavy chains (449 residues) and two light chains (214 residues). Pertuzumab is directed against the extracellular domain of HER2. It binds to subdomain 2 of HER2 (Franklin et al. 2004) and prevents heterodimerization of HER2 with other members of the HER family (HER1, HER3, and HER4). As a result, pertuzumab inhibits ligand-initiated intracellular signaling supporting cell growth arrest and apoptosis, respectively.

Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity in vitro and in vivo when pertuzumab and trastuzumab are given in combination. Additionally, the Fc portion of both their IgG1 framework provides for potent activation of antibody-dependent cell-mediated cytotoxicity (ADCC). In addition, in vitro, both trastuzumab and pertuzumab ADCC are exerted preferentially on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

1.2.2.1 Nonclinical Information on Perjeta IV

For details on nonclinical studies of Perjeta IV, please refer to the Perjeta Investigator's Brochure.

1.2.2.2 Clinical Pharmacokinetics of Pertuzumab

A comprehensive population PK (popPK) analysis was conducted using pertuzumab concentration data obtained from 481 patients across 11 Phase I/II clinical trials in a variety of solid tumors and the pivotal Phase III trial CLEOPATRA in MBC. In the popPK analysis, pertuzumab pharmacokinetics were described by using a linear two-compartment model with a systemic serum clearance of 0.235 L/day and a median terminal half-life of 18 days at doses ranging from 2.0 to 25.0 mg/kg (equivalent to 140−1750 mg for a 70-kg patient). The model supports the use of fixed,

non-weight–based dosing regardless of body weight, albumin, age, sex, race (Japanese vs. non-Japanese), laboratory variables related to hepatic and renal function, and disease variables in patients with MBC and other solid tumors included in the model. The pertuzumab pharmacokinetics observed in Study WO20697 (NEOSPHERE) and Study BO25126 (APHINITY) were consistent with the previous popPK model predictions, suggesting similarity in pertuzumab pharmacokinetics between the patient population included in the NEOSPHERE and APHINITY studies (patients with locally advanced breast cancer, inflammatory breast cancer, or EBC) and patients with advanced malignancies, including the first-line MBC population.

Data from the Phase II trial WO20697 (NEOSPHERE), Phase III trial BO25126 (APHINITY) and the Phase III trial WO20698/TOC4129g (CLEOPATRA) demonstrated that there is no evidence of drug-drug interactions (DDIs) between pertuzumab and trastuzumab or between pertuzumab and docetaxel, paclitaxel, or carboplatin.

1.2.2.3 Efficacy of Perjeta IV

Perjeta IV in combination with Herceptin and chemotherapy has been studied in several EBC and MBC studies. Currently, Perjeta is approved in the neoadjuvant treatment of *patients with* HER2-positive, locally advanced, inflammatory, or EBC and for treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease. Recently, Perjeta, in combination with Herceptin and chemotherapy, was also approved for the adjuvant treatment of HER2-positive EBC.

1.2.2.3.1 Neoadjuvant Setting Studies with Perjeta and Herceptin

Perjeta and Herceptin based regimens were evaluated in several neoadjuvant HER2-positive breast cancer studies. A summary of Perjeta and Herceptin studies in the neoadjuvant setting, including treatment arms and pCR rates, is presented in Table 1.

Table 1 Overview of Key Studies of Neoadjuvant Perjeta in HER2-Positive Early Breast Cancer

Study	Neoadjuvant Treatment	Patients, n	Efficacy Results (%)		
			tpCR	bpCR	GBG pCR
NEOSPHERE[a]					
	H + D	107	21.5	29.0	12.1
	Ptz + H + D	107	39.3	45.8	32.7
	Ptz + H	107	11.2	16.8	5.6
	Ptz + D	96	17.7	24.0	13.5
TRYPHAENA[b]					
	Ptz + H + FEC → Ptz + H + D	73	56.2	61.6	50.7
	FEC → Ptz + H + D	75	54.7	57.3	45.3
	Ptz + TCH	77	63.6	66.2	51.9
BERENICE[c, d]					
	ddAC → Pac + Ptz + H	199	61.8	67.3	48.7
	FEC → D + Ptz + H	201	60.7	65.7	48.8
KRISTINE[e, d]					
	TCH + Ptz	221	55.7	45.7	59.7
	T-DM1 + Ptz	223	44.4	35.0	50.2
GeparSepto[f]					
	Ptz + H + Pac	197	—	—	53.8
	Ptz + H + nab-Pac	198	—	—	61.8
NSABP B52[g]					
	TCH + Ptz	154	41	44	—
	TCH + Ptz + AI	157	46	47	—

AI = aromatase inhibitor; bpCR = breast pathological complete response; D = docetaxel; ddAC = dose-dense doxorubicin and cyclophosphamide; ER = estrogen receptor; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; GBG pCR = German Breast Group pathological complete response (pT0/N0); H = Herceptin; Pac = paclitaxel; Ptz = Perjeta; PgR = progesterone receptor; T = paclitaxel; T-DM1 = trastuzumab emtansine (Kadcyla®); TCH = docetaxel (Taxotere®), carboplatin and Herceptin; tpCR = total pathological complete response.

[a] Gianni et al. 2012.

[b] Schneeweiss et al. 2013.

[c] Primary Clinical Study Report – WO29217. Report 1070920. December 2016.

[d] Included both neoadjuvant and adjuvant treatment with Perjeta and Herceptin.

[e] Primary Clinical Study Report – BO28408. Report 1068872. August 2016.

[f] Untch et al. 2016.

[g] Rimawi et al. 2016.

Although these studies are different in terms of backbone chemotherapy and number of cycles administered, all consistently demonstrated that with the use of dual anti-HER2 therapy and longer duration of chemotherapy higher pCR rates are achieved.

Duration of chemotherapy is also important and impacts pCR rates. In NEOSPHERE, patients received 4 cycles of neoadjuvant therapy, and the highest pCR rate (39.3%) was achieved in the arm where Perjeta was added to Herceptin and chemotherapy. In TRYPHENA and BERENICE, patients received 6 and 8 cycles of neoadjuvant therapy, respectively, and further increases in pCR rates were observed. pCR rates in TRYPHENA ranged from 54.7%–63.6%, and in BERENICE, the overall rate of total pathological complete response (tpCR) was around 62%.

For additional information on the neoadjuvant studies, please see the Perjeta Investigator's Brochure.

1.2.2.3.2 Neoadjuvant Setting Studies with Perjeta and Herceptin in China (PEONY Study)

PEONY (NCT02586025), a randomized, multicenter, double-blind, placebo-controlled, Phase III trial conducted in an Asian population (mainland China, Taiwan, Korea, Thailand), primarily compared the efficacy, safety, and tolerability of Perjeta + Herceptin + doxetaxel versus placebo + Herceptin + docetaxel in the neoadjuvant setting.

PEONY met its primary endpoint: Perjeta + Herceptin + doxetaxel resulted in a clinically meaningful and statistically significant improvement in the tpCR rate by an Independent Review Committee (IRC) versus placebo + Herceptin + docetaxel for the neoadjuvant treatment of HER2-positive early/locally advanced breast cancer in Asian patients. In the intent-to-treat (ITT) population, the tpCR rate by an IRC was 39.3% in the Perjeta arm and 21.8% in the placebo arm; a clinically and statistically significant difference of 17.5% (95% CI 6.9–28.0; $p = 0.0014$). Results were similar to NEOSPHERE, and confirm that Perjeta + Herceptin + doxetaxel provides superior anticancer activity than Herceptin + doxetaxel alone.

1.2.2.3.3 Adjuvant Setting Study with Perjeta and Herceptin

Perjeta and Herceptin-based regimens were evaluated in a single, large, adjuvant, Phase III study. BO25126 (APHINITY) is a randomized, double-blind, placebo-controlled two-arm Phase III study of adjuvant Perjeta plus Herceptin and standard chemotherapy (Perjeta + Herceptin + chemotherapy) versus adjuvant placebo plus Herceptin and standard chemotherapy (placebo + Herceptin + chemotherapy), in patients with operable HER2-positive primary breast cancer.

Treatment of patients with Perjeta, Herceptin, and chemotherapy resulted in a statistically significant and clinically meaningful improvement in iDFS, corresponding to a 19% reduction in the risk of relapse or death, as compared with placebo, Herceptin and

chemotherapy (stratified hazard ratio [HR] = 0.81, 95% CI: 0.66, 1.00; p = 0.0446), in a setting with curative intent. Estimates of iDFS event-free rates were 94.06% vs. 93.24% at 3 years and 92.28% vs. 90.58% at 4 years in the Perjeta, Herceptin, and chemotherapy versus placebo, Herceptin, and chemotherapy arms, respectively. High-risk patients, who were pre-defined by clinical and biologic risk criteria, had the greatest clinical benefit. Patients with node-positive or hormone-receptor negative status had a HR = 0.77 (95% CI: 0.62, 0.96) or a HR = 0.76 (95% CI: 0.56, 1.04), respectively. There were numerically fewer deaths in the Perjeta, Herceptin, and chemotherapy arm (80 deaths [3.3%]) compared to the placebo, Herceptin, and chemotherapy arm (89 deaths [3.7%]) at the first interim analysis of survival.

For additional information on APHINITY, please see the Perjeta Investigator's Brochure.

1.2.2.3.4 Metastatic Setting Study with Perjeta and Herceptin

The Perjeta and Herceptin based regimen was evaluated in the Phase III study WO20698/TOC4129g (CLEOPATRA).

The CLEOPATRA study is a randomized, double-blind, placebo-controlled study of Perjeta and Herceptin with docetaxel compared to placebo and Herceptin with docetaxel in patients with untreated HER2-positive locally recurrent, unresectable or MBC.

The Perjeta-based regimen significantly improved PFS, as assessed by an IRC (median PFS = 18.5 months vs. 12.4 months; HR = 0.62, 95% CI: 0.51, 0.75; p < 0.0001). The addition of Perjeta to standard Herceptin-based treatment also resulted in a statistically significant and clinically meaningful improvement in survival time. Based on the latest data from the trial (the median OS was 56.5 months (95% CI: 49.3 months, NR [not reached]) in the Perjeta + Herceptin + docetaxel arm compared to 40.8 months (95% CI: 35.8, 48.3) in the placebo + Herceptin + docetaxel arm (HR = 0.68; 95% CI: 0.56, 0.84; p < 0.001), a prolongation of OS of 15.7 months.

The magnitude of clinical benefit and the acceptable safety profile of Perjeta in combination with Herceptin and docetaxel compared with placebo in combination with Herceptin and docetaxel were maintained throughout the study.

A subgroup analysis of patients from Asia in the CLEOPATRA study showed that efficacy analyses per region exhibited hazard ratios similar to those of the whole ITT population for PFS (ITT: 0.63; Asia: 0.68; other regions: 0.61) and OS (ITT: 0.66; Asia: 0.64; other regions: 0.66) (Swain et al. 2014).

For additional information, please see the Perjeta Investigator's Brochure.

1.2.2.4 Safety of Perjeta IV

The cumulative clinical experience in approximately 11,445 patients (since Development International Birth Date [11 September 2001] until 07 June 2018) who received Perjeta in company-sponsored interventional Perjeta trials has demonstrated that Perjeta is well

tolerated as monotherapy or in combination with Herceptin and a range of other therapeutic agents, with manageable additional toxicity. No unexpected toxicities were encountered other than those that are known for agents that target the HER family of receptors.

Serious or severe infusion-related symptoms have been rarely observed in patients receiving Perjeta. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported.

1.2.2.4.1 Single-Agent Therapy

There are only a few early and very small studies with single-agent Perjeta. The most commonly reported adverse events in patients receiving single-agent Perjeta were diarrhea, fatigue, nausea, vomiting, and decreased appetite. The majority of adverse events reported were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 or 2 in severity, and the proportion of patients across the Perjeta program who discontinued study drug as a result of an adverse event was low.

1.2.2.4.2 Safety of Combination Therapy

Perjeta has been shown to be well tolerated in combination with Herceptin (WO20697 [NEOSPHERE], BO22280 [TRYPHAENA], WO29217 [BERENICE], WO20698 [CLEOPATRA], MO22324 [PHEREXA], and BO25126 [APHINITY]), with an increase in the incidence but not severity of the common adverse events seen with Perjeta (notably, diarrhea, rash/skin reactions, and fatigue). Perjeta also added little toxicity (predominantly diarrhea, mucosal inflammation, rash/skin reactions, and neutropenia/febrile neutropenia) to the adverse event profile of Herceptin and docetaxel when all three drugs were used concurrently, and had little effect on the doses received, or on interruptions, discontinuations, or treatment-related mortality. Serious or severe infusion-related symptoms have been rarely observed in patients receiving Perjeta. Results from the TRYPHAENA and BERENICE studies showed that Perjeta and Herceptin in combination with an anthracycline-containing chemotherapy (including the dose-dense doxorubicin plus cyclophosphamide [ddAC] regimen used in the BERENICE study) are safe and well tolerated in patients with EBC.

Importantly, despite targeting the same HER2 pathway, Perjeta adds no significant cardiac toxicity and, in particular, does not increase incidence of symptomatic left ventricular systolic dysfunction (LVSD) when given with Herceptin (with or without chemotherapy).

In the pivotal Phase III study WO20698/TOC4129g (CLEOPATRA), the rates of symptomatic and asymptomatic LVSD were not higher in patients receiving Perjeta, Herceptin, and docetaxel than in those receiving placebo, Herceptin, and docetaxel. The incidence of LVSD and LVEF decline in PHEREXA in the pertuzumab arm were similar to the control arm and also in line with other pertuzumab studies in

MBC and EBC. Cardiac safety profiles for the anthracycline-based treatment regimens ddAC→paclitaxel with pertuzumab and trastuzumab and 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)→docetaxel with pertuzumab and trastuzumab in Study WO29217 (BERENICE) (using similar chemotherapy as in the WO40324 study) during the neoadjuvant treatment period were consistent with the known cardiac safety profiles of Perjeta and Herceptin in other studies.

Safety of Combination Therapy in Chinese/Asian Patients

Perjeta has been shown to be well tolerated in combination with Herceptin and docetaxel in the Chinese study YO28762 (PEONY). The safety profile (nature and severity of adverse events) of Perjeta in combination with Herceptin and docetaxel was comparable with that of placebo with Herceptin and docetaxel in the Chinese population, except for a higher incidence of diarrhea, leukopenia, and IRR observed in the pertuzumab arm compared to the placebo arm which is consistent with the known safety profile of pertuzumab in patients with HER2-positive early breast cancer.

A subgroup analysis of patients from Asia in the CLEOPATRA study showed that patients with HER2-positive metastatic breast cancer (MBC) from Asia experienced more toxicities from treatment with pertuzumab, trastuzumab, and docetaxel than patients from other regions. This outcome did not, however, result in a reduction in the median number of study treatment cycles administered in these patients compared with patients from other regions. Despite a higher proportion of docetaxel dose reductions in patients from Asia, survival benefits were comparable between regions. The benefit-risk profile of pertuzumab, trastuzumab, and docetaxel supports this regimen as the first-line therapy for patients with HER2-positive MBC from all geographic regions (Swain et al. 2014).

For a more detailed overview of the safety of Perjeta IV, please refer to the Perjeta Investigator's Brochure.

1.2.3 Pertuzumab SC

1.2.3.1 Nonclinical Information on Pertuzumab SC

1.2.3.1.1 Pharmacokinetic Studies

Three nonclinical PK studies with pertuzumab SC have been conducted: one with mini-pigs and two with cynomolgus monkeys.

Mini-Pig

A study in mini-pigs (Roche Study 1038750) was conducted to determine the absolute bioavailability of a single dose of pertuzumab. Perjeta was administered at 10 mg/kg IV to animals in Group 1. Each animal in Group 2 and Group 3 received 120 mg SC of pertuzumab (co-formulated with 2000 U/mL rHuPH20). In addition, animals in Group 3 received a separate subcutaneously administered dose of 120-mg Herceptin (co-formulated with 2000 U/mL rHuPH20). For animals assigned to Group-3, the two different formulations were administered sequentially.

The mini-pig was chosen because of the similarities between mini-pig and human skin structure.

Following SC administration, pertuzumab was relatively rapidly absorbed with maximum plasma levels observed at 7 – 48 hours post-dose. The half-life of 524 hours for pertuzumab SC was similar to that following IV administration. The average bioavailability of pertuzumab SC was estimated at 73.8%. Co-administration of Herceptin SC had no obvious effect on the SC absorption of 120 mg pertuzumab. No accelerated clearance was observed in any of the 15 animals studied.

Cynomolgus Monkey

Studies with cynomolgus monkeys were conducted to assess the single- and repeat-dose pharmacokinetics/toxicokinetics and toxicity.

In the single-dose study (Genentech Study 00-564-1821, Good Laboratory Practice [GLP]), serum levels of pertuzumab following a single dose of 50 mg/kg of pertuzumab SC have been assessed. Results demonstrate that after SC administration, maximum serum concentrations of pertuzumab (mean ± standard deviation [SD]: 536 ± 41.2 µg/mL) were reached at approximately 2.28 days. Mean apparent clearance (CL/F) was estimated at 6.4 mL/d/kg.

In the repeat-dose study (Genentech Study 00-604-1560, GLP), serum levels of pertuzumab following QW 250 mg/kg for 5 doses of pertuzumab SC have been assessed. Results demonstrate that after SC administration, maximum serum concentrations of pertuzumab (mean ± standard deviation: 3400 ± 223 µg/mL) were reached at approximately 30 days. The area under the serum concentration–time curve (AUC) from 0 to 7 days was approximately (mean ± standard deviation) 13700 ± 1300 day • µg/mL, and the AUC from 14 to 21 days was approximately (mean ± standard deviation) 20700 ± 1320-day • µg/mL.

1.2.3.1.2 Toxicology Studies with Pertuzumab SC

One study in mini-pig and two studies in cynomolgus monkeys were conducted to assess the single- and repeat-dose pharmacokinetics/toxicokinetics and toxicity.

Mini-Pig

In the mini-pig study (Roche Study 1038750, non-GLP), single-dose pertuzumab SC given alone or co-administered with Herceptin SC (see Section 1.2.1.2) was well tolerated. There were no drug-related effects on mortality, clinical observations, food intake, or body weight in male mini-pigs.

Cynomolgus Monkey

Both single-dose SC administration of pertuzumab at 50 mg/kg to male and female cynomolgus monkeys (Genentech Study 00-564-1821, GLP) and repeat-dose SC administration of pertuzumab at 250 mg/kg QW to female cynomolgus monkeys for

4 weeks (Genentech Study 00-604-1560, GLP) were well tolerated. There were no drug-related effects on mortality, clinical observations, body weight, or, as evaluated in Study 00-604-1560 only, clinical pathology parameters. Exposure to pertuzumab was confirmed and no ADAs were detected.

For further information on the nonclinical experience with pertuzumab, please see the Perjeta Investigator's Brochure.

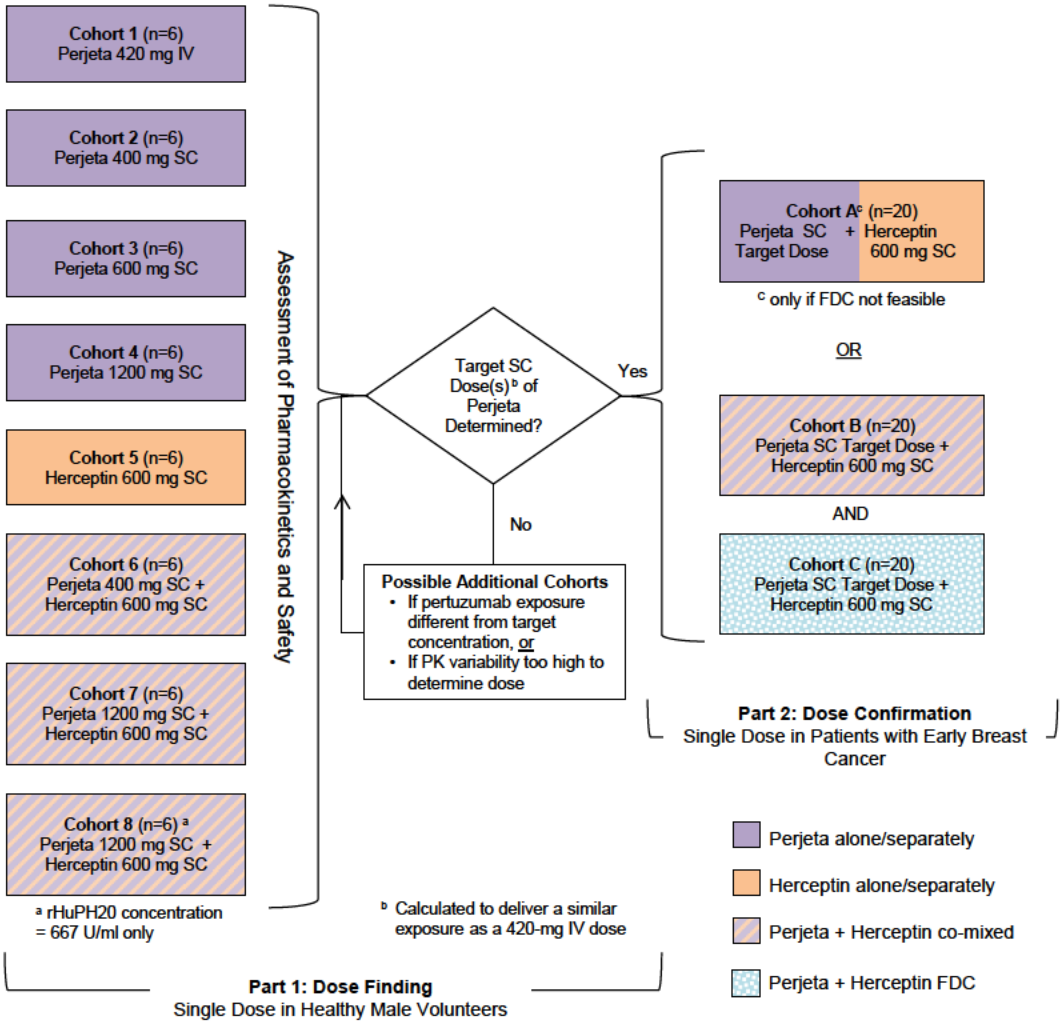
Based on nonclinical studies conducted to date with Perjeta IV and pertuzumab SC, together with the nonclinical and clinical experience with Herceptin IV and SC, no further toxicology evaluation of pertuzumab SC is planned.

1.2.3.2 Clinical Studies with Pertuzumab SC

Pertuzumab SC has been studied in a Phase Ib study (BO30185). This study is an open-label, two-part, two-center study that is designed to identify and subsequently confirm the SC dose of Perjeta (pertuzumab) for the FDC formulation. The dose of Herceptin SC (trastuzumab, 600 mg) was already established in the Phase I study BP22023 and confirmed in the BO22227 (HannaH) study.

The overall schema of BO30185 is shown in Figure 1.

Figure 1 Study BO30185 Schema



FDC=fixed-dose combination; PK=pharmacokinetic; rHuPH20=recombinant human PH20 hyaluronidase.

The objective of Part 1 of the study was dose finding, in which the loading and maintenance doses of pertuzumab SC for the FDC formulation were determined in healthy male volunteers (HMVs). Pertuzumab SC was given alone or co-mixed with Herceptin SC as a single injection, both with rHuPH20. The objective of Part 2 of the study was to confirm the maintenance dose of pertuzumab SC in female EBC patients who have completed standard breast cancer therapy. Enrollment in Part 2 began after the doses of Perjeta SC had been established in Part 1. The overall schema for Part 2 was Cohort A only (co-administration of Perjeta SC [with rHuPH20] and Herceptin SC [with rHuPH20], each agent administered separately) or otherwise Cohort B (Perjeta and Herceptin SC co-mixed product) and Cohort C (the FDC). Cohort A was only to be enrolled if there was a PK interaction between Perjeta and Herceptin observed in Part 1, or if the development of the FDC was not feasible. The Perjeta and Herceptin SC co-mixed product serves as a surrogate for the FDC as the drug substances

(pertuzumab and trastuzumab) in the FDC are considered comparable to the drug substances in the individual SC formulations, and the drug product FDC formulations and the co-mixed solution are also similar.

The PK results from Part 1 of the study showed that a pertuzumab SC dose of 600 mg provides similar C_{trough} and AUC as Perjeta IV 420 mg as determined in HMVs. A pertuzumab SC 600 mg dose administered to EBC patients as a co-mixed formulation with Herceptin SC 600 mg in Part 2 (Dose Confirmation) of the study provided similar C_{trough} and AUC to the 420 mg IV and 600 mg SC cohorts in HMVs in Part 1. Observed and model-predicted pertuzumab PK from the FDC SC administered in Part 2 Cohort C closely matched the co-mixed formulation administered in Part 2 Cohort B. Approximate dose proportionality for SC pertuzumab PK and comparison to historical Perjeta IV 840 mg data (data not shown) confirmed a Perjeta SC 1200 mg loading dose.

The safety profile of Perjeta SC in the study was consistent with the known safety profile of Perjeta IV and is well tolerated when given in combination with Herceptin SC. There were no new safety signals identified.

In Part 1 (Cohorts 1–8), a total of 148 adverse events were reported in 44 out of 48 (91.7%) HMVs. The majority of adverse events were reported of low intensity (Grade 1 or 2). The most common System Organ Class (SOC) was Infections and Infestations, with 22 (45.8%) HMVs experiencing a total of 33 adverse events in this category, of which a majority of events were considered not related to study drug by the investigator. The most commonly observed adverse events (by Prefered Term) across different cohorts were: upper respiratory tract infection (13 [27.1%] HMVs), headache (9 [18.8%] HMVs), drug eruption (9 [18.8%] HMVs), and diarrhea (9 [18.8%] HMVs). Among these common adverse events, study drug related adverse events (assessed by the investigator) were reported in 4 (8.3%), 8 (16.7%), 9 (18.8%), and 7 (14.6%) HMVs. All adverse events that occurred in Part 1 had resolved by the end of Part 1.

In Part 2, all 20 (100%) female EBC patients experienced at least one adverse event, with a total of 102 adverse events reported by the time of clinical data cut-off. The majority of adverse events were reported of low intensity (Grade 1 or 2). The most common SOCs were nervous system disorders (14 [70%] patients), gastrointestinal disorders (10 [50%] patients), and musculoskeletal and connective tissue disorders (10 [50%] patients). The most commonly observed adverse events (by Preferred Term) reported in at least 20% of patients were headache (13 [65%] patients), myalgia (7 [35%] patients), diarrhea (6 [30%] patients), injection-site reaction (ISR: 6 [30%] patients), and nausea (4 [20%] patients). Among these common adverse events, study drug–related adverse events (assessed by the investigator) were reported in 9 (45%), 6 (30%), 4 (20%), 6 (30%), and 1 (5%) patient, respectively. Please see Table 2 for details on adverse events.

Table 2 Summary of Adverse Events for Study BO30185

n (%)	Part 1	Part 2	
	Cohorts 1–8 (N=48)	Cohort B (N = 20) [a]	Cohort C (N = 20) [b]
No. subjects with ≥1 AE	44 (91.7%)	20 (100.0%)	20 (100.0%)
Number of events	148	115	127
Number of SAEs	0	0	1
AE Intensity			
Grade 1	42 (87.5%)	20 (100.0%)	20 (100.0%)
Grade 2	23 (47.9%)	11 (55.0%)	7 (35.0%)
Grade 3	2 (4.2%) [c]	1 (5.0%) [d]	1 (5.0%) [e]
No. subjects with ≥1 study drug related AE	38 (79.2%)	18 (90.0%)	20 (100.0%)
Number of events	87	63	89
Deaths	0	0	0
Withdrawals due to AEs	0	0	0
AESIs	0	0	0
Adverse Events to Monitor			
Diarrhoea	9 (18.8%)	6 (30.0%)	17 (85.0%)
Rash	19 (39.6%)	3 (15.0%)	8 (40.0%)
Mucositis	10 (20.8%)	1 (5.0%)	2 (10.0%)
ARRs	5	6	7
Hypersensitivity and anaphylaxis	4 (8.3%)	1 (5.0%)	0
Neutropenia	0	0	0
Leucopenia	0	0	0
Leucopenic infection	0	0	0
Interstitial lung disease	0	0	0
LVD/CHF	0	2 (10.0%)	0
Pregnancy	0	0	0

AE = adverse event; AESI = adverse events of special interest; ARR = administration-related reaction; LVD = left ventricular dysfunction; SAE = serious adverse event.

[a] Cohort B: pertuzumab 600 mg+ trastuzumab 600 mg (SC co-mixed).

[b] Cohort C: FDC of pertuzumab 600 mg +trastuzumab 600 mg (SC co-formulated).

[c] Diarrhea (Cohort 1); arthropod bite (Cohort 4).

[d] Diarrhea.

[e] Cellulitis (right arm).

The safety, tolerability and PK results of this Phase I study support further development of the FDC. The recommended FDC SC formulation is as follows:

- Loading dose SC: Perjeta 1200 mg + Herceptin 600 mg, with rHuPH20 2,000 U/mL
- Maintenance dose SC: Perjeta 600 mg + Herceptin 600 mg, with rHuPH20 2,000 U/mL

For additional information on the clinical experience with the FDC, please see the Pertuzumab and Trastuzumab FDC Investigator's Brochure.

1.2.4 Background on Recombinant Human Hyaluronidase (rHuPH20)

The feasibility and patient acceptability of SC administration of any drug are dependent on the volume of drug that must be administered.

The enzyme rHuPH20 (Hylenex®) has been developed to improve dispersion and absorption of SC formulations, enabling larger volumes to be administered without reduced tolerability and with improved patient acceptability. Hyaluronidase acts primarily as a permeation enhancer to increase the dispersion and absorption of other co-administered drugs. Hyaluronidase transiently hydrolyses hyaluronan, a component of the SC matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of subcutaneously administered drugs to the systemic circulation (Hylenex Prescribing Information 2016).

The rHuPH20 used in the current study is produced from a second generation of the Hylenex process that has improved yield and purity. This formulation has been combined with trastuzumab to allow safe and comfortable SC injection of volumes of 2–5 mL. The concentration of rHuPH20 is guided by data from a mini-pig study in which trastuzumab was administered subcutaneously. In the presence of either 2,000 or 6,000 U/mL of rHuPH20, there was a more rapid absorption of subcutaneously administered trastuzumab from rHuPH20-containing formulations, while the effect on the absorption rate of trastuzumab was comparable with both rHuPH20 concentrations. Therefore, the lower rHuPH20 concentration of 2000 U/mL was selected.

The highest total rHuPH20 dose administered in a clinical study was 96,000 U (Study HZ2-07-02). This Phase I study investigated the SC injection of adalimumab with different rHuPH20 concentrations in healthy volunteers using different SC volumes of injection (2, 8, and 16 mL). All injections were well tolerated, with no serious adverse events reported. All ISRs such as erythema, pain, and induration were mild (98%) or moderate (2%). Common ISRs observed were erythema, ecchymosis, pain, and induration.

Currently, two monoclonal antibodies (Herceptin and MabThera®/Rituxan Hycela™ [rituximab]) are approved in more then 80 countries for SC therapy in oncology. The MabThera/Rituxan SC 1400 mg dose is delivered in a volume of 11.7 mL and was well tolerated (Davies et al. 2014). The amount of rHuPh20 (23,400 U) in MabThera/Rituxan

SC exceeds the Herceptin SC (10,000 U) and proposed Perjeta maintenance SC rHuPH20 dose that will be administered in this study. All three products use the same rHuPH20 concentration of 2000 U/mL.

For additional details on nonclinical and clinical studies of rHuPh20, please see the prescribing information (Hylenex Prescribing Information 2016).

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Perjeta is available as a concentrated solution for IV infusion. Herceptin is available as a lyophilized powder for solution in IV infusion. When Perjeta and Herceptin are administered via IV infusions, they can be given in any order. Herceptin is infused over a period of 30–90 minutes. Perjeta is infused over 30–60 minutes.

For many patients the long infusion and observation times as well as the need for repeated, invasive IV access are disadvantages of the current therapeutic approach. Furthermore, increasing usage of intravenously administered monoclonal antibodies combined with chemotherapy has placed a strain on medical centers with respect to time and resources required to prepare and administer the infusion. The switch to the SC route of administration for monoclonal antibodies such as Herceptin and MabThera/Rituxan has been demonstrated to reduce the treatment burden for patients, while improving the time and resource utilization at the treatment facility (Rummel et al. 2015; De Cock et al. 2016; Pivot et al. 2013).

In view of the above aspects, a new product combining pertuzumab and trastuzumab in one fixed-dose combination for SC injection has been developed (the FDC). The FDC is a ready-to-use formulation of pertuzumab and trastuzumab co-formulated with rHuPH20, a human recombinant hyaluronidase, developed to improve dispersion of large volumes of drugs (i.e., it functions as a permeation enhancer). The FDC will be administered subcutaneously in the thigh over 5–8 minutes, with an observation time of approximately 15–30 minutes and with non–body-weight dependent dosing.

Available data of subcutaneously administered monoclonal antibodies (trastuzumab [Herceptin] and rituximab [MabThera/Rituxan]), consistently demonstrate that antitumor activity remains the same regardless of administration route (Ismael et al. 2012; Davies et al. 2014; Assouline et al. 2015), and at the same time, patient and healthcare providers (HCPs) prefer SC to IV administration (Pivot et al. 2013). The BO22227 (HannaH) study demonstrated non-inferiority in trastuzumab C_{trough} levels and pCR rate for EBC patients treated with Herceptin SC as compared to treatment with the IV formulation (Ishmael et al. 2012).

Co-mixing of the two monoclonal antibodies in a single infusion bag has been assessed in the VELVET study. The study showed that the combination of vinorelbine, Perjeta, and Herceptin was active in MBC, regardless of whether Perjeta and Herceptin were administered sequentially or in the same infusion bag. There was no evidence that

administering Perjeta and Herceptin together in a single infusion bag altered the safety profile from that seen when Perjeta and Herceptin were administered sequentially in separate infusion bags (Perez et al. 2016; Andersson et al. 2017). In the Phase I BO30185 study, the safety profile of the co-mixture of Herceptin and Perjeta for SC administration was similar to known safety profile of Herceptin and Perjeta IV with no new safety signals detected.

Based on these considerations, it is expected that SC administration of the FDC will result in improved tolerability, reduced dosing errors, increased patient convenience and satisfaction, and improved cost-effectiveness, while maintaining similar efficacy and safety to the IV formulation of the same product.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics, efficacy, and safety of the FDC of pertuzumab and trastuzumab for SC administration compared with the Perjeta IV and Herceptin IV formulations in Chinese patients with HER2-positive EBC.

Specific objectives and corresponding endpoints for the study are outlined below in Table 3.

Table 3 Study Objectives and Endpoints

Co-Primary Objectives	Corresponding Endpoint
• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} of pertuzumab SC within the FDC compared with Perjeta IV	• Serum pertuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)
• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} of trastuzumab SC within the FDC compared with Herceptin IV	• Serum trastuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• tpCR, defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/isypN0), according to local pathologist assessment • iDFS, defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: − Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion) − Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast) − Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than the two above mentioned sites that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer) − Contralateral invasive breast cancer − Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified, if possible) Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as PD or relapse.

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events ;OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

Table 3 Study Objectives and Endpoints (cont.)

Secondary Efficacy Objective (cont.)	Corresponding Endpoints (cont.)
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• iDFS, including second primary non-breast cancer, defined in the same way as iDFS but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) • EFS, defined as the time from enrollment to the first occurrence of one of the following events: – Breast cancer progression (PD) – Breast cancer recurrence (as defined for iDFS endpoint) – Death from any cause Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as PD or relapse. • EFS, including second primary non-breast cancer is defined in the same way as EFS, but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) • DRFI, defined as the time between randomization and the date of distant breast cancer recurrence • OS, defined as the time from randomization to death from any cause

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination;

GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events ;OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

Table 3 Study Objectives and Endpoints (cont.)

Secondary Safety Objective	Corresponding Endpoints
• To evaluate the safety of the SC FDC of pertuzumab and trastuzumab compared with Perjeta IV and Herceptin IV	• Incidence and severity of adverse events and SAEs, with severity determined according to NCI CTCAE v4 • Laboratory test abnormalities according to NCI CTCAE v4 <u>Primary cardiac endpoints</u> • Incidence of a symptomatic ejection fraction decrease ("Heart failure") of NYHA Class III or IV and a drop in LVEF of at least 10-percentage points from baseline and to below 50% • Cardiac death, defined as one of the following: – Definite cardiac death, defined as death due to heart failure, myocardial infarction, or documented primary arrhythmia – Probable cardiac death, defined as sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology <u>Secondary cardiac endpoint</u> • Incidence of an asymptomatic or mildly symptomatic left ventricular systolic dysfunction ("Ejection fraction decreased") of NYHA Class II, defined as an LVEF decrease of $\geq$10-percentage points below the baseline measurement to an absolute LVEF value of $<$50%, confirmed by a second assessment within approximately 3 weeks confirming a decrease of $\geq$10-percentage points below the baseline measurement and to an absolute LVEF value of $<$50%

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events ;OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

Table 3 Study Objectives and Endpoints (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints (cont.)
• To characterize the pharmacokinetics of pertuzumab and trastuzumab following administration of the SC FDC	• Serum pertuzumab concentrations or PK parameters • Serum trastuzumab concentrations or PK parameters
• To compare the pharmacokinetics (including PK parameters such as AUC and C_{max}) following administration of the SC FDC versus Perjeta IV and Herceptin IV (in combination with chemotherapy)	• Serum pertuzumab concentrations or PK parameters during Cycle 7 (pre-dose Cycle 8) • Serum trastuzumab concentrations or PK parameters during Cycle 7 (pre-dose Cycle 8)
• To assess the trastuzumab and pertuzumab PK profile and observed C_{trough} at Cycle 7 (pre-dose Cycle 8)	• Serum pertuzumab concentrations during Cycle 7 (pre-dose Cycle 8) • Serum trastuzumab concentrations during Cycle 7 (pre-dose Cycle 8)
• To compare the pertuzumab exposure in Cycle 5 between Perjeta IV 840 mg and FDC (pertuzumab SC 1200 mg)	• Serum pertuzumab concentrations during Cycle 5
• To evaluate potential relationships between pertuzumab and/or trastuzumab exposure and the efficacy and safety of the SC FDC via a pertuzumab and/or trastuzumab exposure-response analysis	• Relationship between serum concentration or PK parameters for pertuzumab and/or trastuzumab and efficacy endpoints • Relationship between serum concentration or PK parameters for pertuzumab and/or trastuzumab and safety endpoints
• To assess the impact of a potential PK DDI between pertuzumab and trastuzumab following administration of the SC FDC	• Serum concentrations or PK parameters for pertuzumab given in combination with trastuzumab compared with pertuzumab given alone (based on historical data) • Serum concentrations or PK parameters for trastuzumab given in combination with pertuzumab compared with trastuzumab given alone (based on historical data)

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

Table 3 Study Objectives and Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of the SC FDC of pertuzumab and trastuzumab + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• bpCR, defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx) • Clinical response, defined as CR, PR, SD, or PD, prior to surgery. Tumor response will be assessed prior to each new cycle of therapy by clinical examination, mammography, and/or other methods of evaluation as per routine clinical practice. Response will be assessed by the investigator as per routine clinical practice.
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20 with the SC FDC compared with Perjeta IV and Herceptin IV	• Incidence of pertuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of trastuzumab ADAs during the study relative to the prevalence of ADAs at baseline • Incidence of rHuPH20 ADAs during the study relative to the prevalence of ADAs at baseline
• To evaluate potential effects of ADAs	• Relationship between pertuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between trastuzumab ADA status and efficacy, safety, or PK endpoints • Relationship between rHuPH20 ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objectives	**Corresponding Endpoint**
• To explore potential association of tissue-based biomarkers or biomarker profiles to pCR • To assess blood-based biomarkers at baseline and longitudinally to explore changes over time and potential relationship to pCR and long-term efficacy endpoints	• Presence or absence of biomarker(s) and/or biomarker profiles with respect to levels of certain biomarkers and relation to efficacy endpoints

ADA = anti-drug antibody; bpCR = breast pathologic complete response; C_{trough} = steady-state concentration; DRFI=distant breast cancer recurrence; DDI = drug-drug interaction; EFS = event-free survival; FDC = fixed-dose combination; GMR = geometric mean ratio; HCP = health care provider; iDFS = invasive disease-free survival; IV = intravenous; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events ;OS = overall survival; pCR = pathologic complete response; PD = progressive disease; PK = pharmacokinetic; PR = partial response; SC = subcutaneous; SD = stable disease; tpCR = total pathological complete response.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, two-arm, open-label, multicenter, randomized study to investigate the pharmacokinetics, efficacy, and safety of the FDC (pertuzumab and trastuzumab for SC administration) in combination with chemotherapy in Chinese patients with HER2-positive EBC in the neoadjuvant/adjuvant setting.

The study will enroll patients with HER2-positive breast cancer consistent with the indication for treatment with neoadjuvant Perjeta and Herceptin and chemotherapy in routine clinical practice and as recommended in local guidelines.

Approximately 200 patients with HER2-positive, operable or locally advanced/inflammatory breast cancer with a tumor size of >2 cm or node-positive will be randomized to one of the following treatment arms in a 1:1 ratio:

- **Arm A** (Perjeta IV + Herceptin IV): Patients will receive 8 cycles of neoadjuvant chemotherapy: 4 cycles of doxorubicin plus cyclophosphamide (AC) Q3W followed by docetaxel Q3W for 4 cycles. Perjeta + Herceptin will be given IV for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of Perjeta IV and Herceptin IV for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.
- **Arm B** (FDC of pertuzumab and trastuzumab for SC administration): Patients will receive 8 cycles of neoadjuvant chemotherapy: 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. FDC will be given SC for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, patients will undergo surgery. Thereafter, patients will receive an additional 14 cycles of the FDC for a total of 18 cycles. One year of HER2-targeted therapy without any delays would encompass 18 cycles.

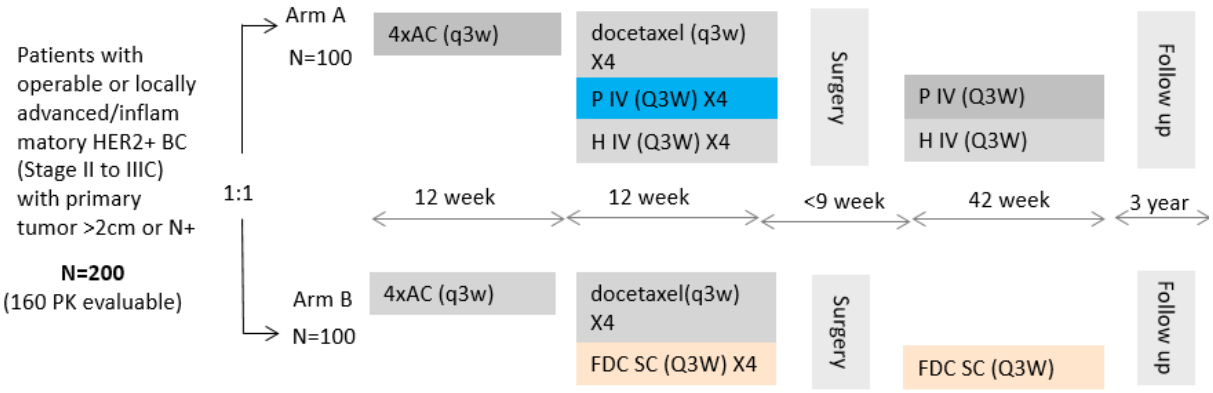
Once eligibility is confirmed, the patient will be randomized to one of the two treatment arms using a permuted blocks randomization procedure and stratified according to the following factors:

- Hormonal receptor status (based on central assessment):
  - Estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive
  - ER-negative and PgR-negative
- Clinical stage at presentation:
  - Stage II–IIIA
  - Stage IIIB–IIIC

A patient may only be randomized once in this trial. Patients randomized into the study will not be replaced. Patients who choose to withdraw after screening, but before randomization, will be replaced.

Figure 2 presents an overview of the study design. The schedules of activities are provided in Appendix 1, Appendix 2, and Appendix 3.

Figure 2 Study Schema



AC = doxorubicin plus cyclophosphamide; BC = breast cancer; FDC = fixed-dose combination of pertuzumab and trastuzumab SC; H = Herceptin; N+ = node positive; P = Perjeta; QW = once a week; Q3W = every 3 weeks.

Note: For Arms A and B, the doses of AC are doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV (AC is given Q3W). The starting dose of docetaxel is 75 mg/m^2 IV in Cycle 5 (the first docetaxel cycle) and then 100 mg/m^2 IV at the discretion of the investigator for Cycles 6–8, if no dose-limiting toxicity occurs (given Q3W). *The 9-week period between neoadjuvant treatment and adjuvant treatment begins when the final dose of neoadjuvant treatment is administered.*

Post-operative radiotherapy will be administered as per local practice, without interruption of the HER2-targeted therapy. Hormone receptor-positive patients should receive adjuvant hormonal treatment as per local practice.

After the end of study treatment, patients will be followed for safety and efficacy for at least 3 years (36 months).

3.1.1 Neoadjuvant Phase

Neoadjuvant therapy will be administered for a total of 8 cycles. In the event of disease progression, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor, whichever occurs first, neoadjuvant therapy will be discontinued prior to the completion of these 8 cycles. For patients in both arms the 8 cycles will take about 24 weeks.

With the exception of patients who experience disease progression, patients whose neoadjuvant chemotherapy is discontinued due to toxicity prior to completion of these 8 cycles, and patients who did not receive non-protocol neoadjuvant therapy will be allowed to continue HER2-targeted adjuvant study treatment as per randomization.

Patients who discontinue neoadjuvant therapy as a result of disease progression must be discontinued from all study treatment and will be managed as per local practice.

Any patient who receives non-protocol cancer-directed therapy prior to surgery will be discontinued from study treatment and will be managed as per local practice.

If the HER2-targeted therapy is held for more than 9 weeks or needs to be permanently discontinued, the patient will be withdrawn from all study treatment, and the patient will continue to be followed post-treatment for at least 3 years after last dose of HER2-targeted therapy, as described in Section 4.6.4.

All patients who discontinue planned study treatment will remain on study for follow-up of secondary and exploratory endpoints, safety and survival unless consent for study participation is withdrawn.

3.1.2 Surgery

Patients in both cohorts are scheduled to undergo surgery after 8 cycles of neoadjuvant therapy. Surgery will be performed no earlier than 14 days following the last infusion or injection of neoadjuvant therapy.

See Section 4.4.1 for details about surgical management of patients.

3.1.3 Adjuvant Phase

All patients who have undergone surgery will continue to receive the same HER2-directed therapy in the adjuvant phase as was administered in the neoadjuvant phase of the study (i.e., Arm A Perjeta IV and Herceptin IV; Arm B the SC FDC of pertuzumab and trastuzumab). Treatment will be given so that in total, 18 cycles of HER2-directed therapy are administered, inclusive of therapy given both in the neoadjuvant and adjuvant setting.

The interval between the last dose of neoadjuvant Perjeta IV and Herceptin IV or the FDC and the first dose of adjuvant Perjeta IV and Herceptin IV or the FDC must be $\leq$ 9 weeks otherwise the patient will be withdrawn from all study treatment. Adjuvant therapy will be discontinued in the event of invasive disease recurrence, second primary invasive malignancy, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Patients whose adjuvant study treatment is discontinued prior to completion of planned therapy will still be followed as per protocol for secondary endpoints unless consent to participate is withdrawn.

After surgery, radiotherapy is to be given as clinically indicated and as per local practice (Section 4.4.2).

Patients with ER-positive and/or PgR-positive tumors should receive adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitor, ovarian ablation) as per local clinical practice.

3.1.4 Safety Data Review

The Sponsor's study team will review adverse events, serious adverse events, and other safety data in the study on a regularly scheduled basis and at the time of the primary analysis.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is expected to occur approximately 4.5 years after the last patient is randomized to the study. The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient (or when all patients have died or the trial is terminated by the Sponsor, whichever is earliest).

The total length of the study, from screening of the first patient to the end of the study is expected to be approximately 5.5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for SC Administration and Development of a Fixed-Dose Combination of Pertuzumab and Trastuzumab for Subcutaneous Use

Available data of subcutaneously administered monoclonal antibodies (trastuzumab [Herceptin] and rituximab [MabThera/Rituxan]) consistently demonstrate that antitumor activity is not impaired by a change in administration route, and at the same time, patient and health care providers prefer SC to IV administration.

Herceptin SC has been shown as a valid treatment alternative to Herceptin IV with a similar safety profile and non-inferior pharmacokinetics and efficacy compared to IV (Ismael et al. 2012). In addition, patient preference and safety results from PrefHer, an open-label, randomized, two-cohort, two-arm crossover study to assess patient preference for trastuzumab administered either subcutaneously or intravenously in the adjuvant breast cancer setting, suggest that subcutaneous administration of Herceptin is the treatment preferred by patients compared to IV administration. Herceptin SC is associated with improved patient convenience, reduced use of hospital resources, and reduced time of HCPs compared to Herceptin IV (Pivot et al. 2013).

MabThera/Rituxan SC has also demonstrated PK non-inferiority compared to the established rituximab IV route for follicular lymphoma and chronic lymphocytic leukemia (Davies et al. 2014; Assouline et al. 2015). SC administration of MabThera/Rituxan was preferred to IV mainly due to reduced time in clinic and patients feeling more comfortable and less emotionally distressed during the SC administration (Rummel et al. 2015).

Therefore, it is expected that SC administration will result in an improved tolerability, reduced dosing errors, enhanced quality of life, increased patient satisfaction and convenience, and improved cost-effectiveness while maintaining similar efficacy and safety to the IV formulation of the same product.

In view of the above aspects, Roche has developed a new product combining Perjeta and Herceptin in one FDC for SC injection. It is expected that SC administration will overcome the limitations.

3.3.2 Rationale for Dose and Schedule of Perjeta IV, Herceptin IV, and the FDC of Pertuzumab and Trastuzumab

The dose and schedule of Perjeta IV and Herceptin IV are consistent with the prescribing information for each agent (those of the standard recommended Q3W regimen). For Herceptin, an 8-mg/kg IV initial loading dose followed by a 6 mg/kg IV maintenance dose Q3W and, for Perjeta, an 840-mg IV loading dose and 420-mg IV maintenance dose Q3W will be administered.

The FDC formulation for SC administration is available in two doses: The FDC loading dose is 1200 mg pertuzumab plus 600 mg trastuzumab plus 30,000 U rHuPH20. The FDC maintenance dose is 600 mg pertuzumab plus 600 mg trastuzumab plus 20,000 U rHuPH20, and will be administered Q3W. rHuPH20 concentration in both FDC formulations is 2000 U/mL.

The loading dose and maintenance dose of pertuzumab SC within the FDC were determined in Part 1 of the Phase I BO30185 study and confirmed in Part 2 of this study. The dose of trastuzumab within the FDC was previously established in a Phase Ib dose-finding study (BO22023) and confirmed in the Phase III study BO22227. rHuPH20, a human recombinant hyaluronidase within the FDC, is given at a standard concentration of 2000 U/ml, which is the approved concentration in both Herceptin SC and Mabthera SC.

3.3.3 Rationale for Choice and Dose of Chemotherapy

The backbone chemotherapy regimens (anthracycline followed by taxane) used with the HER2-directed therapy in the neoadjuvant part of this study are based on published data, routine clinical usage, as well as established clinical practice guidelines (e.g., Senkus et al. 2013; Gradishar et al. 2016; Curigliano et al. 2017) for patients with high-risk HER2-positive EBC, in combination with Perjeta and Herceptin. The doses of chemotherapy in this trial are all consistent with the prescribing information for each agent.

The NCCN preferred neoadjuvant/adjuvant regimens for HER2-positive EBC are AC or ddAC followed by QW paclitaxel with Herceptin given concurrently with paclitaxel. Another recommended regimen is AC followed by docetaxel with Herceptin. Perjeta can be added to Herceptin-containing regimens for HER2-positive EBC patients with a tumor

size >2 cm in diameter or node positive. The St. Gallen Guidelines also recommended dual anti-HER2 therapy with pertuzumab and trastuzumab and chemotherapy in the neoadjuvant setting for high-risk HER2-positive patients. The recommended chemotherapy regimen is anthracycline followed by taxane with concurrent HER2 therapy (Curigliano et al. 2017). AC followed by docetaxel will be used in this study, which is based on routine clinical practice as well as clinical practice guidelines in China (China Breast Cancer Society 2017; CSCO 2018).

In the BERENICE study, ddAC followed by paclitaxel QW or FEC Q3W followed by docetaxel were evaluated. Perjeta and Herceptin were given concurrently with the taxane in each arm (see Section 1.2.2.2). High rates of tpCR with both regimens were achieved with a safety profile consistent with the known toxicities of the treatment regimen, supporting the similar chemotherapy backbone options in this Phase III study.

3.3.4 Rationale for Patient Population

The patient population included in the study is similar to patients enrolled in the WO20697 (NEOSPHERE), BO22270 (TRYPHAENA), and WO29217 (BERENICE) studies (see Section 1.2.2.2). This patient population is at a higher risk of recurrence based on the following clinical characteristics:

- Locally advanced or inflammatory breast cancer
- Node-positive disease and/or primary tumor >2 cm

Because of higher risk for relapse, these patients are in need of the most effective treatment available. Therefore, following surgery, all patients in this study will continue to receive Perjeta + Herceptin in the adjuvant setting as per randomization for a total of 18 cycles of HER2-targeted treatment as standard of care.

The addition of 1 year of Perjeta to standard adjuvant Herceptin and chemotherapy for patients with HER2-positive EBC in APHINITY led to a reduction in the risk of relapse or death by 19% (HR = 0.81; 95% CI: 0.66, 1.00; p = 0.0446), in a setting with curative intent (refer to Section 1.2.2.3.3). Patients with node-positive disease showed clear benefit with addition of pertuzumab with iDFS event-free rates of 91.99% versus 90.15% at 3 years (HR = 0.77: 95% CI: 0.62, 0.96), indicating a 23% reduction in the risk of recurrence or death, as compared with placebo. Importantly, the addition of Perjeta to standard adjuvant Herceptin and chemotherapy reduced the rate of the most life-threatening type of iDFS events, distant metastases (von Minckwitz G et al. 2017). These results support continuing dual blockade in the adjuvant part of the proposed Phase III study.

The totality of the data coming from the Perjeta EBC clinical program support the use of Perjeta plus Herceptin in combination with chemotherapy in patients with high-risk EBC in the neoadjuvant setting and continuing HER2-targeted therapy in the adjuvant setting in this higher-risk patient population.

3.3.5 Rationale for Pharmacokinetic Primary Endpoint (C_{trough})

The co-primary objective of this study is to demonstrate non-inferiority of the Cycle 7 (i.e., pre-dose Cycle 8) pertuzumab serum C_{trough} from pertuzumab SC within the FDC to the Perjeta IV formulation and the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} of trastuzumab SC within the FDC compared with Herceptin IV in Chinese patients with HER2-positive EBC.

The rationale for C_{trough} as a primary endpoint is based on historical in vitro, nonclinical, and clinical data. The well-established mechanism of action of pertuzumab is binding to HER2 receptors. Nonclinical xenograft models have demonstrated that maximum tumor growth inhibition is achieved at concentrations of at least 10–20 µg/mL.

The development program and use of C_{trough} as a primary endpoint is based on the assumption that pertuzumab and trastuzumab C_{trough} after SC administration are at least as high as those C_{trough} resulting from IV infusions. As C_{trough} represents target saturation, demonstrating non-inferiority in C_{trough} will ensure the same degree of receptor saturation as IV administration and therefore the same degree of efficacy and comparable safety regardless of the route of administration.

Based on data from the Phase I study BO30185, other PK parameters, such as AUC are highly correlated with C_{trough}, and are therefore expected to be similar between IV and SC administration. Due to slower absorption following SC dosing, the maximum serum concentration (C_{max}) is not expected to exceed the maximum exposure previously observed in EBC clinical trials.

Therefore a dose of pertuzumab within the FDC that is statistically non-inferior to that of IV administration is believed to maintain the same degree of efficacy observed in studies with Perjeta IV administration.

3.3.6 Rationale for Efficacy Secondary Endpoint (pCR)

To provide evidence that a change in the route of administration will not impair the antitumor activity of Perjeta + Herceptin, pCR will be assessed at the completion of standard neoadjuvant chemotherapy regimens with Perjeta plus Herceptin. The tpCR rates of the FDC and IV formulations will be assessed along with the difference in tpCR rates (SC FDC arm minus IV arm) and the 95% CI calculated to reflect the largest tpCR difference that can be reliably ruled out.

In breast cancer, pCR is an appropriate efficacy endpoint recognized by health authorities (EMA 2012; FDA 2014). Several studies and meta-analysis have consistently shown better long-term outcome for patients who achieve a pCR (compared to patients who do not achieve a pCR) (Cortazar et al. 2014). In addition, pCR allows for direct and early observation of the response to treatment. Refer to Section 1.1 for an overview of pCR.

Approval of Perjeta plus Herceptin in combination with chemotherapy for the neoadjuvant treatment of HER2-positive EBC was granted by the U.S Food and Drug Administration (FDA) and the European Commission primarily based on data from the neoadjuvant Phase II NEOSPHERE and TRYPHAENA studies (see Section 1.2.2.3.1). Both studies showed that pCR in the breast was significantly improved by the addition of Perjeta to Herceptin and chemotherapy.

Therefore, pCR represents a clinically meaningful endpoint to compare efficacy of the SC FDC to the IV formulations.

3.3.7 Rationale for Biomarker Assessments

Specimens obtained from the primary tumor at baseline will be characterized by molecular profiling.

Throughout the development program for Perjeta, comprehensive biomarker research has been carried out. While no additional biomarker(s) other than HER2 have been found that would predict treatment benefit from Perjeta, some biomarkers were found to be associated with disease prognosis independent from treatment assignment.

In the neoadjuvant setting, hormone-receptor status was associated with pCR, where lower pCR were observed in hormone receptor-positive disease. Similarly, *PIK3CA* mutation was associated with a lower likelihood to achieve pCR compared to patients whose tumors were characterized as *PIK3CA* wild-type.

Therefore, in this study, mandatory tumor tissue is collected during screening from all patients to centrally assess HER2 status and hormonal receptor status as part of the patient selection and stratification process. For exploratory purposes, *PIK3CA* status will be determined for all randomized patients as well, but is not required for eligibility.

The study also requires mandatory plasma samples for biomarker research. These plasma samples may be used for extraction of circulating tumor DNA to assess biomarkers in blood and monitor such markers over time and may involve genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Research will not be aimed at distinguishing germline mutations from somatic mutations. NGS methods will not include whole genome sequencing or whole exome sequencing. Such research may help to find out if certain markers in blood are associated with disease prognosis and/or whether certain changes over time may predict recurrent disease.

The trial design (which has no control arm without Perjeta) will not allow the predictive value of any of the markers or marker profiles to be evaluated with respect to benefits conferred by Perjeta.

3.3.8 Rationale for Immunogenicity Assessments

The purpose of the immunogenicity assessments is to determine whether ADAs against pertuzumab, trastuzumab, or rHuPH20 develop, and whether these impact PK, safety, or efficacy (as data allow).

Blood sampling for immunogenicity testing will be done as per visiting schedule (see Appendix 1, Appendix 2, and Appendix 3). All patients will be evaluated for antibodies against pertuzumab, trastuzumab, and rHuPH20 at baseline and during treatment (baseline, pre-dose, Cycles 6, 9, 13, 18, and 22) and during the post-treatment follow-up phase (Months 3, 6, 12, 18, 24, 30, and 36). A three-tiered analytical testing approach will be performed for ADAs against pertuzumab, trastuzumab, and rHuPH20. First, screening for the potential emergence of antibodies will use bridging immunoassays. Second, any samples testing positive will be subsequently re-tested in a confirmatory assay. Third, samples that confirm positive are then diluted further to obtain a value in titer units (for pertuzumab ADAs, a titer is defined as the inverse $\log_{10}$ of the sample dilution at the cutpoint used to define positivity; for trastuzumab and rHuPH20 ADAs, a titer is defined as the dilution factor at or above the cutpoint used to define positivity). Confirmed positive ADA samples will also be tested for the presence of neutralizing antibodies.

All immunogenicity samples will be analyzed in a central laboratory.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 200 Chinese patients with centrally confirmed HER2-positive, Stage II–IIIC breast cancer with a tumor size of >2 cm, or node-positive disease (clinically or on imaging and node positivity confirmed with cytology and/or histopathology) will be randomized in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1
- Female and male patients with Stage II–IIIC (T2–T4 plus any N, or any T plus N1–3, M0), locally advanced, inflammatory, or early-stage, unilateral, and histologically confirmed invasive breast cancer

  Patients with inflammatory breast cancer must be able to have a core-needle biopsy.

- Primary tumor >2 cm in diameter, or node-positive disease (clinically or on imaging, and node positivity confirmed with cytology and/or histopathology)
- HER2-positive breast cancer confirmed by a central laboratory prior to study enrollment

  HER2-positive status will be determined based on pretreatment breast biopsy material and defined as 3+ by immunohistochemistry (IHC) and/or positive by *HER2* amplification by in situ hybridization (ISH) with a ratio of ≥ 2 for the number of *HER2* gene copies to the number of signals for chromosome 17 copies.

  Patients with multifocal tumors (more than one tumor confined to the same quadrant as the primary tumor) are eligible provided at least one focus is sampled and centrally confirmed as HER2 positive.
- Hormone receptor status of the primary tumor, centrally confirmed

  Hormone receptor-positive status can be determined by either known ER-positive and/or known PgR-positive status. Hormone receptor-negative status must be determined by both known ER-negative and known PgR-negative status.
- Patient agreement to undergo mastectomy or breast conserving surgery after neoadjuvant therapy
- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor tissue for central confirmation of HER2, hormone receptor status, and *PIK3CA* mutational analyses
- Baseline LVEF $\geq 55\%$ measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- For women of childbearing potential (WOCBP) who are sexually active: agreement to remain abstinent (refrain from heterosexual intercourse) or use one highly effective non-hormonal contraceptive method with a failure rate of $<1\%$ per year, or two effective non-hormonal contraceptive methods during the treatment period and for 7 months after the last dose of HER2-targeted therapy, and agreement to refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of highly effective non-hormonal contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception (see Section 5.1.3).

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom in combination with a spermicidal foam, gel, film, cream, or suppository, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom with a spermicidal product during the treatment period and for 7 months after the last dose of HER2-targeted therapy to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception (see Section 5.1.3).

- A negative serum pregnancy test must be available prior to randomization for WOCBP (premenopausal women and women < 12 months after the onset of menopause), unless they have undergone surgical sterilization (removal of ovaries and/or uterus)
- No major surgical procedure unrelated to breast cancer within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment

4.1.2 Exclusion Criteria

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

- Stage IV (metastatic) breast cancer
- Patients with a history of invasive breast cancer
- Patients with a history of concurrent or previously treated non-breast malignancies except for appropriately treated 1) non-melanoma skin cancer and/or 2) in situ carcinomas, including cervix, colon, and skin

  A patient with previous invasive non-breast cancer is eligible provided he/she has been disease free for more than 5 years.

- Patients who have received any previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy (selective estrogen receptor modulators, aromatase inhibitors, and antitumor vaccines) for treatment or prevention of breast cancer, or radiation therapy for treatment of cancer
- Patients who have a past history of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) if they have received any systemic therapy for its treatment or radiation therapy to the ipsilateral breast

  Patients are allowed to enter the study if treated with surgery alone.

- Patients with high-risk for breast cancer who have received chemopreventative drugs in the past are not allowed to enter the study

- Patients with multicentric (multiple tumors involving more than one quadrant) breast cancer, unless all tumors are HER2-positive
- Patients with bilateral breast cancer
- Patients who have undergone an excisional biopsy of primary tumor and/or axillary lymph nodes
- Axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy

  Patients with clinically negative axilla (by physical examination and radiographic imaging) may undergo a core or needle biopsy procedure prior to neoadjuvant systemic therapy if in keeping with local practice
- Sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy
- Treatment with any investigational drug within 28 days prior to randomization
- Serious cardiac illness or medical conditions including, but not confined to, the following:
  - History of NCI CTCAE (v4) Grade ≥ 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 ≥ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block, such as second degree AV-block Type 2 [Mobitz 2] or third-degree AV-block)
  - Serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality
  - Angina pectoris requiring anti-anginal medication
  - Clinically significant valvular heart disease
  - Evidence of transmural infarction on ECG
  - Evidence of myocardial infarction within 12 months prior to randomization
  - Poorly controlled hypertension (e.g., systolic > 180 mm Hg or diastolic > 100 mmHg)
- Inadequate bone marrow function, defined as:
  - Absolute neutrophil count $< 1.5 \times 10^9$/L
  - Platelet count $< 100 \times 10^9$/L
  - Hemoglobin < 9 g/dL
- Impaired liver function, defined as:
  - Serum (total) bilirubin $> 1.25 \times$ upper limit of normal (ULN)

    In case of Gilbert's syndrome: a total bilirubin of $2 \times$ ULN is permitted.
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) $> 1.25 \times$ ULN
  - Albumin < 25 g/L

- Inadequate renal function with serum creatinine $> 1.5 \times$ ULN
- Current severe, uncontrolled systemic disease that may interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 7 months after the last dose of HER2-targeted therapy

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Known active liver disease, for example, active viral hepatitis infection (i.e., hepatitis B or hepatitis C), autoimmune hepatic disorders, or sclerosing cholangitis
- Concurrent, serious, uncontrolled infections, or known infection with HIV
- Known hypersensitivity to study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose > 10 mg methylprednisolone or equivalent excluding inhaled steroids)
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, colon, skin, and/or non-melanoma skin carcinoma
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe 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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study with approximately 200 Chinese patients randomized to two treatment arms in approximately 18 sites.

The investigator will use the protocol-approved neoadjuvant chemotherapy regimens with which to treat the patient (see Section 3.1).

Using an interactive voice or web-based response system (IxRS), patients will be randomized in a 1:1 ratio to one of the two treatment arms using a permuted-blocks randomization procedure and stratified according to the following factors:

- Hormonal-receptor status (based on central assessment):
  - ER-positive or PgR-positive
  - ER-negative and PgR-negative

- Clinical stage at presentation
  - Stage II–IIIA
  - Stage IIIB–IIIC

The Study Management Team is, by definition, unblinded given the open-label nature of this study. However, to further protect the integrity of the study, any treatment assignment information, such as the randomization file from the IxRS and PK data, will be withheld from the Sponsor until the primary analysis. Data for safety purposes will not be reviewed at an aggregate level prior to the primary analysis by the Study Management Team.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are Perjeta® IV, Herceptin® IV, and the SC FDC of pertuzumab and trastuzumab.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Perjeta IV

Pertuzumab (RO4368451/F01-01) will be supplied by the Sponsor as a single-use vial containing 14 mL preservative free sterile, colorless to slightly brownish concentrate at a concentration of 30 mg/mL for dilution in a 250 mL polyvinyl chloride (PVC) or non-PVC polyolefin infusion bag of 0.9% sodium chloride. The IV formulation contains 30 mg/mL in L-histidine acetate buffer with excipients sucrose and polysorbate 20. Each vial of drug product concentrate contains a total 420 mg of pertuzumab.

For information on the formulation and handling of Perjeta IV, see the Perjeta Investigator's Brochure.

4.3.1.2 Herceptin IV

Trastuzumab IV (RO0452317/V03-03) will be supplied by the Sponsor and is supplied for use as a freeze-dried preparation at a nominal content of $440\ mg$ per vial for parenteral administration. The drug is formulated in histidine/histidine-HCl, α, α-trehalose dihydrate, and polysorbate 20.

For information on the formulation and handling of Herceptin IV, see the Herceptin Investigator's Brochure.

4.3.1.3 SC Fixed-Dose Combination of Pertuzumab and Trastuzumab

Two different doses of the FDC of pertuzumab and trastuzumab will be supplied by the Sponsor:

- FDC loading dose (RO7198574/F03-01) is a sterile, colorless to slightly brownish solution for injection containing histidine, hydrochloric acid, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each 20-mL vial contains 1200 mg of pertuzumab (RO4368451) and 600 mg of trastuzumab (RO0452317) in 15 mL of solution.
- FDC maintenance dose (RO7198574/F04-01) is a sterile, colorless to slightly brownish solution for injection containing histidine, hydrochloric acid, trehalose, sucrose, polysorbate 20, methionine, and rHuPH20 (2,000 U/mL). Each 15-mL vial contains 600 mg of pertuzumab (RO4368451) and 600 mg of trastuzumab (RO0452317) in 10 mL of solution.

For information on the formulation and handling of the FDC of pertuzumab and trastuzumab, see the Pertuzumab and Trastuzumab FDC Investigator's Brochure.

4.3.1.4 Chemotherapy and Hormone Therapy

Doxorubicin, cyclophosphamide, docetaxel, and adjuvant hormone therapy are administered in accordance with local prescribing information and these drugs are not regarded as IMPs. These drugs will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

Refer to the respective local reference document for information on formulation, preparation, administration, contraindications, and patient monitoring.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any assoicted adverse events, should be reported as described in Section 5.4.5.11.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.2.1.

4.3.2.1 Arm A: Perjeta IV plus Herceptin IV

In Arm A, Perjeta is given as a fixed non–weight-based dose of 840-mg IV loading dose and then 420-mg IV Q3W. Herceptin is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. The order of administration of Perjeta and Herceptin is according to investigator preference. Chemotherapy should be given after Perjeta and Herceptin.

Treatment will continue as scheduled (see Section 4.3.2.3), or until investigator-assessed radiographic or clinical progression or recurrence of disease or unmanageable toxicity.

Weight should be recorded during screening and on Day 1 of each cycle for all patients. The baseline weight for a patient will be that measured on Cycle 1, Day 1. The amount of Herceptin to be administered must be recalculated if the patient's body weight has changed by $>10\%$ (increased or decreased) from the Cycle 1, Day 1 weight. The amount of Herceptin administered is calculated according to the patient's actual body weight with no upper limit.

The dose of doxorubicin, cyclophosphamide, and docetaxel is calculated according to the patient's body surface area (BSA). The BSA and the dose of drug administered must be recalculated if the patient's body weight has changed by $\pm 10\%$ (increased or decreased) from the Cycle 1, Day 1 weight. Recalculation of the dose of drug administered on the basis of smaller changes in body weight or BSA is at the investigator's discretion.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Sections 5.2.1 – 5.2.4. No dose reductions are allowed for Perjeta or Herceptin. If the patient misses a dose of Perjeta or Herceptin for any cycle and the time between doses is ≥ 6 weeks, a reloading dose of Perjeta or Herceptin (840 mg and 8 mg/kg, respectively) should be given. Subsequent maintenance Perjeta (420 mg) and Herceptin (6 mg/kg) doses 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.

After surgery, patients continue to receive Perjeta and Herceptin in the adjuvant setting until a total of 18 cycles of Perjeta and Herceptin have been administered during the study (neoadjuvant and adjuvant). Adjuvant Perjeta and Herceptin treatment should not start until 2 weeks after surgery. If the interval between the first dose of adjuvant Perjeta and Herceptin and the last dose of neoadjuvant Perjeta and Herceptin exceeds 6 weeks, a reloading dose of 840 mg of Perjeta and 8 mg/kg of Herceptin is required. The interval between the last dose of neoadjuvant Perjeta and Herceptin and the first dose of adjuvant Perjeta and Herceptin should be ≤ 9 weeks.

Perjeta IV

The initial dose of Perjeta IV will be administered over 60 (± 10) minutes, and patients will be observed for an additional 60 minutes. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes, and patients will be observed for an additional 30 minutes for infusion-related symptoms such as fever or chills. All infusion-related symptoms must have resolved before Herceptin or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions. Dose reductions for toxicity are not allowed.

Herceptin IV

The initial dose of Herceptin IV will be administered over 90 (± 10) minutes, and patients will be observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever or chills. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (± 10) minutes, and patients will be observed for an additional 30 minutes. All infusion-related symptoms must have resolved before Perjeta or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions. Dose reductions for toxicity are not allowed. Patients can be observed for a longer period at the discretion of the investigator or, if necessary, as per local requirements.

4.3.2.2 Arm B: SC Fixed-Dose Combination of Pertuzumab and Trastuzumab

In Arm B, the FDC is given as a fixed non–weight-based dose. A loading dose of 1200 mg SC pertuzumab and 600 mg SC trastuzumab is then followed by 600 mg SC pertuzumab and 600 mg SC trastuzumab Q3W. Chemotherapy should be given after the FDC.

Treatment will continue as scheduled (see Section 4.3.2.3), or until investigator-assessed radiographic or clinical progression or recurrence of disease or unmanageable toxicity.

Weight should be recorded during screening and on Day 1 of each cycle for all patients. The baseline weight for a patient will be the weight measured on Cycle 1, Day 1. The dose of doxorubicin, cyclophosphamide, and docetaxel is calculated according to the patient's BSA. The BSA and the dose of drug administered must be recalculated if the patient's body weight has changed by ±10% from baseline. Recalculation of the dose of drug administered on the basis of smaller changes in body weight or BSA is at the investigator's discretion.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Sections 5.2.1–5.2.4. No dose reductions are allowed for the FDC. If the patient misses a dose of the FDC for any cycle and the time between doses is ≥6 weeks, a reloading dose of the FDC (1200 mg pertuzumab and 600 mg trastuzumab) should be given. Subsequent maintenance the FDC doses (600 mg pertuzumab and 600 mg trastuzumab) will then be given Q3W, 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.

After surgery, patients continue to receive the FDC in the adjuvant setting until a total of 18 cycles of the FDC have been administered during the study. Adjuvant FDC treatment should not start until at least 2 weeks after surgery. If the interval between the first dose

of adjuvant FDC and the last dose of neoadjuvant FDC is ≥6 weeks, a reloading dose of FDC (1200 mg of pertuzumab and 600 mg of trastuzumab) is required. Subsequent maintenance FDC doses (600 mg pertuzumab and 600 mg trastuzumab) will then be given Q3W, starting 3 weeks later. The interval between the last dose of neoadjuvant FDC and the first dose of adjuvant FDC should be ≤9 weeks.

SC Fixed-Dose Combination of Pertuzumab and Trastuzumab

All doses of the FDC will be administered over 5–8 minutes as a SC injection into the thigh at a rate of no more than 2 mL/min. The loading dose should be administered over 8 minutes, and the maintenance dose should be administered over 5 minutes. The injection rate should be adjusted to a rate that is comfortable for the patient. After the first (loading dose) 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. Patients can be observed for a longer period at the discretion of the investigator or, if necessary, as per local requirements. Injection-related symptoms must have resolved before chemotherapy is started unless deemed clinically not significant by the investigator. Patients who experience injection-related symptoms may be pre-medicated with analgesics and antihistamines for subsequent injections. Dose reductions for toxicity are not permitted.

The thigh is the only location where the FDC should be administered. The injection site of the FDC should be alternated between the left and right thigh. New injections should be given at a distance of at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. The entire SC injection (10 mL volume for the maintenance dose; 15 mL volume for the loading dose) must be given in one site. Splitting the volume into two syringes or injecting at two different sites is not permitted.

4.3.2.3 AC→Docetaxel+HER2-Targeted Therapy

Patients receive doxorubicin 60mg/m^2 IV and cyclophosphamide 600mg/m^2 IV (AC) Q3W for 4 cycles (Cycles 1–4). AC is followed (3 weeks later) by docetaxel 75 mg/m^{2}IV, escalating to 100 mg/m^2 IV if no dose-limiting toxicity occurs (at the discretion of the investigator). HER2-targeted therapy (Perjeta IV plus Herceptin IV or the FDC) is given Q3W from the start of docetaxel (Cycles 5–8; i.e., 4 cycles in total during the neoadjuvant period).

After surgery, patients continue to receive HER2-targeted therapy in the adjuvant setting (Cycles 9–22) until a total of 18 cycles of HER2-targeted therapy have been given.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Sections 5.2.1–5.2.4.

Doxorubicin

Doxorubicin 60mg/m^2 will be administered on Day 1 of each cycle of AC treatment as an IV bolus over 3–5 minutes or as an infusion over 15 – 30 minutes, in accordance with local policy. Patients with BSA of > 2 m^2 should have their dose capped at 120 mg. Dose delays and dose reductions for toxicity are permitted.

Cyclophosphamide

Cyclophosphamide 600 mg/m^2 will be administered on Day 1 of each cycle of treatment as an IV bolus over 3-5 minutes or as an infusion, in accordance with local policy. Patients with BSA of > 2 m^2 should have their dose capped at 1200 mg. Dose delays and dose reductions for toxicity are permitted. Oral cyclophosphamide is not permitted.

Docetaxel

Docetaxel is administered as an IV infusion over 60 (± 10) minutes, after HER2- targeted therapy, at a starting dose of 75 mg/m^2 for the first cycle (Cycle 5). At the investigator's discretion, the dose may be escalated to 100 mg/m^2 for subsequent cycles (Cycles 6–8) provided no dose-limiting toxicity occurs. See Section 5.2.4 for details of dose-limiting toxicity and guidance on dose escalation and dose reductions.

Premedication, including corticosteroids, should be administered according to routine practice. Patients must be closely observed from the start of the infusion for hypersensitivity reactions, which may occur within minutes. Severe hypotension, bronchospasm, or generalized rash/skin reactions/erythema requires immediate discontinuation of docetaxel and appropriate treatment. The infusion may be slowed for minor symptoms, such as flushing or local cutaneous reactions. Patients experiencing severe hypersensitivity reactions should be discontinued from study treatment but maintained in the schedule of activities unless consent is withdrawn. Prophylactic G-CSF may be used to mitigate the risk of hematologic toxicities according to local policies and guidelines. Treatment of neutropenia with G-CSF is permitted according to local policies. In all cases, G-CSF will not be considered as a study drug and will not be provided by the Sponsor. For patients with a history of inflammatory digestive disease, it is recommended to refer them to their gastroenterologist for assessment before initiating treatment with docetaxel.

4.3.2.4 Other Required Medication

After surgery, patients with hormone receptor-positive disease should receive adjuvant hormone therapy according to guidelines provided in Section 4.4.3. Postoperative radiotherapy is to be given as clinically indicated and as per local practice (see Section 4.4.2 and Appendix 10).

All patients may receive full supportive care including anti-emetics (e.g., serotonin antagonists such as ondansetron, benzodiazepines), antidiarrheal agents (e.g., loperamide), short-term corticosteroids to treat or prevent allergic or infusion reactions, H_1 and H_2 antagonists (e.g., diphenhydramine, cimetidine), analgesics (e.g., paracetamol or acetaminophen, meperidine, opioids), and antibiotics as clinically indicated.

All concomitant medication (administered within 7 days prior to initiation of study drug) and treatment for breast cancer must be reported in the eCRF including:

- Date and extent of primary surgery and subsequent re-excision surgery (for positive margins), if applicable. Medication given in association with the surgical procedure (e.g., the premedication and anesthetic) need not be reported.
- Any locoregional radiation therapy (extent or volume and total dose)
- Any hormone therapy or surgical and radiation-induced ovarian ablation and drug-induced ovarian suppression (type, drug name, dose and schedule, anticipated duration of therapy)
- Bisphosphonate therapy
- Any other medication that is necessary for the management of the patient

All concomitant medications are to be reported until the end of study treatment visit (28 days after the last dose of study treatment). Thereafter, only medication applicable for long-term reporting must be reported, including:

- Breast cancer treatments (e.g., hormone therapy)
- Anti-cancer treatments given to treat a recurrence
- Medications related to the treatment of serious adverse events that are applicable for long-term reporting (e.g., treatment for heart failure)

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (Perjeta® IV, Herceptin® IV, and the FDC) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. 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 on the Drug Inventory Log.

4.3.4 Continued Access to Perjeta IV, Herceptin IV, and the FDC

Currently, the Sponsor does not have any plans to provide study drugs (Perjeta IV, Herceptin IV, and the FDC) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing Perjeta IV, Herceptin IV, and the FDC in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Surgery

Patients in both cohorts are scheduled to undergo surgery after eight cycles of neoadjuvant therapy. Patients may undergo breast-conserving surgery or mastectomy according to routine clinical practice.

Before starting neoadjuvant treatment, the primary tumor site should be marked using the method, which is routine clinical practice (e.g., skin tattoo or surgical clip) to enable appropriate surgical excision in case of tumor regression during neoadjuvant therapy. Patients with clinically positive axillary nodes by physical examination or by any radiographic imaging at baseline must undergo fine-needle aspiration or core-needle biopsy prior to randomization. SLNB is not allowed prior to neoadjuvant therapy.

Surgical management options for axillary lymph nodes include SLNB (after neoadjuvant treatment) and ALND of Level I and II lymphatics at the moment of breast surgery. The choice of the axillary procedure will be based on the clinical status of axilla, T stage, and local practice.

In patients with clinically negative axillary nodes at baseline, axillary surgical management after completion of neoadjuvant therapy should include SLNB or ALND. SLNB is the preferred method of axillary surgical management, if an experienced team is available. If SLNB is conducted, it is strongly recommended that more than one lymph node (2 to 3 minimum) be removed. All patients with positive macrometastases in sentinel nodes should undergo ALND regardless of the number of positive nodes, and it is recommended that at least 10 lymph nodes be removed for pathologic examination.

Patients with clinically positive axillary lymph nodes at baseline should undergo ALND at time of definitive surgery (after neoadjuvant therapy). It is recommended that at least 10 lymph nodes be removed for pathologic examination.

For sentinel nodes involving the internal mammary chain, refer to local, national, or international guidelines.

Level III axillary dissections should only be performed for patients with gross disease in the Level II nodes.

Investigators may follow more up-to-date guidelines on axilla management based on emerging data once they have been incorporated into institutional, local, national, or international guidelines (e.g., NCCN, ESMO, St. Gallen, Lisbon Conference, or American Society of Clinical Oncology [ASCO] Clinical Practice Guidelines).

Following completion of neoadjuvant therapy and surgery, pCR (ypT0/is, ypN0) will be established via local review. Pathologists who review study specimens must utilize the evaluations and assessments outlined in the Pathology Manual. Further details regarding pathology evaluation and assessment are outlined in the Pathology Manual (see Appendix 9).

For patients whose tumor remains inoperable after neoadjuvant treatment, locoregional and/or systemic management will be done as per local standard practice. These patients will be withdrawn from study treatment and will remain on study for follow-up of secondary and exploratory endpoints unless they have withdrawn consent from study participation.

Copies of the pathology report(s) from the patient's primary (main) surgery must be submitted to the Sponsor within 6 weeks of the date of surgery. If additional information on lymph nodes at surgery is present in other reports, these reports should also be submitted to the Sponsor. A standardized pathology summary form must also be completed and sent to the Sponsor.

Pathology report(s) along with pathology summary forms will be reviewed centrally by an independent pathologist.

4.4.2 Radiotherapy

Before actively enrolling patients, each center must define a radiotherapy policy for treating patients in the trial. General guidelines are given in Appendix 10. If indicated, radiotherapy is given after chemotherapy and surgery, during adjuvant HER2-targeted therapy and hormone therapy (for hormone-receptor positive disease).

4.4.3 Hormone Therapy

Before actively enrolling patients, each center must set a policy for the use of tamoxifen, ovarian ablation, or both for patients in the trial. Study sites must also set their local policy for the use of registered aromatase inhibitors. For hormone receptor positive-breast cancer, aromatase inhibitors will be allowed as adjuvant hormone therapy for postmenopausal patients and with ovarian suppression or ablation for premenopausal patients in countries where it has been registered for this indication. Its use must be consistent with the registered label. Hormone therapy is given after chemotherapy and surgery during adjuvant antibody therapy.

No other hormone therapy for primary breast cancer is allowed, including pure anti-estrogens and progestational agents, unless it becomes approved for adjuvant therapy during the conduct of the trial.

Female patients must be classified according to one of the menopausal status definitions described in Table 4.

Female patients should be treated according to the recommendations in Table 5; however, investigators may follow local practice guidelines. Male patients should be treated according to local practice.

Table 4 Menopausal Status Definitions

Status	Criteria
Premenopausal	• < 12 months since last menstrual period, AND • No prior bilateral ovariectomy, AND • Not receiving estrogen replacement, OR • Biochemical evidence of premenopausal status, according to local practice
Postmenopausal	• > 12 months since last menstrual period with no prior hysterectomy, OR • Prior bilateral ovariectomy, OR • Biochemical evidence of postmenopausal status, according to local practice

Table 5 Recommendations for Hormone Therapy for Female Patients

Clinical Scenario	Hormone Therapy
Hormone receptor-negative	Not permitted
Hormone receptor-positive [a] and premenopausal [b]	The following regimens are permitted: • Tamoxifen for 5–10 years with or without ovarian suppression, as per local policy • Ovarian suppression or ablation with aromatase inhibitors 5 years)
Hormone receptor-positive [a] and postmenopausal [b]	The following regimens are permitted: • Aromatase inhibitor for 5 years • Aromatase inhibitor for 2–3 years, followed by tamoxifen to complete a total of 5 years • Tamoxifen for 2–3 years, followed by an aromatase inhibitor to complete a total of 5 years • Tamoxifen for 5–10 years, as per local policy • Tamoxifen for 5 years, followed by an aromatase inhibitor for 5 years

[a] Hormone receptor positivity is defined as positive estrogen receptor or progesterone receptor or both. The investigator may treat the patient with adjuvant hormone therapy according to local or central results, but central results of hormone receptor status will be used in data analyses for the study (see Section 4.5.3).

[b] Menopausal status criteria: see Table 4.

4.4.4 Permitted Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Patients are permitted to use the following therapies during the study:

- Acceptable methods of contraception must be used when the female patient or male partner is not surgically sterilized or does not meet the study definition of postmenopausal (≥ 12 months of amenorrhea). See Section 5.1.3 for a list of permitted methods of contraception
- H_1 and H_2 antagonists (e.g., diphenhydramine, cimetidine)
- Cardiovascular medications: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers and diuretics (for treatment of arterial hypertension with a goal to reduce blood pressure < 140/90 mmHg), beta blockers, calcium channel blockers and digoxin (for heart rate control), thrombocyte aggregation inhibitors
- Analgesics/anti-inflammatories (e.g., paracetamol/acetaminophen, meperidine, opioids)

- Short-term use of corticosteroids to treat or prevent allergic or infusion reactions
- Standard premedications for neoadjuvant chemotherapy, including corticosteroids and antiemetics
- Standard therapies for (preexisting medical conditions and) medical and/or surgical complications
- Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) at the investigator's discretion
- Colony-stimulating factors (e.g., G-CSF)
- Blood transfusions at the investigator's discretion
- Estrogen-receptor (ER) antagonists (e.g., tamoxifen) or aromatase inhibitor (AI) for postmenopausal patients or tamoxifen with or without ovarian suppression for premenopausal patients or aromatase inhibitor with ovarian suppression for premenopausal patients initated after surgery, as per local practice and guidelines in Section 4.4.3

  Endocrine therapy must not be given concurrently with neoadjuvant therapy.
- Gonadotropin-releasing hormone (GnRH) agonists for fertility preservation
- Vitamin and mineral supplements
- Bisphosphonates (to be used in accordance with the approved labeled indication and/or nationally recognized treatment guidelines)
- Any other medication not included in the list of prohibited medications

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience an infusion-related reaction may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion- and injection-related reactions manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.4.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator and must be reported on the appropriate eCRF.

4.4.5 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment

- Any targeted anti-cancer therapy (e.g., lapatinib, neratinib)
- Regular systemic treatment with steroids

  Exceptions include short-term corticosteroid only to treat and prevent allergic or infusion reactions. In the case of short-term corticosteroid administration, the dose must not exceed >20 mg/day of dexamethasone (or equivalent) for >7 consecutive days.
- Any investigational agent, except for those used for this study
- Any systemically active oral, injected, or implanted hormonal method of contraception (see Section 5.1.3 for acceptable contraception methods) except for progesterone-coated intrauterine devices (IUDs) that had been previously implanted
- Hormone-replacement therapy (HRT)
- Use of erythropoiesis-stimulating agents (e.g., erythropoietin)
- Herbal remedies initiated for cancer treatment

  Other herbal remedies are discouraged but permitted and must be reported on the appropriate eCRF.
- Topical estrogens (including any intra-vaginal preparations), megestrol acetate, and selective ER modulators used with prophylactic intent are prohibited

  In the adjuvant setting, postmenopausal women with significant vaginal discomfort associated with anti-estrogen therapy may be considered for intermittent use of low-dose topical estrogens if non-prescription methods are unsuccessful at ameliorating symptoms.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1, Appendix 2, and Appendix 3. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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. Re-screening is only allowed one time.

4.5.2 Core Biopsy

The diagnosis of primary breast cancer will be performed as per local standard of care.

Submission of tumor tissue from the core biopsy of the primary tumor (preferred) or involved lymph node (if primary tumor cannot be biopsied) is mandatory for the trial. Fine-needle aspiration material is not acceptable. The tissue will be used to assess HER2 and ER/progesterone receptor (PgR) status and for *PIK3CA* mutation analysis. Samples must be FFPE, and tumor blocks are preferred. If it is not possible to submit tumor blocks, sites must provide 13 freshly cut slides. Tumor blocks will be returned to the site if there is any remaining tissue after central testing and sampling for biomarker research; slides will not be returned.

A 14-gauge needle is recommended, using an automatic device fired 3–4 times into the lesion to collect sufficient tumor tissue.

4.5.3 HER2 Screening for Eligibility and Central Assessment of Hormone Receptor Status

Patients should be initially screened for HER2 status by the local laboratory and should have an HER2 score of 3+ by IHC or *be positive for HER2* (*c-erbB2*) gene amplification by ISH (i.e., fluorescence in situ hybridization [FISH], silver in situ hybridization [SISH], or chromogenic in situ hybridization [CISH]) to qualify for central laboratory screening (see Figure 3). *Sites will also have the option to send samples with a local IHC score of 2+ for direct ISH testing by the central laboratory.*

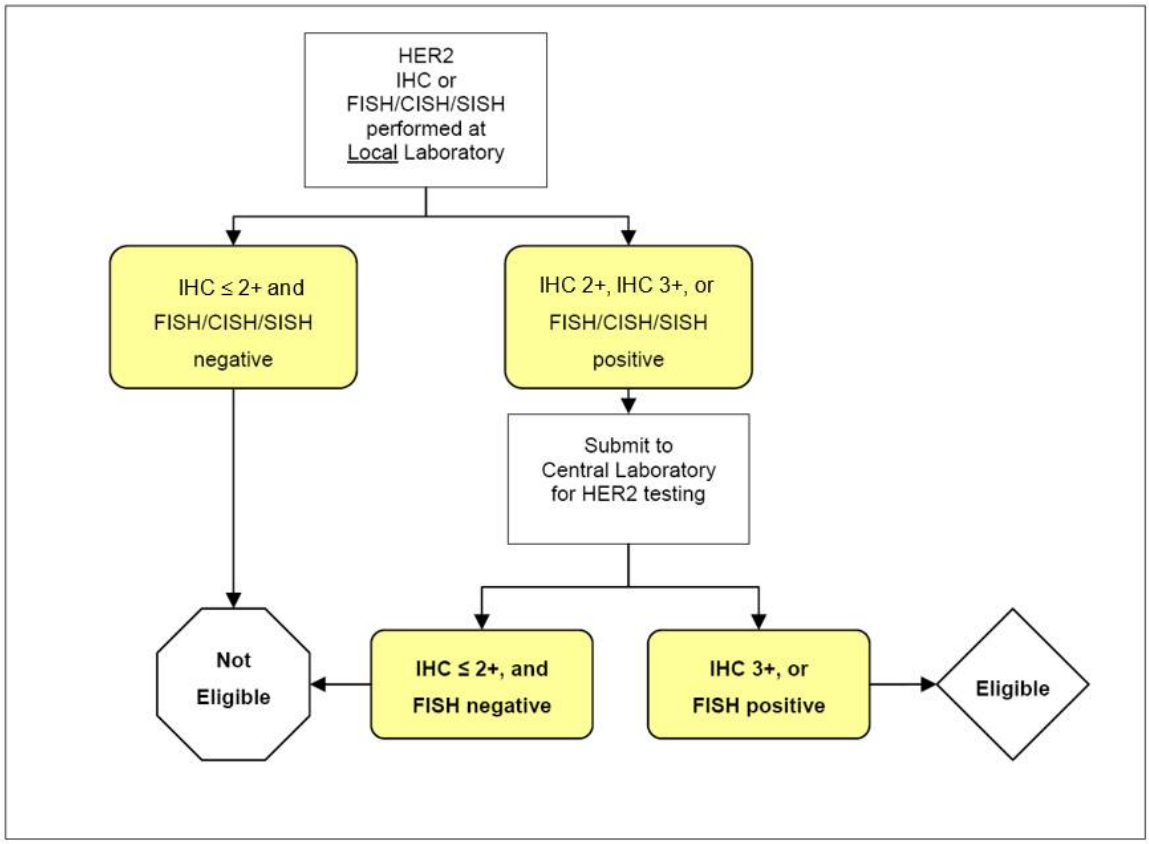
For central confirmation, HER2 positivity is defined as IHC 3+ in >10% of immunoreactive cells or *c-erbB2* gene amplification by ISH (ratio of *c-erbB2* gene signals to centromere 17 signals ≥2.0).

Central laboratory confirmation of a positive HER2 status is required prior to enrollment in the study. The outcome of this assessment will be communicated to the investigator.

In addition, central assessment of hormone receptor status (ER and PgR) will be conducted according to ASCO/College of American Pathologists guidelines (Hammond et al. 2010). The results will be communicated to the investigator. The investigator may treat the patient with adjuvant hormone therapy according to local or central results, but central results of hormone receptor status will be used in data analyses for the study.

Only patients who are HER2-positive by central confirmation will be allowed to enter the study; patients with overall negative and equivocal scores will be excluded from entry into the study.

Figure 3 HER2 Screening Procedure



CISH = chromogenic in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = *in situ hybridization*; FISH = fluorescence in situ hybridization; SISH = silver in situ hybridization.

Note: HER2 positivity by central testing is defined as the following: IHC 3+ in > 10% of immunoreactive cells or HER2 gene amplification by ISH (ratio of HER2 gene signals to centromere 17 signals ≥ 2.0).

4.5.4 Medical History, Concomitant Medication, and Demographic Data

Medical history will include clinically significant diseases within the last 5 years, breast cancer history (including prior cancer therapies and procedures and tumor characteristics [e.g., hormone receptor status, local HER2 status]), complete cardiovascular history, cardiac risk factors, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study drug.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded because racial and regional differences in toxicity have been reported in previous Perjeta trials. These differences are thought to be due to known pharmacogenomic differences in taxane elimination in different racial groups.

4.5.5 Physical Examinations

Physical examination includes an assessment of vital signs, physical measurements (body weight in kilograms and height in centimeters), and an examination of the breast, neck, axilla, chest, and abdomen. ECOG Performance Status will also be assessed. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The initial breast cancer assessment should be performed by the physician who will assess the patient's tumor for clinical response during neoadjuvant therapy.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF form. If the patient shows disease progression, this should be recorded on the Disease Status eCRF form.

4.5.6 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure (while the patient is in a seated position), and temperature.

4.5.7 Radiology

4.5.7.1 Breast Imaging

Bilateral mammogram must be obtained at screening and at treatment completion or treatment discontinuation visit. A mammogram prior to surgery (at Cycle 8) is recommended. Mammograms are mandated every 12 months during the follow-up period. Patients who have undergone mastectomy do not require mammograms of reconstructed breast(s).

The bilateral mammogram at screening, pre-surgery, and study completion or early termination can be replaced by another conventional imaging method, such as magnetic resonance imaging (MRI) or ultrasound per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual patient.

4.5.7.2 Tumor Staging

Baseline distant sites tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated, within 28 days prior to randomization.

As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- Stage IIA–IIB: Bone scan is to be performed in presence of bone pain and/or elevated ALP; abdominal/pelvic PET/CT scan in case of elevated ALP, abnormal liver function tests, abdominal symptoms or abnormal physical examination; and chest PET/CT scan if pulmonary symptoms are present.

- Stage IIIA–IIIC: Bone scan and PET/CT scan of chest, abdomen, pelvis; liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

4.5.8 Cardiac Function

All patients must have a LVEF measurement of at least 55% by ECHO (preferably) or MUGA scan prior to enrollment. The same method of LVEF assessment (ECHO or MUGA) should be used for the same patient throughout the study and, to the extent possible, should be obtained at the same institution. Investigators must be aware of local institutional regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories, and patients in this study require monitoring on more than four occasions within 1 year. Patients must also have an assessment for history of cardiac events, a physical examination, and a baseline ECG prior to enrollment to exclude any cardiac condition that would render them ineligible for participation in this trial. An ECG will also be performed after completion of anthracycline chemotherapy (and prior to the first cycle of HER-2 targeted therapy/taxane) and thereafter as clinically indicated. Cardiac function will be assessed locally according to the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3). ECG, ECHO, and MUGA scan reports are considered source documents and should be retained in the patient's medical records.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, differential count (percentage or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). During adjuvant HER2-targeted treatment, complete blood counts, including differential and platelets, are scheduled as per local practice for adjuvant Herceptin monotherapy.
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN) or urea, creatinine, albumin, total bilirubin, ALP, ALT, AST, total bilirubin and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN. Bicarbonate should only be tested at sites where this test is part of the standard safety laboratory panel.

  Limited serum chemistry includes only creatinine, ALP, AST, ALT, total bilirubin, and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN.
- Pregnancy test: all women of childbearing potential (see definition in Section 4.1.1) will have a serum pregnancy test at a local laboratory within 7 days prior to the first administration of study medication. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. Urine pregnancy tests are allowed during and after treatment (and as clinically

indicated) according to the Schedule of Activities (see Appendix 1, Appendix 2, and Appendix 3). Any positive urine pregnancy test must be confirmed with a serum (beta-human chorionic gonadotropin) β-HCG evaluation at the local laboratory. Pregnancy test results must be available prior to the next scheduled study treatment. Women who have undergone surgical sterilization or are postmenopausal are exempt from pregnancy assessments.

The following samples will be sent to the Sponsor or a designee for analysis:

- Serum and plasma samples for immunogenicity (ADA) assessments (pertuzumab, trastuzumab, rHuPH20)
- Serum samples for PK analysis (pertuzumab and trastuzumab)
- Newly collected tumor tissue sample obtained at baseline for determination of HER2, ER and PgR status (mandatory) and for *PIK3CA* mutation analysis

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 13 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10 – 12 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained. In case the submitted tumor tissue specimen is not sufficient to allow eligibility at screening the submission of an additional sample is required.

  Tumor tissue should be of good quality based on total and viable tumor content with cellular context and tissue architecture preserved regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy, or incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception(s):

- Serum and plasma samples collected for PK and immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Tumor tissue slides and blood-based samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

- For enrolled patients, remaining tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.9.1 PK Sampling

The primary endpoint of this study is C_{trough} and therefore adherence to the PK assessment schedule is of utmost importance. For each day of a scheduled PK assessment, the exact time of Perjeta and Herceptin or FDC administration and blood collection for PK assessments will need to be recorded in the eCRF.

Blood samples for PK analysis will be collected as described in Appendix 1, Appendix 2, and Appendix 3.

For PK samples that are required on the day of IV dosing, the PK blood samples need to be drawn from the arm not receiving the Perjeta and Herceptin infusion for patients in Arm A. If a patient is unable to provide venous access of the opposite arm from the infusion arm, the hand or leg may be used for PK blood sampling.

For patients in Arm B, blood should be drawn from the arm. If a patient is unable to provide venous access from the arm, the hand or leg may be used for PK blood sampling. If the leg is used to collect a PK blood sample, the area where the FDC has been administered must be avoided.

Collecting blood for PK samples from a central line and/or port is not allowed. However, if there is no possible way to avoid a central line and/or port, it is better to collect the PK sample than to not collect it at all, but the site of collection must be documented on the sample requisition form. For cases where a central line/port must be used, the PK sample must be collected prior to chemotherapy administration. If the central line and/or port has been used for a saline flush, avoid collecting the PK sample until 5 minutes has passed, to avoid dilution of the PK sample.

Blood samples drawn prior to drug administration will give information on serum trough levels of pertuzumab and trastuzumab.

The time of sampling at the end of the Perjeta and Herceptin infusions (IV arm) must be within 15 minutes after each infusion has ended and before chemotherapy is administered.

On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days (SC and IV arms) all samples must be taken on the exact day of the visit schedule whenever possible (a ± 2 day window is allowed if necessary).

If a patient's Cycle 8 dose is going to be delayed by more than 2 days, the Cycle 7 C_{trough} (i.e., pre-dose Cycle 8) sample should be collected 21 days after the infusion in Cycle 7.

The time of sampling is at the discretion of the investigator with the requirement to record the exact date and time of sampling.

For the follow-up Months 3 and 6 samples, a window of ± 7 days from the scheduled visit date is allowed.

The procedures for the collection, handling, and shipping of PK samples are specified in the laboratory manual.

4.5.10 Clinical Tumor Response Evaluations

Clinical breast examination (CBE) includes examination of the breast, axilla, and supraclavicular fossa. Patients with breast tumors > 2 cm at baseline will have their clinical response assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), as determined by CBE. Other methods of evaluation (i.e., mammogram or ultrasound) can be used in addition, as per local practice. Patients whose disease does not meet this criterion (i.e., those with only node-positive disease and tumors ≤ 2 cm) will have their clinical response assessed as CR, SD, or PD (but not as PR, since the tumors are too small to measure this response accurately), as determined by CBE. Other methods of evaluation (i.e., mammogram or ultrasound) can be used in addition, as per local practice. All patients, irrespective of the size and measurability of the primary tumor and locoregional lymph nodes, are evaluable for disease progression by CBE (with other methods of evaluation in addition, as per local practice) and will be included in the calculation of clinical response rate.

During the neoadjuvant treatment period (prior to surgery), tumor response will be assessed prior to each new cycle of therapy by CBE (mandatory) and other methods of evaluation in addition, (as per local medical practice) according to the schedule of activities (see Appendix 1). Response will be assessed as CR, PR, SD, or PD by the investigator. Provided that the patient's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, presurgery, and final visit/withdrawal can be replaced by MRI or ultrasound at the investigator's discretion, but the same method of assessment must

be used throughout for an individual patient. Tumor measurements should be made by the same investigator or radiologist for each patient during the study to the extent that this is feasible. In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumor response. These photos must include a ruler for documentation purposes.

After completion of neoadjuvant therapy and prior to surgery, an additional tumor response assessment is required, including a CBE and mammogram. Other methods of evaluation can be used in addition.

After surgery, CBE will continue according to the schedule of activities (see Appendix 2) to detect signs of locoregional relapse.

Results of any additional methods of assessment (such as ultrasound, X-rays, or MRI) may be included in the assessment of response as per routine practice (results and modalities will be collected in the eCRF). If the lesion shows clear signs of progression, the patient will be withdrawn from study treatment and provided with the local standard of care.

Discovery of ipsilateral or contralateral DCIS or LCIS during neoadjuvant treatment period will not be considered PD. However, invasive contralateral breast carcinoma will be classified as PD.

Clinical responses will be assessed locally and will not be independently reviewed.

4.5.11 Pathologic Response Evaluation

Pathologic response will be assessed by the local pathologist using guidelines provided in a Pathology Manual (see Appendix 9). A complete pathologic response (pCR) is defined as the absence of residual invasive disease on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes (tpCR; i.e., ypT0 or ypTis, ypN0) based on microscopic examination of the surgical specimen following neoadjuvant therapy, in line with the U.S FDA and European Medicines Agency (EMA) guidance for industry on pCR endpoints. tpCR rate is the main efficacy endpoint of the study. Molecular assay for analysis of sentinel lymph nodes after neoadjuvant therapy is not allowed.

Copies of the pathology report(s) from the patient's primary (main) surgery must be submitted to the Sponsor within 6 weeks of the date of surgery. If additional information on lymph nodes at surgery is present in other reports, these reports should also be submitted to the Sponsor. In addition, a standardized pathology summary form must also be completed and sent to the Sponsor along with the pathology reports.

Pathology report(s) along with pathology summary forms will be reviewed centrally, by an independent pathologist who will be blinded to treatment arm.

4.5.12 Diagnosis of Breast Cancer Progression or Recurrence

During the neoadjuvant treatment, diagnosis of disease progression or second primary breast cancer should be supported by clinical, laboratory, radiological, and/or histological finding. In the adjuvant period, all patients must be followed to assess disease recurrence, second primary cancer, and survival. The designation of disease recurrence, whether local, regional or distant, or a diagnosis of a second primary cancer can be made only when clinical, laboratory, radiological and/or histological findings support diagnosis. During the adjuvant portion of this study, disease status should be clinically evaluated and documented every 3 months for up to 1 year after completion of HER2-targeted therapy and at intervals of every 6 months for up to 3 years, thereafter.

The diagnosis of a breast cancer progression, recurrence or second primary tumor should be confirmed histologically whenever clinically possible. 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. The date of disease recurrence should be reported as the date of first diagnosis of a lesion (i.e., an objective finding), not the date of occurrence of the first symptom.

Recurrent disease includes local, regional, and distant recurrence and contralateral invasive breast cancer. Patients who are diagnosed with in situ breast disease or second (non-breast) malignancies should be maintained in regular follow-up wherever possible to fully capture any subsequent recurrent breast cancer events. In cases of diagnostic doubt (e.g., ill-defined, palpable mass in an irradiated breast), histologic or cytologic confirmation of recurrence should be obtained whenever possible.

Some patients may develop a suspicious recurrence that leads quickly to death without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such patients.

Types of recurrent disease are listed below, along with acceptable methods of confirmation of recurrence. The method of assessment used to confirm recurrence should be as per local practice. Invasive disease must be positively identified in accordance with the pathology guidance.

a) Local invasive recurrence

- In the ipsilateral breast after previous lumpectomy

  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.

  – Positive histology or cytology

- Ipsilateral after previous mastectomy

  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.

  – Positive histology or cytology

b) Regional recurrence

   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.

   – Positive histology or cytology, or
   – Chest X-ray, PET/CT-scan or MRI (especially in case of internal mammary lymph nodes, if no biopsy was performed)

c) Distant recurrence

   Defined as evidence of tumor in all areas, with the exception of those described in Sections a) and b) above

   The following criteria apply:

   - Skin, subcutaneous tissue, and lymph nodes (other than local or regional)
     – Positive cytology, aspirate or biopsy, or
     – Radiological (by PET/CT scan or MRI or ultrasound) evidence of metastatic disease
   - Bone
     – X-ray, PET/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 or
     – Positive cytology or histology (practically rarely performed with the exception of solitary nodules)

     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.

- Liver
  - Abdominal PET/CT scan, liver scan, ultrasound, or MRI consistent with liver metastases, or
  - Liver biopsy or fine-needle aspiration

  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.
- CNS (please note that these recurrences should be reported at any time)
  - MRI or PET/CT scan, usually in a patient with neurologic symptoms, consistent with CNS metastases or
  - Biopsy or cytology (e.g., for a diagnosis of meningeal involvement). However, meningeal involvement may also be diagnosed by PET/CT scan or MRI and depending from the general status of the patient additional investigations (including cytology of the cerebrospinal fluid).

d) Contralateral invasive breast cancer
   - Positive cytology or histology

e) Second primary malignancy (breast or other cancer)

   Any positive diagnosis of a second (non-breast) primary cancer, with the exception of non-melanoma skin cancers and carcinoma in situ of any site, will be considered an event in the analysis of the invasive disease-free survival including second primary non-breast cancer endpoint, however, they will not be included in the iDFS endpoint.

   LCIS 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.

   Note: Patients diagnosed with a second primary malignancy not requiring systemic therapy (i.e., chemotherapy, hormonal therapy, targeted treatment, etc) and with no evidence of breast cancer recurrence will remain on study and should continue with study treatment according to the protocol and schedule of activities, if considered by the investigator to be in the patient's best interest, whenever possible.

f) 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, iDFS including second primary non-breast cancer, DFS, and OS.

g) Other events

The following events are NOT considered recurrent disease, but must be recorded:

- Ipsilateral and contralateral LCIS
- Ipsilateral and contralateral DCIS
- Carcinoma in situ of the cervix
- Basal or squamous cell carcinoma of the skin

Following recurrence, all patients should be followed for survival according to the schedule of activities (see Appendix 3). In addition, LVEF assessments should continue to be performed every 6 months for 2 years after discontinuation of IV or the FDC and then annually for an additional year. Heart failure occurring at any time during the study and for up to 3 years after the last patient completed HER2-targeted therapy must be reported irrespective of the initiation of alternative treatment and irrespective of any causal relationship. Pregnancy tests should also continue and pregnancies should be reported until 7 months after the last dose of study treatment, irrespective of disease progression or relapse or the initiation of alternative treatment. Related serious adverse events and non-breast second primary malignancies (reportable as serious adverse events) should also be reported until the end of the study.

4.6 TIMING OF ASSESSMENTS

4.6.1 Procedures for Enrollment of Eligible Patients

After written informed consent has been obtained, the study site will report preliminary screening of the patient to the Sponsor or the Sponsor's representatives. After all required screening test results have been performed (according to the inclusion and exclusion requirements) and central HER2 positivity has been confirmed, the patient can be enrolled into the study by using the IxRS. Baseline tests not obtained during the screening period or within the specified window should then be completed. Patient identification numbers will be allocated sequentially in the order in which patients are screened. Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 3 days after randomization.

The investigator or designee will then enter the patient's data into the eCRF, which will be used for electronic data capture (EDC). A patient enrollment list must be maintained by the investigator.

4.6.2 Assessments During Treatment

Please see Appendix 1 and Appendix 2 for the schedule of activities to be performed during the treatment period.

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of activities (see Appendix 1 and Appendix 2) or in

the relevant section of the protocol. Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of activities.

Otherwise, during the treatment period, a window of ±3 days applies to all visits, unless otherwise specified.

All assessments must be performed before study treatment administration on Day 1 of the cycle or up to 3 days prior, unless otherwise specified.

During the treatment period, pregnancy test and LVEF results must be available prior to the administration of the next treatment cycle.

4.6.3 Assessments at the Treatment Completion/Discontinuation Visit

Patients who complete study treatment (defined as 8 cycles of chemotherapy and 18 cycles of HER2-targeted therapy) or discontinue from all study treatment early will be asked to return to the clinic 28 days (±3 days) after the last dose of study drug for a follow-up visit. If a patient has PD or relapse, the visit at which this is determined may be used as the treatment completion/early discontinuation visit.

Please see Appendix 2 for the schedule of activities to be performed at the treatment completion/discontinuation visit.

4.6.4 Follow-Up Assessments

After study treatment is complete and the end of study treatment safety follow-up visit has taken place, all patients should continue to be followed according to the schedule outlined in Appendix 3. In the case of premature discontinuation of chemotherapy (but continuation of HER2-targeted therapy), patients should continue to be followed as per Appendix 1 and Appendix 2. If all study treatment is discontinued early (for disease progression, relapse, or another reason), patients should continue to be followed according to Appendix 3. *Patients who did not receive any HER2-targeted therapy will not be required to give PK or ADA blood samples during follow-up.*

All patients must be followed until approximately 3 years after the last patient's last treatment, even if their assigned treatment is discontinued early. For this reason, some patients will be followed for more than 5 years (because of the 12-month projected recruitment period).

All participating sites will be informed of the approximate end of follow-up date for the study shortly after the last patient is enrolled.

The schedule of follow-up visits and tests for this study (see Appendix 3) is the minimum required. Investigators may wish to see their patients more frequently according to their routine practice.

After the treatment completion/discontinuation visit, adverse events should be followed as outlined in Section 5.6 and Section 5.7. See Appendix 3 for the schedule of follow-up assessments.

Details of whether a patient completed the full treatment and follow-up period or withdrew from participation in the study early (see Section 4.5.12) will be captured in the eCRF (study completion/discontinuation visit).

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy (patients must discontinue all study medication)
- Heart failure (NYHA Class III and IV; patients must discontinue all study medication)
- A confirmed significant LVEF decrease (LVEF decrease ≥ 10 percentage points from baseline and to an LVEF value of below 50% [see Appendix 7]). Confirmation should be completed within approximately 3 weeks [patients must discontinue all study medication].
- Anaphylaxis (patients must discontinue the relevant study drug if it is clear which drug was responsible. If Perjeta or Herceptin or the FDC are deemed responsible, then the patient must discontinue all study medication). Patients who experience any of the following events will be discontinued from study treatment:
  - Grade 4 allergic reaction
  - Grade 3 or 4 hypersensitivity reaction
  - ARDS
  - Bronchospasm
- Patients whose disease progresses before the end of neoadjuvant therapy will be withdrawn from study treatment and treated as clinically indicated, according to local clinical practice

For further details on study drug modifications and discontinuations see Sections 5.2.1–5.2.4. Patients who discontinue study drug prematurely will be asked to return to the clinic for a treatment discontinuation visit (see Section 4.6.3) and may undergo follow-up assessments (see Section 4.6.4).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit 28 (±3) days after the last dose of study drug (see Appendix 1 for additional details).

After study treatment discontinuation, information on survival follow-up and new anti-cancer therapy (if applicable) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months for the first year and every 6 monthly thereafter until end of study or death (unless the patient withdraws consent or the Sponsor terminates the study).

4.7.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.7.3 Study Discontinuation

The Sponsor has 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 severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The pertuzumab and trastuzumab drug substance in the FDC for SC administration is identical to the drug substance in the IV formulations. Therefore, the safety plan for patients in this study is based on clinical experience with Perjeta IV and with Herceptin IV and SC in completed and ongoing studies, as well as the clinical experience with Perjeta SC (alone or co-mixed with Herceptin) in the Phase I Study BO30185.

The anticipated important safety risks for Perjeta and Herceptin are outlined below. Please refer to the most recent Perjeta Investigator's Brochure (for important safety risks for Perjeta IV administration), the Herceptin Investigator's Brochure (for important safety risks for Herceptin IV and SC administration), and the Pertuzumab and Trastuzumab FDC Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Perjeta

5.1.1.1 Hypersensitivity Reactions/Anaphylaxis and Administration Related Reactions (Infusion or Injection)

Like other monoclonal antibodies**,** Perjeta IV has been associated with administration-related reactions (ARRs). ARRs include:

- Infusion-related reactions (i.e., a systemic reaction with symptoms such as chills, diarrhea, fatigue, headache, nausea, and pyrexia).

  Such reactions are likely to be due to a release of cytokine(s) and typically occur during, or very shortly after, the administration of monoclonal antibodies, but they may also show a delayed onset. In general, infusion-related adverse events are more frequent and severe with the first infusion, and decrease in number and severity over time. The majority of adverse events resolve fully.

- Injection-related reactions may manifest themselves as
  - Systemic reactions, similar to the infusion-related reactions
  - Local injection-site reactions (ISRs) with signs and symptoms such as erythema, induration, swelling, pain, hypoaesthesia and discomfort

Hypersensitivity reactions/anaphylaxis is a systemic reaction, mediated by interactions between factors released from IgE and mast cells, resulting in an antigen-antibody reaction. Hypersensitivity reactions/anaphylaxis AEs are likely to start mildly and increase in number and severity over time. Patients who experience a Grade 4 allergic reaction or acute respiratory distress syndrome (ARDS) should be discontinued from treatment. Since there is the potential for a delayed onset, patients should be instructed to contact the treating physician with any concerns. ARRs may be difficult to distinguish from hypersensitivity reaction; therefore, the true relation of an event to administration of study treatment is difficult to ascertain, particularly when treatment regimens involve combination therapy.

Perjeta will be administered by staff trained to monitor for and respond to medical emergencies in a setting with emergency equipment.

For patients in Arm A, the initial IV infusion of Perjeta will be given over 60 (±10) minutes, followed by an observation period of 60 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes (±10) with an observation period of 30 minutes. The observation period should be completed prior to the subsequent Herceptin infusion. The initial IV infusion of Herceptin will be administered over 90 (±10) minutes, after which the patient will be observed for 30 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over 30 (±10) minutes, followed by an observation period of 30 minutes. Patients can be observed for a longer period at the discretion of the investigator or, if necessary, as per local requirements.

Premedication with antipyretics, antihistamines, or corticosteroids may be administered before infusions of Perjeta and Herceptin.

Patients in Arm B (receiving the FDC) will be monitored for at 30 minutes after the first FDC loading dose and 15 minutes following subsequent injections for any adverse effects. If ARRs occur, patients will be monitored until complete resolution of signs and symptoms. Patients can be observed for a longer period at the discretion of the investigator or, if necessary, as per local requirements.

Please refer to the Perjeta Investigator's Brochure for the most recent data related to the risk of hypersensitivity reactions.

5.1.1.2 Symptomatic Left Ventricular Systolic Dysfunction

Like Herceptin, Perjeta is directed at the HER2 receptor and may be associated with a risk of symptomatic LVSD.

Cardiac dysfunction may manifest as an asymptomatic or mildly symptomatic decrease in LVEF (NCI CTCAE, Grade 1 and Grade 2) or as a symptomatic decreased in LVEF/CHF (NCI CTCAE, Grade ≥ 3; NYHA Class III or IV). A LVEF decline ≥ 10 percentage points from baseline to an absolute value of $< 50\%$ requires clinical follow-up for Perjeta studies.

A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported in Perjeta studies. In the pivotal Phase III trial WO20698/TOC4129g (CLEOPATRA), the rates of symptomatic and asymptomatic LVSD were not higher in patients receiving Perjeta than in those patients receiving placebo. The incidence of symptomatic LVSD was 1.5% (6/408) for patients receiving Perjeta with Herceptin and docetaxel (events in the treatment period only) and 1.5% (7/396) in placebo arm.

In BERENICE, in the neoadjuvant period, a total of 3 patients (1.5%) in dose-dense docetaxel arm and no patients (0%) in the FEC-docetaxel arm experienced four NYHA III/IV Heart Failure events, all of which occurred during treatment with the anti-HER2 therapy.

The overall incidence of primary cardiac events in APHINITY (defined as heart failure [NYHA Class III or IV] and a drop in LVEF of at least 10 ejection fraction (EF) points from baseline AND to below 50%, or cardiac death was low ($< 1\%$ of patients in pertuzumab and placebo arms).

In summary, the incidence of symptomatic cardiac failure (defined by incidence of investigator-assessed symptomatic LVSD/CHF as per study protocol in each combination therapy study, or by the Standardised MedDRA Query [SMQ] 'Cardiac Failure [wide] for the pooled single-agent population across Perjeta studies, where the

pooled data were available) was low (approximately 1.0% – 1.5%). Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of decreased LVEF. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy.

Perjeta has not been studied in patients with a pretreatment LVEF value of < 50%, a prior history of CHF, decreases in LVEF to < 50% during prior Herceptin adjuvant therapy, conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment, or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent.

Subjects with significant cardiac disease or baseline LVEF < 55% are not eligible for this study. As in all Perjeta trials, enrolled patients need to undergo routine cardiac monitoring by ECHO or MUGA scan. During the screening/baseline period, complete medical history information will be collected from all patients to explore possible risk factors for treatment-associated CHF. Monitoring of LVEF is required while subjects are receiving study treatment and for 3 years following discontinuation of IV HER2-targeted therapy or the FDC, (see Appendix 1, Appendix 2, and Appendix 3). If symptomatic LVSD (heart failure; SAE of NCI CTCAE v4 Grade 3 or 4; NYHA Class III or IV) develops, the patient must be monitored carefully with repeat LVEF assessments. Symptomatic LVSD should be treated and followed according to standard medical practice. Refer to the algorithm in Appendix 7 for decisions regarding the continuation or discontinuation of anti-HER2 study medication based on LVEF assessment in asymptomatic patients.

Please refer to the Perjeta Investigator's Brochure for the most recent data relating to risk of LVSD and CHF.

5.1.1.3 Epidermal Growth Factor Receptor (HER1)-Related Toxicities

Although Perjeta targets HER2, because of its role in heterodimerization with other members of the HER family (e.g., EGFR), it may cause toxicities associated with the use of EGFR tyrosine kinase inhibitors, which include diarrhea, rash/skin reactions and mucositis.

Diarrhea

Diarrhea has been observed in approximately 50% of patients treated with pertuzumab in the Phase II single-agent studies and in up to 90% of patients in combination therapy studies. Diarrhea was NCI CTCAE Grade 1 or 2 in the majority of cases.

Rash/Skin Reactions

Rash/skin reactions have been observed in approximately 17% of patients treated with pertuzumab in the Phase II single-agent studies and in up to 73% of patients in combination studies. The rash was generally mild to moderate in intensity and NCI CTCAE Grade 1 or 2.

The rash/skin reaction appeared to be treatable in some patients with standard acne therapies, including topical and oral antibiotics.

Mucositis

Mucositis has been observed in approximately 15% of patients treated with pertuzumab in the Phase II single-agent studies and in up to 50% of patients in combination studies. The most common preferred terms reported were mucosal inflammation and stomatitis.

It is possible that mucositis and/or diarrhea that occur with the addition of pertuzumab to docetaxel plus trastuzumab may lead to an increase in leukopenic events. Breaches in mucosal surfaces may allow the entry of microorganisms into the circulation, resulting in a higher incidence of fever/infection in patients with neutropenia.

Please refer to the Perjeta Investigator's Brochure for the most recent data relating to the risk of EGFR-related toxicities.

5.1.2 Risks Associated with Herceptin

Serious adverse reactions, including LVSD, ARRs, hypersensitivity, allergic-like reactions, and pulmonary events, have been observed in patients receiving Herceptin therapy. For some patients, symptoms progressively worsened and led to further pulmonary complications. Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported.

Fatalities have occurred within hours and up to 1 week following Herceptin IV administration. On very rare occasions, patients have experienced the onset of administration-related symptoms or pulmonary symptoms more than 6 hours after the start of the Herceptin administration. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur. Patients who are experiencing dyspnea at rest due to complications of co-morbidities may be at increased risk of a fatal infusion-related reaction. Therefore, these patients should not be treated with Herceptin.

5.1.2.1 Administration-Related Reactions, Allergic-Like Reactions, and Hypersensitivity

Herceptin has been associated with administration-related reactions (ARRs). ARRs are defined as systemic 'infusion-related reactions' associated with IV administration of Herceptin and systemic reactions associated with SC administration. In some studies, local ISRs were excluded from the ARR definitions. A revised definition of ARRs

potentially associated with IV and SC administration of Herceptin was used in the BO22227 (HannaH) study and is applicable to all future and ongoing Herceptin IV and SC studies. This definition is based on a modified version of the anaphylactic reaction SMQ (as modified by the addition of the following four MedDRA Preferred Terms: hypersensitivity, drug hypersensitivity, infusion-related reaction, and injection-site hypersensitivity). The revised definition of ARRs differs from that in previous studies in the MBC and EBC settings which reported only 'infusion reactions' or 'infusionrelated reactions' associated with Herceptin administration and makes comparison of the rates of ARRs between studies difficult.

Serious adverse reactions to Herceptin IV that have been reported infrequently include dyspnea, hypotension, wheezing, bronchospasm, asthma, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, and angioedema. Although such events were not reported in the clinical trial with Herceptin SC, caution should be exercised, as these events have been associated with the IV formulation.

These reactions were usually associated with the first administration of Herceptin and generally occurred during or immediately following administration.

In the pivotal BO22227 (HannaH) study, the overall incidence of ARRs in the Herceptin IV arm was 37.2% (111/298) compared with 47.8% (142/297) in the Herceptin SC arm. Most of the ARRs occurred in the neoadjuvant treatment phase, with an incidence of 32.6% in the Herceptin IV arm and 38.4% in the Herceptin SC arm. Fewer ARRs were reported during the adjuvant treatment phase of the study. All but one of the ARRs was Grade 1 or Grade 2 in intensity and the distribution was balanced between the study phases in terms of the most common AEs and SOCs.

There was a higher rate of Herceptin SC injection-site reactions compared with the Herceptin IV infusion (11.1% in Herceptin SC vs. 0.3% in Herceptin IV). With few exceptions, all of these events were of Grade 1 intensity.

Serious reactions to Herceptin IV have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids.

Please refer to the Herceptin Investigator's Brochure for the most recent data related to the risk of ARRs, allergic-like reactions, and hypersensitivity reactions.

5.1.2.2 Pulmonary Events

Caution is recommended with the use of the Herceptin SC formulation as severe pulmonary events have been reported with the use of the Herceptin IV formulation in the post-marketing setting. These events have occasionally been fatal. They may occur as part of an ARR or with delayed onset. In addition, cases of interstitial lung disease, including lung infiltrates, acute respiratory distress syndrome (ARDS), pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and

respiratory insufficiency have been reported with Herceptin IV. These events have been most common with the first infusion, and their severity has decreased with subsequent infusions. Serious reactions have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids. ARDS has been reported with a fatal outcome.

Please refer to the Herceptin Investigator's Brochure for the most recent data related to the risk of pulmonary events.

5.1.2.3 Symptomatic Left Ventricular Systolic Dysfunction

Heart failure (NYHA Class II – IV) has been observed in patients who have received Herceptin therapy alone or in combination with docetaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This event may be moderate to severe and has been associated with death. Risk factors for Herceptin-associated LVSD include increased age, concomitant administration with anthracyclines, and declining LVEF while on Herceptin treatment. If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with standard medications for this purpose.

The rates of cardiac dysfunction observed in large Herceptin adjuvant trials in EBC are $<4\%$ with event rates comparable across the studies. In the HannaH study, the proportion of patients who experienced a significant decrease in LVEF (defined as a drop in LVEF ≥ 10 percentage points to a value of $<50\%$) was similar in each treatment arm (12 [4.2%] patients in Herceptin IV and 11 [3.8%] patients in Herceptin SC).

Because the half-life of Herceptin is approximately $28-38$ days, Herceptin may persist in the circulation for up to 7 months after the last dose of Herceptin. Patients who receive anthracyclines after the last dose of Herceptin may possibly be at increased risk of LVSD. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks (7 months) after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Most patients who developed heart failure in the Phase III trials of Herceptin in MBC and EBC improved with standard medical treatment. This treatment included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on weekly therapy with Herceptin without experiencing additional clinical cardiac events.

Please refer to the Herceptin Investigator's Brochure for the most recent data related to the risk of LVSD.

5.1.3 Pregnancy and Contraception (Risks Associated with Both Perjeta and Herceptin

ICH M3 Guidance requires precautions to be taken to minimize risk to fetus or embryo when enrolling women of childbearing potential. This includes the use of one highly effective or two effective contraceptive measures, excluding pregnancy at baseline (serum test) (see Section 4.1.1), continued pregnancy testing up to 7 months following Perjeta and Herceptin administration (follow-up period based on PK considerations), and continued monitoring of HER2-targeted therapy-exposed pregnancy.

Reproductive toxicity was identified during nonclinical studies with Perjeta. Perjeta administered to pregnant cynomolgus monkeys during organogenesis led to delayed renal development, oligohydramnios, and embryo-fetal deaths. However, reproductive toxicity studies with Herceptin conducted in female cynomolgus monkeys revealed no trastuzumab-related embryotoxicity or effects on fetal development. There are no clinical studies of Herceptin or Perjeta in pregnant women. IgGs are known to cross the placental barrier. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Therefore, neither Perjeta nor Herceptin should be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

For women of childbearing potential (i.e., women who have not reached menopause yet [$\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause]) who have not undergone removal of ovaries and/or uterus, agreement must be obtained to use one highly effective (resulting in a failure rate of $<$ 1% per year) non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient or partner, or both, while receiving study treatment and for 7 months following the last dose of Perjeta and Herceptin or FDC. Women who have had a tubal ligation or bilateral ovariectomy do not require additional contraception.

Men with female partners of childbearing potential participating in the study must agree to take reliable and effective contraceptive measures while receiving study treatment and for 7 months following the last dose of Perjeta and Herceptin or FDC. Men must refrain from donating sperm during this same period. Male study participants whose partners are pregnant must remain abstinent or use a condom during the entire pregnancy to avoid exposing the embryo.

Methods of birth control that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly effective forms of contraception. The following non-hormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient

  Periodic abstinence (e.g., calendar, ovulation, symptothermal postovulation methods), and withdrawal are not acceptable methods of contraception

- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

  For female patients, the vasectomized male partner should be the sole partner.

Alternatively, two of the following effective forms of contraception may be used instead:

- Placement of non-hormonal IUD or intrauterine system

  Consideration should be given to the type of device being used, as there are higher failure rates quoted for certain types (e.g., steel or copper wire).

- Condom with spermicidal foam/gel/film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method is acceptable, which is defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ suppository.

Based on PK considerations, contraception methods must continue for the duration of study treatment and for at least 7 months after the dose of Perjeta and Herceptin.

5.1.3.1 Breastfeeding

It is not known whether Herceptin or Perjeta is excreted in human milk. As maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during Perjeta and Herceptin or FDC therapy and not to breastfeed for at least 7 months following the last dose.

5.1.4 Warnings and Precautions for Docetaxel, Doxorubicin, and Cyclophosphamide

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for docetaxel, doxorubicin and cyclophosphamide.

5.1.5 Warnings and Precautions for Anti-Estrogen Therapy and Radiotherapy

No evidence available at the time of finalization of this study protocol indicated that special warnings and precautions were appropriate other than those noted in the currently approved prescribing information for anti-estrogen therapy and radiotherapy.

5.2 MANAGEMENT OF PATIENTS WHO EXPERIENCE SPECIFIC ADVERSE EVENTS

5.2.1 Dose Delays, Discontinuation, and Modifications (General)

If any of the individual study drugs must be delayed for a day or more, all agents should be delayed for the same time frame, with the possible exception of delays for LVEF decline after anthracycline therapy (see Section 5.2.5.1).

Patients who discontinue chemotherapy due to toxicity should not be automatically withdrawn from all study treatments. Perjeta and Herceptin IV or the FDC SC should be completed for a total of 18 cycles as per protocol, but surgery may be brought forward if clinically indicated.

If HER2-targeted therapy is withheld for more than 2 cycles (>9 weeks) or needs to be permanently discontinued for treatment-related toxicity, the patient will be withdrawn from all study treatment and treated at the discretion of the investigator as clinically indicated. The patient will continue to be followed post-treatment as described in Section 4.6.4.

5.2.2 Dose Delays and Modifications for Perjeta IV, Herceptin IV, and the FDC

HER2-targeted therapy dose modifications are not permitted. Administration may be delayed to assess or treat adverse events, such as cardiac adverse events or myelosuppression, and to maintain synchrony with chemotherapy administration.

During the neoadjuvant and adjuvant treatment periods, a dose delay of up to (and including) 6 weeks (i.e., up to and including 9 weeks between doses) will be permitted to allow recovery to baseline. Following a dose delay of less than 3 weeks (i.e., <6 weeks between doses), HER2-targeted therapies do not need to be reloaded (only the maintenance dose needs to be given). For a dose delay of 3 weeks or more (i.e., ≥ 6 weeks between doses), a reloading dose of Perjeta and Herceptin (840 mg and 8 mg/kg, respectively) or the FDC (1200 mg pertuzumab and 600 mg trastuzumab) should be administered.

5.2.3 Dose Delays and Modifications for Anthracycline-Based Chemotherapy (AC)

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information and managed as per local practice.

5.2.4 Dose Delays and Modifications for Taxanes (Docetaxel)

All dose modifications for docetaxel alone are based on the dose level changes outlined below in Table 6.

Table 6 Dose Levels for Docetaxel

	Dose Level 0	Dose Level −1	Dose Level −2	Dose Level −3
Docetaxel (mg/m^2)	100	75 (starting dose)	60	Discontinue

Re-escalation is not permitted following a dose reduction.

A dose-limiting toxicity to docetaxel is defined as the occurrence of one or more of the following:

- Febrile neutropenia
- Grade 4 neutropenia (neutrophils $<0.5\times10^9$/L) for >5 days or a neutrophil count $<0.1\times10^9$/L for more than 1 day
- Grade 2 non-hematologic adverse events (NCI CTCAE, v4), such as peripheral neuropathy, unless the toxicity is deemed manageable by the investigator (e.g., nausea and vomiting)

General dose modification guidelines:

- If a Grade 3 or 4 non-hematologic toxicity is experienced, docetaxel may be reduced from 100 mg/m^2 to 75 mg/m^2, and again to 60 mg/m^2, if required.
- If a taxane-related hypersensitivity reaction occurs despite premedication, treatment as medically indicated will be instituted.

- For hypersensitivity reaction of Grade ≤3, continuation of docetaxel is at the investigator's discretion.
- If a Grade 4 hypersensitivity is experienced, docetaxel must be permanently discontinued.
- If a Grade ≥3 enterocolitis is experienced, permanent discontinuation of docetaxel is recommended.
- Taxane-related fluid retention will be treated as per the investigator's discretion.
- If the taxane must be discontinued before completion of the scheduled cycles, the remaining Perjeta IV and Herceptin IV or the FDC SC doses should be administered.

See Table 7 for the management of taxane-related neurosensory toxicity and Table 8 for taxane-related musculoskeletal pain. Instructions for management of all other toxicities related to docetaxel are listed in Table 9.

Table 7 Dose Modifications for Taxane-Related Neurosensory Toxicity

Paresthesias/Dysesthesias	1–7 Days Duration	Persistent for >7 Days or Causing the Next Cycle to be Delayed
Grade 1 Paresthesias/dysesthesias that do not interfere with function	Maintain docetaxel dose.	Maintain docetaxel dose.
Grade 2 Paresthesias/dysesthesias interfering with function, but not activities of daily living	Maintain docetaxel dose. [a]	Decrease docetaxel by one dose level. [b]
Grade 3 Paresthesias/dysesthesias with pain or with function impairment interfering with activities of daily living [c]	First episode: Decrease docetaxel one dose level. [a] Second episode: Discontinue docetaxel.	Discontinue docetaxel.

[a] Must be resolved to Grade ≤1 on Day 1 of the next cycle.

[b] Hold docetaxel for persistent Grade 2 neurotoxicity. When Grade ≤1, resume treatment with dose modification for docetaxel. If Grade 2 toxicity persists after 3 weeks of delay, discontinue docetaxel.

[c] For persistent paresthesias and dysesthesias that are disabling or life-threatening, docetaxel should be discontinued.

Table 8 Dose Modifications for Taxane Musculoskeletal Pain Not Controlled by Analgesics [a]

Musculoskeletal Pain	1–7 Day Duration	Persistent for > 7 Days or Causing the Next Cycle to be Delayed
Grade 1	Maintain docetaxel dose.	Maintain docetaxel dose.
Grade 2	Maintain docetaxel dose.	Maintain docetaxel dose, OR Decrease docetaxel one dose level. [b]
Grade 3	First episode: Decrease docetaxel one dose level.	First episode: Decrease docetaxel one dose level, [b] OR Discontinue docetaxel.
	Second episode: Discontinue docetaxel.	Second episode: Discontinue docetaxel.

[a] The use of narcotics and non-steroidal anti-inflammatory drugs (NSAIDs) is encouraged to maintain the dose of docetaxel, if possible.

[b] Delay docetaxel for persistent Grade 2 or 3 musculoskeletal pain. When the symptom achieves Grade ≤ 1, resume treatment with dose modification for docetaxel. If Grade 2 or Grade 3 toxicity persists after delay, discontinue docetaxel.

Table 9 Dose Modifications and Delays for Docetaxel Alone

Adverse Event (Category) [a]	Modifications for AEs That Occur during a Cycle but Resolve prior to the Next Treatment Cycle [b]	Modifications for AEs that Require a Delay in Administration of the Treatment Cycle [c]
Hematologic: neutrophil count decreased (investigations)		
Grades 2, 3, and 4	Maintain dose.	Docetaxel: • Hold until ≥1500/mm^3. • For recovery that takes 1–3 weeks, maintain dose and add G-CSF. • If receiving G-CSF and recovery takes: – 1 week: Maintain dose. – 2–3 weeks: Decrease one dose level.
Hematologic: platelet count decreased (investigations)		
Grades 2, 3	Maintain dose.	• Hold until ≥75,000/mm^3. • If recovery takes: – 1 week: Maintain dose. – 2–3 weeks: Decrease one dose level.
Grade 4	Decrease by one dose level.	Decrease by one dose level.

AE = adverse event; G-CSF = granulocyte colony-stimulating factor; NCI CTCAE v4 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Notes: Dose modifications must be based on AEs that occur during the cycle (Column 2) and AEs present on the scheduled cycle Day 1 (Column 3). Dose modifications must be based on the AE requiring the greatest modification.

[a] NCI CTCAE v4.

[b] Resolved means that AEs requiring dose modification are Grade ≤1 (except absolute neutrophil/granulocyte count [which must be ≥1500/mm^3 for docetaxel] and bilirubin [which must be less than or equal to the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[c] Hold and check weekly. With the exception of absolute neutrophil/granulocyte count and bilirubin, resume treatment when toxicity is Grade ≤1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted therapy as planned to complete 18 cycles of treatment.

Table 9 Dose Modifications and Delays for Docetaxel Alone (cont.)

Adverse Event (Category) [a]	Modifications for AEs That Occur during a Cycle but Resolve prior to the Next Treatment Cycle [b]	Modifications for AEs That Require a Delay in Administration of the Treatment Cycle [c]
Blood and lymphatic system disorders: febrile neutropenia		
Grades 3, 4	Decrease by one dose level, add G-CSF support, or discontinue.	
Gastrointestinal disorders (if related to chemotherapy): diarrhea		
Grade 2	Maintain dose.	Decrease by one dose level.
Grade 3	Decrease by one dose level.	Decrease by one dose level.
Grade 4	Decrease by two dose levels or discontinue.	Decrease by two dose levels or discontinue.
Gastrointestinal disorders (if related to chemotherapy): mucositis oral (stomatitis)		
Grade 2	Maintain dose.	Decrease by one dose level.
Grade 3	Decrease by one dose level.	Decrease by one dose level.
Grade 4	Decrease by two dose levels or discontinue.	Decrease by two dose levels or discontinue.
Gastrointestinal disorders (if related to chemotherapy): vomiting (despite antiemetics)		
Grade 2	Decrease by one dose level (optional).	Decrease by one dose level.
Grades 3, 4	Decrease by one dose level or discontinue.	Decrease by two dose levels or discontinue.

AE = adverse event; G-CSF = granulocyte colony-stimulating factor; NCI CTCAE v4 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0..

Notes: Dose modifications must be based on AEs that occur during the cycle (Column 2) and AEs present on the scheduled cycle Day 1 (Column 3). Dose modifications must be based on the AE requiring the greatest modification.

[a] NCI CTCAE v4.

[b] Resolved means that AEs requiring dose modification are Grade ≤ 1 (except absolute neutrophil/granulocyte count [which must be $\geq 1500/mm^3$ for docetaxel] and bilirubin [which must be less than or equal to the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[c] Hold and check weekly. With the exception of absolute neutrophil/granulocyte count and bilirubin, resume treatment when toxicity is Grade ≤ 1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted therapy as planned to complete 18 cycles of treatment.

Table 9 Dose Modifications and Delays for Docetaxel Alone (cont.)

Adverse Event (Category) [a]	Modifications for AEs That Occur during a Cycle but Resolve prior to the Next Treatment Cycle [b]	Modifications for AEs That Require a Delay in Administration of the Treatment Cycle [c]
Gastrointestinal disorders (if related to chemotherapy): enterocolitis [d]		
Grades 3, 4	Provide immediate supportive care and discontinue (at the discretion of the investigator)	
Hepatic function: bilirubin or AST or ALP increased (investigations)		
Grade 2	Decrease by one dose level.	• Hold until bilirubin returns to the baseline grade, and AST and ALP have returned to Grade ≤1. • Subsequently decrease by one dose level.
Grade 3	Decrease by two dose levels.	Decrease by two dose levels.
Grade 4	Discontinue.	Discontinue.
Other clinically significant AEs [e]		
Grade 3	Decrease by one dose level.	Decrease by one dose level.
Grade 4	Decrease by two dose levels or discontinue.	Discontinue.

AE = adverse event; G-CSF = granulocyte colony-stimulating factor; NCI CTCAE v4 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Notes: Dose modifications must be based on AEs that occur during the cycle (Column 2) and AEs present on the scheduled cycle Day 1 (Column 3). Dose modifications must be based on the AE requiring the greatest modification.

[a] NCI CTCAE v4.

[b] Resolved means that AEs requiring dose modification are Grade ≤1 (except absolute neutrophil/granulocyte count [which must be ≥1500/mm^3 for docetaxel] and bilirubin [which must be less than or equal to the baseline grade]) on Day 1 of the next scheduled cycle (i.e., treatment can be given without delay).

[c] Hold and check weekly. With the exception of absolute neutrophil/granulocyte count and bilirubin, resume treatment when toxicity is Grade ≤1. If toxicity has not resolved after 3 weeks of delay, discontinue docetaxel and proceed with targeted therapy as planned to complete 18 cycles of treatment.

[d] Recognition of symptoms of severe enterocolitis is critical as this requires appropriate supportive care. In case of symptoms of abdominal pain with tenderness, fever, diarrhea and mucositis, with or without neutropenic fever, supportive care should be started immediately.

[e] Determination of clinically significant AEs is at the discretion of the investigator.

5.2.5 Management Guidelines

Supportive care and medical management of adverse events are at the discretion of the investigator and as per local policy, unless specifically listed below.

5.2.5.1 Symptomatic LVSD and/or LVEF Decline

There is a risk of LVSD with Perjeta, as with Herceptin, because each of these antibodies is directed at the HER2 receptor, which is present in cardiac tissue.

All patients enrolled in Perjeta studies undergo regular LVEF monitoring by ECHO (preferred) or MUGA scan. A decrease in LVEF has been observed in patients receiving Perjeta and Herceptin; however, the majority of patients show improvement or return to baseline function on follow-up (see Sections 1.2.1.3 and 1.2.2.4).

Patients in both arms should not start anti-HER2 drugs if their LVEF is $< 50\%$ after anthracycline therapy.

Patients who experience an asymptomatic decrease in LVEF after anthracycline therapy may continue to receive the taxane component of chemotherapy at the discretion of the investigator. HER2-targeted therapy may be subsequently initiated (or restarted) in accordance with the algorithm in Appendix 7. The delay in initiating (or restarting) HER2-targeted therapy should not exceed 6 weeks.

Monitoring of LVEF is required as per the schedule of activities. If severe symptomatic LVSD (CHF) develops (NYHA Class III or IV) or there is a confirmed significant LVEF decrease (LVEF decrease ≥ 10 percentage points from baseline and to an absolute LVEF value of $< 50\%$), the patient must discontinue HER2-targeted therapy. This should be recorded in the eCRF as per Table 10. Symptomatic LVSD (CHF) should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist, and the results of this evaluation should be reported on the eCRF.

Appendix 7 summarizes the management of study medication in patients who develop an asymptomatic decrease in LVEF. The decision to initiate HER2-targeted therapy and whether to continue or stop therapy should be based on two factors: measured LVEF and changes in LVEF from baseline. If a significant LVEF decrease occurs, this decrease should be confirmed by a second assessment within approximately 3 weeks showing also a significant decrease.

All patients must have a baseline LVEF $\geq 55\%$. LVEF will be monitored regularly according to the Schedule of Activities (see Appendix 1, Appendix 2, and Appendix 3). If an investigator is concerned that an adverse event may be related to LVSD, an additional LVEF measurement should be performed as soon as possible and within 3 weeks.

Symptomatic LVSD (CHF) will be assessed as "heart failure" on the basis of NCI CTCAE criteria v4 and NYHA classification (see Appendix 8).

CHF should be treated and monitored according to standard medical practice.

Asymptomatic LVEF decline (LVEF assessment scheduled in Appendix 1, Appendix 2, and Appendix 3) will be reported in the eCRF as per NCI CTCAE criteria v4 (see Table 10). The intensity of asymptomatic LVEF decline described above will be reported on the basis of NCI CTCAE criteria v4 ("ejection fraction decreased").

The incidence of CHF will also be recorded throughout the study.

5.2.5.2 Hypersensitivity/Anaphylaxis and Administration-Related Reactions (Infusion or Injection)

Administration of monoclonal antibodies, including Perjeta and Herceptin, may cause ARRs (please refer to Sections 5.1.1.1 and 5.1.2.1).

Local-site reactions are captured separately from systemic reaction in the eCRF.

Patients with pre-existing pulmonary compromise who are treated with Herceptin may be at increased risk of severe or serious ARRs. Therefore, careful consideration must be made before enrolling patients with chronic pulmonary disease into the study.

Study treatment will be administered by staff trained to monitor for and respond to medical emergencies in a setting with emergency equipment.

Infusion of Perjeta should be stopped in subjects who develop dyspnea or clinically significant hypotension (defined per investigator's discretion).

Patients who experience any of the following events will be discontinued from study treatment:

- Grade 4 allergic reaction
- Grade 3 or 4 hypersensitivity reaction
- ARDS
- Bronchospasm

Patients who experience ARRs may be managed by:

- Slowing or stopping the Perjeta or Herceptin IV infusion
- Stopping the injection of FDC
- Providing supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids as appropriate at the investigator's discretion, as per local practice
- Subsequently premedicating with analgesia and antihistamines as per local practice

In order to be able to calculate time to onset of such reactions, the occurrence of adverse events has to be documented with the date and time of the onset and duration of the event (i.e., resolution of the event).

If a subject experiences an ARR, the diagnosis should be used for the primary adverse event term (e.g., "administration-related reaction," or "anaphylactic reaction").

The individual sign(s) and symptom(s) of the reaction should then be captured on the dedicated Infusion-Related Reaction or Injection Reaction eCRF forms (see Section 5.4.5).

If a patient experiences a local and a systemic reaction following administration of the study drug, two separate adverse events will need to be recorded.

Patients will be monitored until complete resolution of signs and symptoms of any systemic reactions.

5.2.5.3 EGFR-Related Toxicities

Although Perjeta targets the HER2 receptor, it inhibits heterodimerization with other members of the HER family (e.g., EGFR [HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors such as diarrhea, mucositis, and skin reactions (e.g., dry skin, pruritus, or nail disorders).

Diarrhea

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication (e.g., loperamide) should be considered and patients should be treated with fluids and electrolyte replacement, as clinically indicated. In the case of no improvement of diarrhea despite anti-diarrheal treatment, HER2-targeted therapy should be held. HER2-targeted therapy can resume once the diarrhea is under control.

Rash/Skin Reactions

Treatment recommendations for EGFR-associated rash/skin reactions include topical or oral antibiotics, topical pimecrolimus, and topical steroids or systemic steroids (for severe reactions). These agents may be used in patients experiencing Perjeta-related rash/skin reactions, as clinically indicated, although they have not been studied in this context.

Mucositis

Mucositis is generally not considered preventable. Although for some cytotoxic agents, mucositis may be reduced by cooling the mouth using ice chips before and during the infusion.

5.3 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.5.

5.3.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.4.5.8 and 5.4.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.3.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.4.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.4.3; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2 for reporting instructions).

5.3.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2 for reporting instructions). AESIs for this study are as follows:

- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of HER2-targeted therapies must be reported in an expedited manner with use of the Serious Adverse Event Form and classifying the event as an Event of Special Interest that is immediately reportable
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.4.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Heart failure
- Asymptomatic declines in LVEF

5.3.4.1 Heart Failure

Symptomatic LVSD (referred to as heart failure) should be reported as a serious adverse event. If the diagnosis is heart failure, it should be reported as such, and not as individual signs and symptoms of heart failure. In the eCRF, signs and symptoms should be recorded. A cardiac consultation is recommended for patients who develop symptomatic LVSD (heart failure). Heart failure should be graded according to NCI CTCAE v4 (Grade 2, 3, 4, or 5), as well as according to the NYHA the AE term to describe symptomatic dysfunction, as per NCI CTCAE v4.

Heart failure occurring during the study and up to 3 years after the last patient discontinues HER2-targeted therapy must be reported irrespective of causal relationship and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

5.3.4.2 Asymptomatic Declines in Left Ventricular Ejection Fraction

Asymptomatic declines in LVEF should not be reported as adverse events because LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF of ≥ 10 percentage-points from baseline to an LVEF $< 50\%$ must be reported as an adverse event with the term of ejection fraction decreased, as per NCI CTCAE v4. In addition, a comment in the adverse events comments field should confirm that the event was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of Perjeta and Herceptin must be reported in an expedited manner as a non-serious AESI on the serious adverse event form, and a comment should be added to the adverse events comments field, confirming that the event was asymptomatic.

Both cases should be reported as "ejection fraction decreased" and graded according to NCI CTCAE v4 (see Section 5.4.3).

Table 10 summarizes the reporting conventions for LVSD and heart failure.

Table 10 Reporting Conventions for Left Ventricular Systolic Dysfunction/Congestive Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF of <10 percentage points from baseline or to an LVEF of $\geq 50\%$	No additional reporting required; LVEF results to be reported on eCRF.	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline to an LVEF of $<50\%$	AE [a] (eCRF AE eForm)	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of Perjeta and Herceptin or the FDC	AE (eCRF AE eForm) and report as a non-serious AESI on an SAE form	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure/CHF (symptomatic LVSD) [b]	AE (eCRF AE eForm) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; AESI = adverse event of special interest; CHF = congestive heart failure; eCRF = electronic Case Report Form; e-Form = electronic form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.

[a] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

[b] Any symptomatic LVSD event must be reported as "heart failure."

5.3.4.3 Administration-Related Reactions: Infusion-Related Reactions, Injection-Related Reactions, and Injection Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or injection should be captured as a specific diagnosis (e.g., "infusion-related reaction", "injection-related reaction", "injection-site reaction", "anaphylactic reaction") on the Adverse Event eCRF.
If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF, Injection Reaction eCRF, or Injection-Site Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Injection Reaction eCRF.

See Table 11 for the reporting conventions for infusion-related reactions, injection-related reactions, and injection-site reactions.

Table 11 Reporting Conventions for Infusion-Related Reactions, Injection-Related Reactions and Injection-Site Reactions

Adverse Event	Term to Be Used on AE eCRF Form	Symptoms to Be Entered on eCRF Form
Systemic Infusion Reaction	"Infusion-related reaction"	Infusion-related reaction
Systemic Injection Reaction	"Injection-related reaction"	Injection-related reaction
Local Injection Reaction	"Injection-site reaction"	Injection-site reaction

5.4 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.3.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections5.5–5.7.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.3.2 for seriousness criteria), severity (see Section 5.4.3), and causality (see Section 5.4.4).

5.4.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.5.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events irrespective of relationship to study drug will be reported until the treatment completion or discontinuation visit (28 days after the last dose of study drug). After this period, only drug-related serious adverse events, heart failure, pregnancies, and non−breast-related second primary malignancies, irrespective of causal relationship, should continue to be collected (see Sections 5.3.4 and 5.5.2).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.7.

5.4.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.4.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4) will be used for assessing adverse event severity. Table 12 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 12 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.5.2 for reporting instructions), per the definition of serious adverse event in Section 5.3.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.5.2 for reporting instructions), per the definition of serious adverse event in Section 5.3.2.

5.4.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 13):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 13 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.4.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.4.5.1 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related, injection-related, or ISRs (see Section 5.3.4.3), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.4.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.4.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.5.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.4.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.4.5.3 for details on recording persistent adverse events).

5.4.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.4.5.3 for details on recording persistent adverse events).

5.4.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.4.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.5.2).

5.4.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.4.1) that are attributed by the investigator solely to progression of breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.5.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.7.

5.4.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.4.5.9 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on clinical, laboratory, radiological, and/or histological findings. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.4.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.3.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care

- Planned hospitalization required by the protocol (e.g., for study drug administration, insertion of access device for study drug administration).

  Hospitalization for re-excision surgery for residual breast cancer following primary surgery, breast reconstruction surgery, prophylactic contralateral mastectomy, prophylactic ovariectomy, and ovariectomy (to induce premature menopause) are also not considered adverse events in this trial.

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4.5.11 *Cases of Accidental Overdose or Medication Error*

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- *Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose*
- *Medication error: accidental deviation in the administration of a drug*

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For Perjeta IV, Herceptin IV, and the SC FDC of pertuzumab and trastuzumab, adverse events associated with special situations should be recorded as described below for each situation:

- *Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.*

- *Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*

In addition, all special situations associated with Perjeta IV, Herceptin IV, and the SC FDC of pertuzumab and trastuzumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- *Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.*
- *Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.*

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.3.2; see Section 5.5.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.3.3; see Section 5.5.2 for details on reporting requirements)
- Pregnancies (see Section 5.5.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.5.1 Emergency Medical Contacts

Medical Monitor Contact Information for Shanghai and China

Roche Medical Responsible: [redacted], M.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.5.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.5.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.5.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the treatment completion or discontinuation visit (28 days after the last dose of study drug). Thereafter, related serious adverse events, heart failure (reportable as a serious adverse event), and non-breast second primary

malignancies (reportable as a serious adverse event) should be reported until the end of the study. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the end of the study are provided in Section 5.7.

5.5.3 Reporting Requirements for Pregnancies

5.5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of Perjeta and Herceptin or the FDC. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue all study drugs and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In order to learn more about the effects of pertuzumab and trastuzumab on pregnancy, additional information on any Perjeta- and/or Herceptin-exposed pregnancy and infant will be requested by Roche/Genentech Drug Safety at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 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 congenital abnormality, a guided questionnaire will be sent out by Roche/Genentech Drug Safety. The investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy or the infant is requested or becomes available.

5.5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

5.6 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.6.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.6.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.7 ADVERSE EVENTS THAT OCCUR AFTER THE END OF THE STUDY

After the end of the study, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported directly to Roche Safety Risk Management via telephone or fax machine using the paper Serious Adverse Event Reporting Form and fax cover sheet.

5.8 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Perjeta Investigator's Brochure
- Herceptin Investigator's Brochure
- Pertuzumab and Trastuzumab FDC Investigator's Brochure

The Sponsor 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 ANALYSIS POPULATIONS

6.1.1 Per Protocol PK Analysis Population

The primary analysis will be performed in the Per Protocol PK analysis population. Patients will be assigned to treatment groups as treated.

The Per Protocol PK analysis population will include all patients enrolled who adhered to the protocol. Patients will be excluded from the Per Protocol PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced.

Reasons for exclusion may include patients missing the C_{trough} pre-dose Cycle 8 PK sample, patients with a C_{trough} sample collected with at least 2 days deviation from the planned date on Day 21 (i.e., before Day 19 or after Day 23), patients given a dose amount that significantly deviates from the planned dose, patients with a dose delay of more than 7 days, an injection site other than thigh is used, etc. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.1.2 Intent-to-Treat Population

Additional analyses will be performed in the ITT population. The ITT population is defined as all randomized patients. Patients will be assigned to treatment groups as randomized by the IxRS.

6.1.3 Safety Analysis Population

The safety analysis population will include all patients who receive at least one dose of study medication (i.e., chemotherapy, Perjeta and Herceptin IV, or the FDC). Patients who do not receive any dose of their study medication (i.e., chemotherapy, Perjeta and Herceptin IV, or the FDC) will be excluded from the safety-evaluable population. Patients will be assigned to treatment groups as treated.

6.2 DETERMINATION OF SAMPLE SIZE

Sample size calculations are based on the coefficient of variation (CV)% for the C_{trough} of trastuzumab observed from previous studies in MBC and EBC patients after Q3W treatment. With a CV of 60% assumed, a minimum of 80 patients per arm (i.e., a total of

160 patients) is needed to demonstrate C_{trough} non-inferiority with a power of 80% if the true means of the two formulations do not differ (GMR = 1). The sample size is increased to 200 (i.e., 100 patients per arm), as it is expected 80% of patients would be PK evaluable.

6.3 PRIMARY ANALYSIS

The co-primary endpoints of this study are observed pertuzumab and trastuzumab trough concentration (C_{trough}) at Cycle 7 (i.e., the measured pre-dose concentration value at Cycle 8), following 3 cycles of Perjeta IV and Herceptin IV or FDC (pertuzumab and trastuzumab SC). Pertuzumab and trastuzumab C_{trough} will be analyzed at the time of the primary analysis, which will occur after the last patient has completed (all) neoadjuvant therapy and has undergone surgery.

The Per Protocol PK analysis population as described in Section 6.1.1 will be the primary analysis population used for this analysis.

The non-inferiority of the SC and IV dose of pertuzumab and trastuzumab will be assessed by a one-sided testing procedure. The C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose will be estimated together with the two-sided 90% CI based on the log-transformed trough concentration values. The null hypothesis will be rejected and non-inferiority will be concluded if the lower bound of the 90% CI of the GMR is ≥ 0.8.

A hierarchical testing procedure for the co-primary endpoints will be used to adjust for multiple comparison.

The following hypotheses will be tested:

- H0: The SC dose is inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose is not greater than 0.8) versus
- H1: The SC dose is non-inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose is equal or greater than 0.8)

The hierarchical testing procedure will follow the steps below:

1. Test the Cycle 7 pertuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level. If positive, continue to Step 2; otherwise, stop.
2. Test the Cycle 7 trastuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level.

6.4 SECONDARY ANALYSES

For all secondary analyses the Per Protocol PK analysis population (see Section 6.1.1) will be used. The ITT population will also be used for key secondary endpoint analyses and will be described further in the Statistical Analysis Plan (SAP).

6.4.1 Efficacy Analyses

The following analyses (see Table 3 for endpoint definitions) will be analyzed outside of a hypothesis-testing framework and according to the methodology provided below. Further details on this will be written in the SAP.

Rates of tpCR will be calculated in each treatment arm and will be assessed using the difference between FDC tpCR rate and IV tpCR rate and corresponding 95% Clopper Pearson CIs. The difference between the FDC tpCR rate and IV tpCR rates along with corresponding 95% Hauck-Anderson CIs will also be calculated. The lower bound of the CI will reliably reflect the largest pCR difference that could be considered unlikely. The observed tpCR difference and 95% CI will form the basis of a discussion around the differences in efficacy that can be ruled out.

For all time-to-event (TTE) endpoints, iDFS, iDFS including second primary non-breast cancer, EFS, EFS including second primary non-breast cancer, distant recurrence-free interval (DRFI), and OS described in Table 3, the Kaplan-Meier approach will be used for analysis. Estimates of the proportion of patients who are event-free at landmark timepoints for each treatment cohort will be provided. The estimated HR and corresponding CI will also be obtained using Cox regression models. Patients who are either without distant disease recurrence, alive, or lost to follow-up for the respective endpoints will be censored at their last known date in the study and event free. Patients with no post-baseline assessments will be censored at the date of enrollment plus 1 day. The TTE endpoints will not be analyzed at the time of the primary analysis; further details on censoring and timing will be written in the SAP.

6.4.2 Safety Analyses

The safety analysis population will consist of all randomized patients who received at least one dose of study drug and will be grouped according to actual treatment received: Arm A to Perjeta IV and Herceptin IV; Arm B to the FDC of pertuzumab and trastuzumab.

Patients who do not receive any amount of their study medication (i.e., chemotherapy, Perjeta and Herceptin IV, or the FDC) will be excluded from the safety population. Safety will be evaluated by the use of descriptive analyses of incidence and severity of AEs and SAEs; laboratory test abnormalities; incidence of a symptomatic LVSD (otherwise referred to as heart failure), defined as the occurrence of symptomatic LVEF decrease or definite or probable cardiac death; and incidence of LVSD, defined as an absolute decrease in LVEF of at least 10 percentage points below the baseline measurement and to below 50%) by LVEF measurements over the course of the study.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and adverse event severity will be graded according to the NCI-CTCAE, v4. CHF, in addition, will be graded according to the New York Heart Association (NYHA) functional classification. All AEs, including

SAEs, will be summarized by treatment arm and CTCAE grade. In addition, AEs leading to discontinuation of study treatment will be summarized by treatment arm. For each patient's AEs, the maximum severity recorded will be used in the summaries.

Laboratory toxicities will be defined based on local laboratory normal ranges and NCI-CTCAE, v4. Selected laboratory abnormalities such as worst toxicity grade and toxicity grade shift from baseline will be summarized by treatment arm. Change from baseline in targeted vital signs and laboratory results will also be assessed.

Selected AEs of particular importance (see Section 5.3.4) will also be analyzed, similar to the method for AEs.

For this study the following will be used to characterize reactions related to the administration of study drug(s):

- Investigator-assessed ARRs, including:
  - ISRs (local), defined as any local morphological or physiological change at or near the SC injection site
  - Injection-related reactions (systemic), defined as any system reaction in response to the SC injection of study drug
  - Infusion-related reactions (systemic), defined as any system reaction in response to the IV infusion of study drug

ARRs potentially associated with IV or SC administration of study drug(s), defined as AEs in the SMQ "Anaphylactic Reaction (wide)," Roche Standard AEGT "Anaphylaxis and Hypersensitivity" and "Infusion-Related Reactions and Hypersensitivity," or the dictionary-derived term "Cytokine Release Syndrome" occurring during infusion/injection or within 24 hours of the end of administration, should be assessed as to whether considered related or unrelated to study drug by the investigator. Please see Sections 5.1.1.1 and 5.2.5.2 for additional information about ARRs.

Cardiac-specific AEs will focus on the incidence of patients with heart failure (NYHA, NCI-CTCAE [heart failure] Grades 2, 3, 4, and 5). LVEF data summaries will include the incidence of patients with LVEF decreases with an absolute decrease of at least 10 percentage points from baseline and to below 50%.

Cardiac AEs will be categorized according to the following endpoint criteria:

- Primary cardiac endpoint:
  - Incidence of a symptomatic ejection fraction decrease ("heart failure") of NYHA Class III or IV and a drop in LVEF of at least 10-percentage points from baseline and to below 50%

  - Cardiac death, defined as either:
    - Definite cardiac death (due to heart failure, myocardial infarction, or documented primary arrhythmia); or
    - Probable cardiac death (sudden unexpected death within 24 hours of a definite or probable cardiac event [e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia] without documented etiology)
- Secondary cardiac endpoints:
  - Incidence of an asymptomatic or mildly symptomatic LVSD ("ejection fraction decreased") of NYHA Class II, defined as an LVEF decrease of ≥ 10 percentage points below the baseline measurement to an absolute LVEF value of $< 50\%$, confirmed by a second assessment within approximately 3 weeks confirming a decrease of ≥ 10 percentage points below the baseline measurement and to an absolute LVEF value of $< 50\%$

The assessment of the cardiac endpoint will be based on data from randomization until the start of any new therapy for recurrence of disease. Therefore, any asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF should be confirmed within approximately 3 weeks, even during follow-up phase.

Safety analyses will be performed at the primary analysis and may be performed at additional timepoint during the study as necessary.

6.5 EXPLORATORY ANALYSES

6.5.1 PK Analyses

Exploratory analyses will include characterization of the pharmacokinetics of pertuzumab and trastuzumab following FDC SC administration. PK variables will be presented by listings and descriptive summary statistics including arithmetic mean, geometric mean, median, range, standard deviation and CV, and 95% CIs.

Modeling of the PK data may be performed using a population approach based on a model previously developed on a combined SC and IV dataset from the BO30185 study. The structural and statistical model will be defined using a non-linear mixed-effects model (NONMEM). The model will be parametrized in terms of clearances and volumes, and the individual measures of exposure (i.e., C_{trough} and $AUC_{0-\tau}$) will be predicted from the final PK model.

Predicted C_{trough} may be considered as a supportive endpoint of the measured/observed C_{trough}. The aim of using predicted C_{trough} is to take into account possible deviations from the protocol (i.e., sampling schedule or dosing interval) and extra-noise (i.e., precision of analytical measurement). Any potential differences between the outcomes of the statistical test performed on observed and predicted C_{trough} will be discussed in the final study report.

Comparability of the SC and IV dose of pertuzumab may be assessed by comparing the AUC_{0-T} resulting from the administration of each formulation.

Comparability of the pertuzumab C_{trough} level observed at Cycle 12 in the post-surgery period following IV and SC administration may be assessed as an exploratory analysis (i.e., the measured pre-dose concentration value at Cycle 13).

Potential exposure-response relationships may be assessed through exploratory analyses in terms of efficacy and safety of the FDC and pertuzumab exposure. The primary efficacy variable will be pCR and safety variables will be dependent on study data. Exposure metrics may include pertuzumab C_{max}, minimum serum concentration (C_{min}), and AUC.

An assessment of PK drug-drug interaction (DDI) may be evaluated in an exploratory analysis. The impact of pertuzumab on the PK of trastuzumab will be evaluated by comparing trastuzumab PK after FDC administration. Additionally, trastuzumab PK data collected in this study can be compared to historical data evaluating Herceptin SC monotherapy to confirm no apparent impact of pertuzumab on trastuzumab.

A comparison of pertuzumab exposure in Cycle 5 between Perjeta IV 840 mg and FDC (pertuzumab 1200 mg SC) may be regarded as exploratory.

6.5.2 Efficacy Analyses

To further assess the tpCR endpoint, exploratory analyses will be conducted analyzing:

- Breast pathological complete response (bpCR), defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx)

Analysis methods of the exploratory pCR endpoints will be the same as those for the secondary tpCR endpoint.

In the neoadjuvant period, clinical response will also be analyzed and response will be assessed as CR, PR, SD, or PD by the investigator as per routine clinical practice (see additionaly Section 4.5.12). Clinical response rate prior to surgery will be summarized and reported. For patients who have clinical response assessed during neoadjuvant therapy but not immediately prior to surgery, and patients who do not undergo surgery, the last recorded clinical response assessment will be considered in the analysis. Patients without any assessment of clinical response prior to surgery will be considered non-responders in the analysis.

6.5.3 Immunogenicity Analyses

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by treatment group. When determining post baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study-drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units or 4 times the dilution factor) than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be negative for ADAs if they are ADA negative at all timepoints. Patients are considered to be treatment unaffected if they are ADA positive at baseline but do not have any post baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample. Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post baseline samples are negative, or if they are ADA positive at baseline but do not have any post baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, and PK endpoints will be analyzed and reported via descriptive statistics (as data allow).

6.5.4 Biomarker Analyses

Biomarker analyses will be exploratory and will assess correlations between biomarker status and efficacy and/or safety, including but not limited to the following outcomes:

- Expression levels of biomarker or biomarker panels with efficacy of study treatment including levels of HER2
- Association of *PIK3CA* mutation status with efficacy
- Evaluation of rates of concordance between local and central assessment of hormone receptor status

Descriptive statistics and similar methods as in the above sections will be applied to exploratory analyses as appropriate. In addition, various types of multivariate analyses may be conducted as the data indicate.

6.6 INTERIM AND FINAL ANALYSES

No formal, statistical interim analyses are planned prior to the primary analysis. The final analysis will occur 3 years after the last patient's last treatment.

6.7 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for patient discontinuations from the study treatment and from the study will be listed and summarized. Enrollment, study treatment administration, and major protocol deviations will be evaluated for their potential effects on the interpretation of study results.

For safety-evaluable patients, study drug administration and dose modifications data will be tabulated or listed by cohort, using descriptive statistics to summarize the total doses where applicable.

6.8 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using descriptive statistics (e.g., means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate). Summaries will be presented overall and by treatment group

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Non-eCRF data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or 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.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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 of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND 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 health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This study is being sponsored by F. Hoffmann-La Roche Ltd. The Sponsors will perform study management, including project management, data management, and clinical monitoring. Source data verification for critical parameters will be conducted for all patients enrolled.

Approximately 18 sites in China will participate to enroll approximately 200 patients. Randomization will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study *(see Section 8.4 for more details)*, and redacted Clinical Study Reports and other summary reports will be *made available* upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Andersson M, López-Vega JM, Petit T, et al. Efficacy and safety of pertuzumab and trastuzumab administered in a single infusion bag, followed by vinorelbine: VELVET Cohort 2 final results. Oncologist 2017;22:1–9.

Andrulis IL, Bull SB, Blackstein ME, et al., for the Toronto Breast Cancer Study Group. Neu/erbB-2 amplification identifies a poor prognosis group of women with nodenegative breast cancer. J Clin Oncol 1998;16:1340–9.

Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics and safety of subcutaneous rituximab plus fludarabine and cyclophosphamide for patients with chronic lymphocytic leukaemia. British Journal of Clin Pharm 2015;80:1001–9.

Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019–27.

Berruti A, Generali D, Kaufmann M, et al. International expert consensus on primary systemic therapy in the management of early breast cancer: highlights of the Fourth Symposium on Primary Systemic Therapy in the Management of Operable Breast Cancer, Cremona, Italy. J Natl Cancer Inst Monogr 2011;43:147–51.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

Broglio KR, Quintana M, Foster M, et al. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. JAMA Oncol 2016;2:751–60.

Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Annals of Oncology 2014;25:1871–88.

China Breast Cancer Society. China Breast Cancer Society Guideline 2017. China Oncology 2017;27(9):695–760.

[CSCO] Chinese Society of Clinical Oncology. Guideline for Breast Cancer in 2018, V1.

Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies – improving the management of early breast cancer: St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of Oncology 2015;26:1533–46.

Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164–72.

Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Annals of Oncology 2017; 28:1700–12.

Davies A, Merli F, Mihaljevic B, et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. Lancet Oncol 2014;15:343–52.

De Cock E, Kritikou P, Sandoval M, et al. Time savings with rituximab subcutaneous injection versus rituximab intravenous infusion: a time and motion study in eight countries. PLoS One 2016;11(6):e0157957.

[EMA] European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man, Revision 4 [resource on the Internet]. Oncology Working Party. 2012 [cited 11 November 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf.

[FDA] U.S. Food and Drug Administration. Guidance for industry. Pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval [resource on the Internet]. 2014 [cited 11 November 2017]. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm305501.pdf.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods, and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.

Dent S, Oyan B, Honig A, et al. HER2-targeted therapy in breast cancer: a systematic review of neoadjuvant trials. Cancer Treatment Reviews 2013;39:622–31.

Fallowfield L, Atkins L, Catt S, et al. Patients' preference for administation of endocrine treatments by injection or tablets: results from a study of women with breast cancer. Ann Oncol 2006;17:205–10.

Franklin MC, Carey KD, Vajdos FF, et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell 2004;5:317–28.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods, and major patterns in GLOBOCAN 2012. Int. J. Cancer 2015;136:359–86.

Garg A, Quartino A, Li J, et al. Population pharmacokinetic and covariate analysis of pertuzumab, a HER2-targeted monoclonal antibody, and evaluation of a fixed, non-weight-based dose in patients with a variety of solid tumors. Cancer Chemother Pharmacol 2014;74:819–29.

Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncology 2012;13(1):25–32.

Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Breast Cancer. Version 2 [internet]. 2016. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol 2008;26:814–9.

Hammond ME, Hayes DF, Wolff AC, et al. American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract 2010;6:195–7.

Harbeck N, Thomssen C, Gnant M. St. Gallen 2013: brief preliminary summary of the consensus discussion. Breast Care (Basel) 2013;8:102–9.

Hylenex® recombinant (hyaluronidase human injection) U.S. Package Insert 2016. Halozyme Therapeutics, Inc. Available from: https://hylenex.com/downloads/approved-uspi-lbl301feb2016.pdf.

Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I – III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomized trial. Lancet Oncol 2012;13:869–78.

Jackisch C, Hegg R, Stroyakovskiy D, et al. HannaH phase III randomised study: association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer 2016;62:62–75.

Kendler DL, Bessette L, Hill CD, et al. Preference and satisfaction with a 6-month subcutaneous injection versus a weekly tablet for treatment of low bone mass. Oseoporos Int 2010;21:837–46.

Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97:188–94.

Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. J Clin Oncol 2007;25:2650–5.

Olayioye MA, Neve RM, Lane HA, et al. The erbB signaling network: receptor heterodimerization in development and cancer. EMBO J 2000;19:3159–67.

Pauletti G, Dandekar S, Rong H, et al. Assessment of methods for tissue-based detection of the HER-2/neu alteration in human breast cancer: a direct comparison of fluorescence in situ hybridization and immunohistochemistry. J Clin Oncol 2000;18:3651–64.

Perez EA, López-Vega JM, Petit T et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. Breast Cancer Res 2016;18:126.

Pivot X, Gligorov J, Müller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol 2013;14(10):962–70.

Primary Clinical Study Report – WO29217– A multicenter, multinational, phase II study to evaluate Perjeta in combination with Herceptin and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer. Report No.1070920. December 2016.

Primary Clinical Study Report – BO28408 – A randomized, multicenter, open-label, two-Arm, phase III neoadjuvant study evaluating trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for patients with HER2-positive breast cancer. Report No.1068872. August 2016.

Rimawi MF, Cecchini RS, Rastogi P, et al. Evaluating pathologic complete response rates in patients with hormone receptor-positive, HER2-positive breast cancer treated with neoadjuvant therapy of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) with or without concurrent estrogen deprivation therapy. San Antonio Breast Cancer Symposium, December 6 – 10, 2016. Available from: https://www.oncoletter.ch/files/cto_layout/Kongressdateien/SABCS2016/S306.pptx

Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–84.

Rubin I, Yarden Y. The basic biology of HER2. Ann Oncol 2001;12(Suppl 1):S3–8.

Rummel M, Kim TM, Plenteda C, et al. PrefMab: final analysis of patient preference for subcutaneous versus intravenous rituximab in previously untreated CD20+ diffuse large B-cell lymphoma and follicular lymphoma. 57th ASH Annual Meeting and Exposition, 5–8 December 2015.

Sawyer DB, Zuppinger C, Miller TA, et al. Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and antierbB2: potential mechanism for trastuzumab-associated cardiotoxicity. Circulation 2002;105:1551–4.

Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized Phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24(9):2278–84.

Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi7–23.

Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235(4785):177–82.

Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244(4905):707–12.

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER-2 for metastatic breast cancer. N Engl J Med 2001;344:783–92.

Spring L, Greenup R, Reynolds K, et al. Pathological complete response after neoadjuvant chemotherapy predicts improved survival in all major subtypes of breast cancer: systematic review and meta-analyses of over 18,000 patients Cancer Res 2016:76(14 Suppl):1439.

Swain SM, Im YH, Im SA, et al. Safety profile of pertuzumab with trastuzumab and docetaxel in patients from Asia with human epidermal growth factor receptor 2-positive metastatic breast cancer: results from the phase III trial CLEOPATRA. Oncologist 2014;19:693–701.

Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol 2007;25(28):4414–22.

Theriault RL, Carlson RW, Allred C, et al. NCCN practice guidelines in oncology. Breast cancer Version 3 [Internet];2013. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Timolati F, Ott D, Pentassuglia L, et al. Neuregulin-1 beta attenuates doxorubicininduced alterations of excitation-contraction coupling and reduces oxidative stress in adult rate cardiomyocytes. J Mol Cell Cardiol 2006;41:845–54.

Toikkanen S, Helin H, Isola J, et al. Prognostic significance of HER-2 oncoprotein expression in breast cancer: a 30-year follow-up. J Clin Oncol 1992;10:1044–8.

Untch M, Jackisch C, Schneeweiss A, et al; German Breast Group (GBG); Arbeitsgemeinschaft Gynäkologische Onkologie—Breast (AGO-B) Investigators. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016;17(3):345–56.

von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017;377:122–31.

Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007;25:118–45.

World Health Organization. Breast cancer fact sheet. GLOBOCAN 2018 [resource on the internet; cited 1 November 2018]. Available from: http://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf.

Zhao JJ, Cheng H, Jia S, et al. The p110a isoform of PI3K is essential for proper growth factor signaling and oncogenic transformation. Proc Natl Acad Sci 2006;3:16296–300.

Appendix 1 Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance.

	Screening	Baseline	Treatment Period														
			3-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
Informed consent [b]	x																
Medical history and demographics	x																
Complete physical examination [c, d]	x		x													x	
Limited physical examination [d]				x	x	x	x			x	x						
Vital signs [e, d]	x		x	x	x	x	x			x	x					x	
ECOG Performance Status [c, d, f]		x	x [g]	x	x	x	x			x	x					x	
Height [d]	x																
Weight [c, d, h]	x		x	x	x	x	x			x	x					x	
Tumor staging [i]	x																
Bilateral mammogram (or another imaging method as per local practice) [j]	x															x	
Clinical tumor assessment/breast examination [d, k]	x		x	x	x	x	x			x	x					x	

Appendix 1: Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

	Screening	Baseline	Treatment Period														
			3-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
ECG (12-lead)	x						x										
LVEF (ECHO or MUGA) [l]	x						x [m]				x						x
Hematology/Biochemistry [n]		x	x [g]	x	x	x	x			x	x					x	
Pregnancy test [o]		x				x					x						
FFPE tumor tissue sample for central HER2/HR testing and *PIK3CA* mutation [p]	x																
Local HER2 and hormone receptor status (HER2, ER, PgR) [q]	x																
Pathologist post-surgery pathologic response tumor assessment [r]																	x
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [s]							x [t,u]	x	x	x [t,u]	x [t,u]	x	x	x	x	x [t,u]	
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A)		x [v]								x [t]							
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [s]							x [w]	x	x	x [w]	x [w]	x	x	x	x	x [w]	

Appendix 1: Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

	Screening	Baseline	Treatment Period														
			3-Week Cycles				3-Week Cycles										
Cycle			1	2	3	4	5			6	7					8	Surgery [a]
Day	–28 to –1	–7 to –1	1	1	1	1	1	2	15	1	1	2	4	8	15	1	1
ADA sampling: Pertuzumab/Trastuzumab/ rHuPH20 SC (Arm B)		x [v]								x [w]							
Plasma sample for ctDNA (biomarker) [x]		x [v]														x	
Perjeta IV (Arm A) [y]							x			x	x					x	
Herceptin IV (Arm A) [y]							x			x	x					x	
FDC SC (Arm B) [z]							x			x	x					x	
Doxorubicin [aa]			x	x	x	x											
Cyclophosphamide [aa]			x	x	x	x											
Docetaxel [bb]							x			x	x					x	
Adverse events [cc]			All AEs and SAEs (see Section 5.3)														
Concomitant medication [dd]		x	Continuous														

AC = doxorubicin and cyclophosphamide; ADA = anti-drug antibody; β-HCG = human chorionic gonadotripin; CBE = clinical breast examination; CT = computed tomography; ctDNA = circulating tumor DNA; C_{trough} = steady-state concentration; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; FDC = fixed-dose combination of pertuzumab and trastuzumab for SC administration; FFPE = formalin-fixed, paraffin-embedded; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquistion; NCCN = National Comprehensive Cancer Network; PgR = progesterone receptor; PK = pharmacokinetic; Q3W = every three weeks; RBR = Research Biosample Repository; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event.

Appendix 1: Schedule of Activities for Patients Receiving AC Q3W→Docetaxel in the Neoadjuvant Phase (cont.)

Notes: Cycle 1, Day 1 = first dose of study drug. Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. Clinical visits must be scheduled within ±3 days of the day specified. On dosing days, PK samples need to be taken on the exact day of the visit schedule. On non-dosing days, PK samples must be taken within ±2 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[a] Surgery will be performed no earlier than 14 days following the last infusion or injection of neoadjuvant therapy. The interval between the last dose of neoadjuvant Perjeta and Herceptin IV or FDC and the first dose of adjuvant Perjeta and Herceptin IV or FDC should be ≤9 weeks.

[b] Results of standard-of-care tests or examinations performed prior to obtaining informed consent may be used; such tests do not need to be repeated for screening.

[c] Must be performed pre-dose on dosing days.

[d] Assessment may be done within 3 days prior to treatment day.

[e] Vital signs (respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature) will be taken before the administration of study treatment and before and after Perjeta and Herceptin infusions/FDC injections.

[f] ECOG Performance Status should be assessed when the patient undergoes clinical tumor assessment and breast examination (i.e., prior to each new cycle of therapy during neoadjuvant treatment and at least every 3 months during the adjuvant treatment period [Cycle 9, Cycle 13, Cycle 17, and Cycle 21] and at the treatment completion or discontinuation visit).

[g] Screening measurements can be used as Day 1 assessments if performed within 3 days prior to Cycle 1.

[h] Weight will be measured during screening and on Day 1 of each cycle. If variation of ±10% occurs, as compared with baseline, the Herceptin IV and chemotherapy doses will be recalculated.

[i] Baseline tumor staging procedures are not mandatory and should be performed as per local practice, in alignment with national guidelines and as clinically indicated within 28 days of randomization. See Section 4.5.7.2.

[j] Provided that the patient's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery, and treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual patient. If another method is used, this must be performed within the 28-day screening window. If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end-of-study mammogram.

[k] Clinical breast examination (CBE) will be performed at screening. During the neoadjuvant treatment period, tumor response assessment will be performed prior to each new cycle of therapy by CBE (mandatory) and other methods of evaluation as per routine clinical practice.

[l] For patients whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each patient and is preferably performed and assessed by the same assessor. All LVEF assessments will be performed during Days 15 – 21 of three-week cycles prior to the cycle indicated here to allow evaluation of the results before the next treatment cycle. LVEF assessment may also be performed on Day 1 of treatment but results must be available before treatment is administered.

[m] Patients should not start HER2-targeted therapy if their LVEF is < 50% after anthracycline treatment. This ECHO/MUGA assessment should be performed prior to administration of any treatment at Cycle 5.

[n] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Biochemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, albumin, ALP, ALT, AST, total bilirubin and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN. Bicarbonate should only be tested at sites where this test is part of the standard safety laboratory panel. During the treatment period, bloods for hematology/biochemistry must be taken predose but may be taken within 3 days prior to treatment day.

[o] For all women of childbearing potential and for all women not meeting the definition of postmenopausal (refer to Section 5.1.3 for definition), pregnancy test must be performed via serum β-HCG at baseline within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to every third treatment cycle starting at Cycle 4 (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. A pregnancy test at 7 months (i.e., between 6–9 months follow up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.

[p] FFPE tumor tissue sample will be collected for mandatory central confirmation of HER2, hormone receptor status, and *PIK3CA* mutation analysis. After signing of the Informed Consent Form, retrieval and submission of tumor tissue sample can occur outside the 28-day screening period. Fine-needle aspiration is not acceptable.

[q] Hormone receptor–positive patients are to be prescribed endocrine therapy according to the guidelines after completion of pre-operative chemotherapy and surgery. Local HER2/HR assessment can occur outside the 28-day screening period.

[r] Pathological response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines to be provided in the Pathology Manual.

[s] The date and time of PK sampling must be carefully recorded in all cases. On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (± 2 days is allowed if necessary), with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded) (see Appendix 4). If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be taken 21 days after Cycle 7 administration. This exception does not apply to any other cycles.

[t] Take sample pre-infusion.

[u] Take additional PK sample at the end of the infusion. The time of sampling must be within 15 minutes after each infusion has ended.

[v] Sample can be taken after randomization but prior to drug administration on Cycle 1, Day 1.

[w] Take sample pre-injection.

[x] Mandatory plasma samples collected at baseline, at Cycles 8 and 10, the treatment completion or treatment discontinuation visit and at 3-year follow up.

[y] All patients in Arm A receive a Perjeta loading dose of 840 mg IV on Cycle 5, Day 1 (the first day of docetaxel treatment). Thereafter (Cycles 6 – 22), all patients receive a Perjeta maintenance dose of 420 mg IV. All patients in Arm A receive a Herceptin loading dose of 8 mg/kg IV on Cycle 5, Day 1 (the first day of docetaxel treatment). Thereafter (Cycles 6 – 22), all patients receive Herceptin at 6 mg/kg IV. The order of administration of Perjeta and Herceptin is according to the investigator's preference.

[z] All patients in Arm B receive a FDC SC loading dose of 1200 mg pertuzumab and 600mg trastuzumab on Cycle 5, Day 1 (the first day of docetaxel treatment). Thereafter (Cycles 6 – 22), all patients receive maintenance dose of 600mg pertuzumab and 600mg trastuzumab.

[aa] All patients receive doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV given every 3 weeks, for four cycles (Cycles 1 – 4), according to local practice guidelines.

[bb] The starting dose of docetaxel is 75mg/m^2 IV in Cycle 5 given every 3 weeks. At the investigator's discretion, the dose may be escalated to 100 mg/m^2 IV for subsequent cycles (Cycles 6 – 8) provided no dose-limiting toxicity occurs.

[cc] After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by protocol-mandated intervention should be reported. After initiation of study drugs, all adverse events and serious adverse events will be collected until the treatment completion or discontinuation visit (28 days after the last dose of study drug). Non-serious adverse events occurring prior to study drug administration (Cycle 1, Day 1) will be reported in the medical history unless adverse event reporting is deemed more appropriate. After the treatment completion or discontinuation visit, drug-related serious adverse events and adverse events and serious adverse events that qualify for long-term reporting will continue to be collected (see Sections 5.3.4 and 5.5.2).

[dd] Concomitant medications will be recorded until the end of the treatment period.

Appendix 2 Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance.

Cycle (3 weeks)	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Treatment Completion/ Discontinuation [a]
Day	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Complete physical examination															x
Limited physical examination [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status [b, c]	x				x				x				x		x
Weight [b, d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Bilateral mammogram (or another imaging method as, per local practice) [e]															x
Clinical breast examination [b, f]	x				x				x				x		x
LVEF (ECHO or MUGA) [g]	x			x			x			x			x		x
Hematology/Limited Biochemistry [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test [i]		x			x			x			x			x	x
Perjeta IV (Arm A) [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Herceptin IV (Arm A) [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
FDC SC (Arm B) [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [l]	x [m,n]	x [m,n]	x [m,n]	x [m,n]	x [m]					x [m]				x [m]	

Appendix 2: Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase (cont.)

Cycle (3 weeks)	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Treatment Completion/ Discontinuation [a]
Day	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A)	x [m]				x [m]					x [m]				x [m]	
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [l]	x [o]	x [o]	x [o]	x [o]	x [o]					x [o]				x [o]	
ADA sampling: Pertuzumab/Trastuzumab/ rHuPH20 SC (Arm B)	x [o]				x [o]					x [o]				x [o]	
Plasma sample for ctDNA (biomarker)		x													x
Adverse events	All AEs and SAEs (see Section 5.3)														
Concomitant medication	Continuous														

ADA = anti-drug antibody; AE = adverse event; β-HCG = human chorionic gonadotripin; CT = computed tomography; ctDNA = circulating tumor DNA; C_{trough} = steady-state concentration; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FDC = fixed-dose combination of pertuzumab and trastuzumab for SC administration; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquistion; PK = pharmacokinetic; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event; ULN = upper limit of normal.

Notes: Cycle 1, Day 1 = first dose of study drug. Clinical visits must be scheduled within ±3 days of the day specified. On dosing days, PK samples need to be taken on the exact day of the visit schedule. On non-dosing days, PK samples must be taken within ±2 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

Appendix 2: Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase (cont.)

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[a] Treatment completion or discontinuation visits will optimally be scheduled for 28 (±3 days) following the last dose of study medication and will include all evaluations scheduled for the final visit.

[b] Assessment may be done within 3 days prior to treatment day.

[c] ECOG Performance Status should be assessed when the patient undergoes clinical tumor assessment and breast examination (i.e., at least every 3 months during the adjuvant treatment period [Cycle 9, Cycle 13, Cycle 17, and Cycle 21] and at the treatment completion or discontinuation visit).

[d] Weight will be measured during screening and on Day 1 of each cycle. If variation of ± 10% occurs, as compared with baseline, the Herceptin IV and chemotherapy doses will be recalculated.

[e] Provided that the patient's clinical status has not changed, the screening mammogram can be performed up to 42 days prior to the start of treatment. The mammogram at screening, pre-surgery, and treatment completion or discontinuation visit can be replaced by other conventional imaging methods such as MRI or ultrasound as per local medical practice, at the investigator's discretion, but the same method of assessment must be used throughout for an individual patient. If a mammogram has been conducted as part of routine preventive care within 4 months of the treatment completion or discontinuation visit, it may be used in lieu of the end of study mammogram.

[f] During the adjuvant treatment period, clinical breast examination should be performed to detect signs of locoregional relapse at least every 3 months (Cycle 13, Cycle 17, and Cycle 21) and at the treatment completion or discontinuation visit.

[g] For patients whose LVEF cannot be assessed by ECHO, LVEF may be assessed by MUGA. The same method should be used throughout the study for each patient and is preferably performed and assessed by the same assessor. All LVEF assessments will be performed during Days 15–21 of 3-week cycles prior to the cycle indicated here to allow evaluation of the results before the next treatment cycle. LVEF assessment may be performed on Day 1 of treatment but results must be available before treatment is administered.

[h] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: creatinine, alkaline phosphatase (ALP), AST, ALT, total bilirubin, and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN. During the treatment period, bloods for hematology/biochemistry must be taken pre dose, but may be taken within 3 days prior to treatment day.

[i] For all women of childbearing potential and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea) who have not undergone surgical sterilization, pregnancy tests must be performed via serum β-HCG at baseline within 7 days prior to the first administration of study medication (with result available prior to dosing). Urine pregnancy tests should be repeated during the treatment period within 7 days prior to every third treatment cycle starting at Cycle 4 (and as clinically indicated), as well as at the treatment discontinuation visit and every 3 months thereafter until 6 months after discontinuation of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Treatment period pregnancy test results must be available prior to the drug infusion/injection. Pregnancy test at 7 months (i.e., between 6–9 month follow-up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.

Appendix 2: Schedule of Activities for All Patients in the Adjuvant Pertuzumab and Trastuzumab Treatment Phase (cont.)

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[j] All patients receive a Perjeta maintenance dose of 420 mg IV. All patients receive Herceptin at 6 mg/kg IV. The order of administration of Perjeta and Herceptin is according to investigator preference.

[k] All patients receive maintenance dose of 600 mg SC pertuzumab and 600 mg SC trastuzumab.

[l] The date and time of PK sampling must be carefully recorded in all cases. On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (±2 days is allowed if necessary) with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[m] Take sample pre-infusion.

[n] Take additional PK sample at the end of the infusion. The time of sampling must be within 15 minutes after each infusion has ended.

[o] Take sample pre-injection.

Appendix 3 Schedule of Activities for All Patients in the Treatment-Free Follow-Up

	Follow-Up Visits [a]								
Month from the last dose of study drug	3	6	9	12	18	24	30	36	Every 6 months until end of study
Limited physical examination [b]	x	x	x	x	x	x	x	x	x
Vital signs [b]	x	x	x	x	x	x	x	x	x
ECOG Performance Status [b]	x	x	x	x	x	x	x	x	x
Assessment for recurrence [c]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Clinical breast examination	x	x	x	x	x	x	x	x	x
Bilateral mammogram				x		x		x	
Hematology/Limited Biochemistry [d]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
LVEF (ECHO or MUGA) [e]		x		x	x	x		x	
Pregnancy test [f]	x	x							
PK sampling: Pertuzumab/Trastuzumab IV (Arm A) [g, h]	x	x							
ADA sampling: Pertuzumab/Trastuzumab IV (Arm A) [h]	x	x		x	x	x	x	x	
PK sampling: Pertuzumab/Trastuzumab SC (Arm B) [g, h]	x	x							
ADA sampling: Pertuzumab/Trastuzumab/rHuPH20 SC (Arm B) [h]	x	x		x	x	x	x	x	
Plasma samples for ctDNA (biomarker)								x	
Survival	x	x	x	x	x	x	x	x	x
Adverse events	AEs and SAEs are continuously monitored (see Section 5.4.1).								

Appendix 3: Schedule of Activities for All Patients in the Treatment-Free Follow-Up (cont.)

ADA = anti-drug antibody; AE = adverse event; β-HCG = human chorionic gonadotripin; ctDNA = circulating tumor DNA; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquistion; PK = pharmacokinetic; rHuPH20 = recombinant human PH20 hyaluronidase; SAE = serious adverse event.

Notes: Parentheses (x) indicate that the item is optional and required only if symptoms or clinical suspicion are present.

[a] Visit to be performed within ± 15 days. These visits are based on time from last dose of study drug and not time from treatment completion/discontinuation visit, (i.e., 3-Month Follow-Up Visit is 3 months after last dose of study drug). After recurrence, all patients should continue to follow Appendix 4 for survival, LVEF assessments and pregnancy tests (pregnancies should be reported until 7 months after the last dose of study treatment, irrespective of disease progression or relapse or the initiation of alternative treatment). Related serious adverse events and non-breast second primary malignancies (reportable as serious adverse events) should also be reported until the end of the study.

[b] To be followed up every 3 months for 1 year, then every 6 months for an additional 2 years, then according to routine practice. After disease progression or relapse, patients need to only be followed for survival (i.e., physical examination, vital signs, and Performance Status do not need to be assessed).

[c] Assessment of distant disease recurrence to be performed if clinically indicated to exclude metastatic disease and within a timelines as per current standard of practice (see Section 4.5.12).

[d] Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (% or absolute for neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Limited biochemistry: creatinine, ALP, AST, ALT, total bilirubin, and direct/indirect bilirubin (if needed). Bilirubin fractions (direct and indirect) need to be measured only if total bilirubin is greater than ULN

[e] After completion of HER2-directed therapy, LVEF is to be performed every 6 months for 2 years, then again 1 year later. For patients who discontinue HER2-directed therapy early for disease progression/relapse or due to adverse events (other than heart failure or LVEF decline), LVEF assessments should be performed every 6 months for 2 years, then annually for an additional year or until the initiation of alternative systemic therapy. For patients who discontinue HER2-directed therapy for heart failure or LVEF decline, LVEF assessments should be continued regardless of initiation of alternative systemic anti-cancer therapy until resolution, improvement to baseline status, no further improvement can be expected, or death. Additional LVEF assessments may be required for these patients (beyond those specified in the table) according to the investigator's clinical judgment. The results of these assessments should be reported.

[f] At 3 and 6 months after the last dose of study treatment. Any positive urine pregnancy test must be confirmed with a serum β-HCG test. Pregnancy test at 7 months (i.e., between 6–9 month follow up) can be performed if indicated. Note that patients are required to continue contraception for 7 months after study treatment is complete.

[g] The date and time of PK sampling must be carefully recorded in all cases. During follow-up, samples must be taken ± 7 days of the required sampling day, with the timing of PK sampling during the day left to the investigator (however, the time should be carefully recorded).

[h] *Patients who did not receive any HER2-targeted therapy will not be required to give PK or ADA blood samples during follow-up.*

Appendix 4 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples – Arm A

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance. On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (i.e., there is no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (±2 days is allowed if necessary). During follow-up, a window of ±7 days is allowed.

Visit	Timepoint	Sample Type
Baseline (Day –7 to Day –1)	NA	Pertuzumab/Trastuzumab ADA (serum)
		Pertuzumab biomarker (plasma)
Cycle 5	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
	Day 2	Pertuzumab/Trastuzumab PK (serum)
	Day 15	Pertuzumab/Trastuzumab PK (serum)
Cycle 6	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
Cycle 7	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
	Day 2	Pertuzumab/Trastuzumab PK (serum)
	Day 4	Pertuzumab/Trastuzumab PK (serum)
	Day 8	Pertuzumab/Trastuzumab PK (serum)
	Day 15	Pertuzumab/Trastuzumab PK (serum)
Cycle 8	Day 1 pre-infusion [a]	Pertuzumab/Trastuzumab PK (serum)
	Day 1 pre-infusion	Pertuzumab biomarker (plasma)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
Cycle 9	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)

ADA = anti-drug antibody; C_{trough} = steady-state concentration; NA = not applicable; PK = pharmacokinetic.

[a] If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be collected 21 days after Cycle 7 administration.

Appendix 4: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples – Arm A (cont.)

Visit	Timepoint	Sample Type
Cycle 10	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab biomarker (plasma)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
Cycle 11	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
Cycle 12	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
	Day 1 post-infusion	Pertuzumab/Trastuzumab PK (serum)
Cycle 13	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
Cycle 18	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
Cycle 22	Day 1 pre-infusion	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
Treatment Completion/ Discontinuation	NA	Pertuzumab biomarker (plasma)
Month 3 Follow-Up	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
Month 6 Follow-Up	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab ADA (serum)
Month 12 Follow-Up	NA	Pertuzumab/Trastuzumab ADA (serum)
Month 18 Follow-Up	NA	Pertuzumab/Trastuzumab ADA (serum)
Month 24 Follow-Up	NA	Pertuzumab/Trastuzumab ADA (serum)
Month 30 Follow-Up	NA	Pertuzumab/Trastuzumab ADA (serum)
Month 36 Follow-Up	NA	Pertuzumab/Trastuzumab ADA (serum)
		Pertuzumab biomarker (plasma)

ADA = anti-drug antibody; C_{trough} = steady-state concentration; NA = not applicable; PK = pharmacokinetic.

[a] If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be collected 21 days after Cycle 7 administration.

Appendix 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples – Arm B

This study is driven by the primary endpoint C_{trough}. Therefore, adherence to the PK assessment schedule is of utmost importance. On dosing days, PK samples must be taken on the exact day when HER2-targeted therapy is administered (i.e., there is no window allowed). On non-dosing days, all samples must be taken on the exact day of the visit schedule whenever possible (±2 days is allowed if necessary). During follow-up, a window of ±7 days is allowed.

Visit	Timepoint	Sample Type
Baseline (Day –7 to Day –1)	NA	Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
		Pertuzumab biomarker (plasma)
Cycle 5	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
	Day 2	Pertuzumab/Trastuzumab PK (serum)
	Day 15	Pertuzumab/Trastuzumab PK (serum)
Cycle 6	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Cycle 7	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
	Day 2	Pertuzumab/Trastuzumab PK (serum)
	Day 4	Pertuzumab/Trastuzumab PK (serum)
	Day 8	Pertuzumab/Trastuzumab PK (serum)
	Day 15	Pertuzumab/Trastuzumab PK (serum)
Cycle 8	Day 1 pre-injection [a]	Pertuzumab/Trastuzumab PK (serum)
	Day 1 pre-injection	Pertuzumab biomarker (plasma)
Cycle 9	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Cycle 10	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab biomarker (plasma)

ADA = anti-drug antibody; C_{trough} = steady-state concentration; NA = not applicable; PK = pharmacokinetic.

[a] If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be collected 21 days after Cycle 7 administration.

Appendix 5: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples – Arm B (cont.)

Visit	Timepoint	Sample Type
Cycle 11	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
Cycle 12	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
Cycle 13	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Cycle 18	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Cycle 22	Day 1 pre-injection	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Treatment Completion/ Discontinuation	NA	Pertuzumab biomarker (plasma)
Month 3 Follow-Up	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Month 6 Follow-Up	NA	Pertuzumab/Trastuzumab PK (serum)
		Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Month 12 Follow-Up	NA	Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Month 18 Follow-Up	NA	Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Month 24 Follow-Up	NA	Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Month 30 Follow-Up	NA	Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
Month 36 Follow-Up	NA	Pertuzumab/Trastuzumab/rHuPH20 ADA (plasma and serum)
		Pertuzumab biomarker (plasma)

ADA = anti-drug antibody; C_{trough} = steady-state concentration; NA = not applicable; PK = pharmacokinetic.

[a] If the Cycle 8 dose administration is going to be delayed by more than 2 days, the Cycle 8 pre-dose sample must be collected 21 days after Cycle 7 administration.

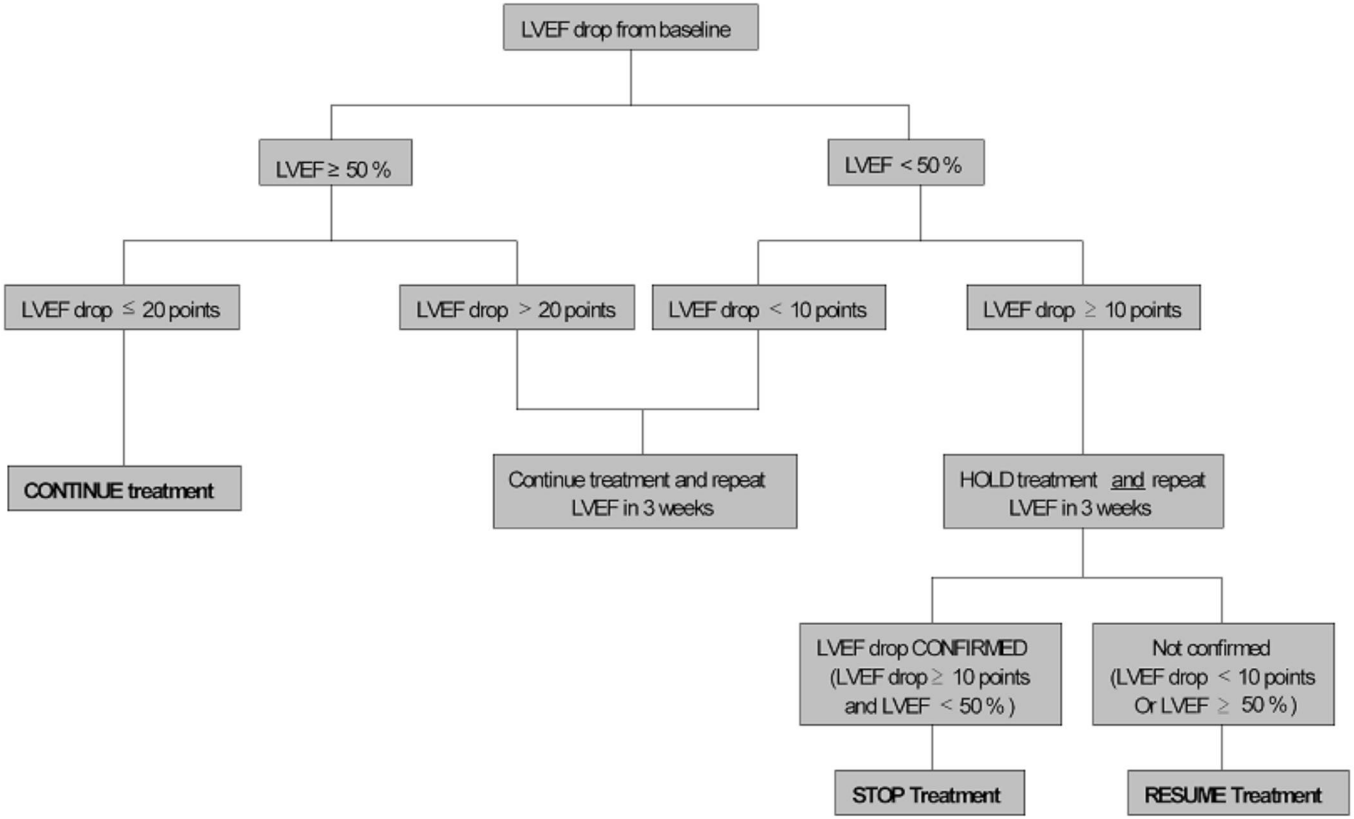
Appendix 6
ECOG Performance Status

Grade	ECOG
0	Fully active; able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light 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

ECOG = Eastern Cooperative Oncology Group.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649 – 55.

Appendix 7 Asymptomatic Decline in LVEF: Algorithm for Continuation[a] and Discontinuation of HER2-Targeted Study Medication



LVEF = left ventricular ejection fraction.

[a] Patients should not start anti-HER2 drugs if their LVEF is < 50% after anthracycline treatment. LVEF should recover to ≥ 50% before starting anti-HER2 drugs.

Appendix 8 NYHA Functional Classification System for Heart Failure and LVSD National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 Grading

NYHA Functional Classification System for Heart Failure	
Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

LVSD National Cancer Institute Common Terminology Criteria for AEs Version 4 Grading					
Investigations					
	Grade				
	1	2	3	4	5
Ejection fraction (EF) decreased [a]	—	Resting EF 50% – 40%; 10% – 19% drop from baseline	Resting EF 39% – 20%; > 20% drop from baseline	Resting EF < 50%	—
Cardiac Disorders					
	Grade				
	1	2	3	4	5
Heart failure [b]	Asymptomatic with laboratory (e.g., BNP [B-natriuretic peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death

BNP = B-natriuretic peptide; EF = ejection fraction; LVSD = left ventricular systolic dysfunction.

[a] Definition: the percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.

[b] Definition: a disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or the ability to do only at an elevation in the filing pressure.

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 9 Pathology Manual

F. HOFFMANN-LA ROCHE LTD

Fixed-Dose Combination of Pertuzumab and Trastuzumab for SC administration (FDC) (RO7198574)

Study YO41137:

Manual for Pathological Response Evaluation Following Neoadjuvant Chemotherapy

Definition of Pathologic Complete Response (pCR)

1 INTRODUCTION

For patients with operable breast cancer, pre-operative (also known as "neoadjuvant") therapy has been shown in several randomized trials to result in survival outcomes similar to those with adjuvant therapy, with the added benefit of improving breast conservation rates (Mauri et al. 2005). In trials of pre-operative therapy, it has been consistently demonstrated that patients who have eradication of invasive disease in the breast (and lymph nodes) (i.e., those who achieve a pathologic complete response [pCR]) have an improved prognosis compared with those who have residual invasive disease present in the surgical specimen after completion of pre-operative therapy (non-pCR). (Mauriac et al. 1991; Semiglazov et al. 1994; von Minckwitz et al., 2012). For example, in the National Surgical Adjuvant Breast and Bowel Project Studies B-18 and B-27, the hazard ratios (HRs) for disease-free survival (DFS) were 0.47 and 0.49, respectively, for patients who achieved a pCR compared with those who did not; the HRs for overall survival (OS) were 0.32 and 0.36, respectively (Rastogi et al. 2008).

Various definitions of pCR have been commonly utilized in clinical trials, but all have demonstrated prognostic value. In the earliest studies of pre-operative therapy, the absence of residual disease in the breast alone (referred to as breast pCR; bpCR; ypT0 or ypTis) was mainly considered. However, it has been reported that a pCR in both breast and residual nodes (total pCR; tpCR; ypT0 or ypTis, ypN0) is associated with a prolonged DFS and possibly OS (Hennessy et al. 2005) when compared with patients who have residual disease in the axilla after neoadjuvant therapy. Furthermore, axillary nodal involvement at initial diagnosis is a well-established risk factor for breast cancer recurrence and death, and thus, the eradication of all malignant disease from the breast and ipsilateral axillary lymph nodes is a common primary goal of systemic neoadjuvant therapy. The presence of residual ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) following neoadjuvant therapy should be reported, but its prognostic significance remains controversial (Mazouni et al. 2007, von Minckwitz et al., 2012).

Pathological complete response with eradication of invasive and in situ disease in the breast and invasive disease in the lymph nodes, a more stringent definition than bpCR and tpCR, has been used as the definition of pCR for studies conducted by the German Breast Group (GBG pCR; ypT0, ypN0). Although any in situ residue will be subjected to surgery and radiotherapy in the course of normal practice, there is also concern that residual in situ disease alone might sometimes be an indicator of residual invasive disease that was missed. Any residual invasive carcinoma detected by pathological examination in the breast or lymph nodes precludes posttreatment classification as a complete pathological response (pCR).

Patients with isolated tumor foci in lymph nodes (ypN0 (i+)) are not classified as having a complete pathological response. The presence of axillary nodal tumor deposits of any

size, including cell clusters 0.2 mm or smaller, excludes a complete pathological response.

Residual disease after neoadjuvant systemic therapy includes a broad range of responses from minimal residual disease (with a similar prognosis to pCR) to bulky disease indicating frank resistance to treatment. The prognosis for patients with residual disease is worse than for those with a pCR however there is a spectrum of risk based upon the extent of residual disease.

For the purposes of this study, the definition of tpCR after neoadjuvant systemic therapy is the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes (ypT0/is, ypN0). bpCR and GBG pCR rates are important exploratory endpoints in the study.

2 GENERAL GUIDANCE

It is recommended that the "Protocol for the Examination of Specimens From Patients with Invasive Carcinoma of the Breast" maintained and available online by the College of American Pathologists be used as a general reference guidance to supplement the material found in this manual as needed.

At the time of publication of this manual the web address for the College of American Pathologists is:

www.cap.org

At the time of publication of this manual, the guidance may be found in the following section:

CAP Home >Protocols and Guidelines > Cancer Protocols >Invasive Breast

3 SURGICAL COMMUNICATION AND SPECIMEN HANDLING

Breast surgery after neoadjuvant systemic therapy should be performed according to locally approved guidelines for breast surgery. It is advised that when possible, the area of carcinoma be removed in a single specimen. The pathologist should be informed of the site of the primary tumor in the breast (particularly within mastectomy specimens) as well as the presence of any accompanying markers (e.g., metallic clips) or clustered microcalcification that would indicate the presence of the residual tumor bed, and whether there is more than one primary tumor in the breast.

Sutures or similar identifiers should be placed by the surgeon post specimen removal to orient the specimen. The specimen should be sent within an hour to a pathology laboratory.

Guidance for surgeons regarding axillary management is provided in the protocol.

4 SPECIMEN HANDLING AND FIXATION

Multiple ink colors are recommended to identify each of the oriented margins of the specimen. See Section 5 for details of specimen imaging and description of the macroscopic findings. The sliced specimen (described below) should be allowed to fix in formalin (twice the volume of the specimen) for at least 24 hours. It is at the pathologist's discretion as to whether the sections for histopathologic analysis are taken before or after the specimen slices have been fixed. Note that some procedures (see Section 5 and Section 6) are performed on the fresh tissue, prior to fixation.

5 IDENTIFICATION OF THE TUMOR BED

Placement of clips (or other markers) into the tumor bed will have been conducted prior to neoadjuvant systemic therapy. The surgeon and pathologist should discuss the patient's clinical history and response to therapy to ensure optimal evaluation of the tumor site. This is critically important because pCR is defined by exclusion and is therefore reliant on appropriate sampling of the correct area in the breast.

For patients with significant clinical response, the breast resection specimen should be radiographed to identify that the tumor clips/markers have been adequately excised. If the surgery was "lumpectomy," then the specimen should be radiographed upon receipt, and then radiographed a second time after the specimen margins have been oriented and inked, and the specimen has been serially sliced. In this manner, removal of any clips and microcalcifications is confirmed in the intact specimen and location can be determined within the specimen. For "total mastectomy" specimens, it is only necessary to radiograph the specimen after it has been inked and sliced. If radiographs are not obtained (e..g, a mass of poorly responsive tumor), then digital photographs or detailed diagrams should represent the specimen slices.

The macroscopic appearance of tumor bed after neoadjuvant treatment is commonly an ill-defined fibrous density, rather than a discrete tumor mass. Also, the tumor bed might be better identified by combined visual inspection and gentle palpation of the tissue slices than by visual inspection alone. Therefore, it is important to have an experienced pathologist or assistant perform careful macroscopic examination of the tissues and correlate those findings with the images and clinical history of the location and response of the primary tumor.

The macroscopic residual primary tumor bed must be measured and reported in three dimensions. Also, any additional tumors in the breast should be measured and reported in three dimensions, with an estimated location and measurement of their distance from the main tumor bed. The distance of any tumor bed from surgical margins must also be reported.

It should be noted that the residual tumor bed may have poorly delineated borders, and it is better to consider adjacent "satellite tumors" as part of the main tumor unless they are more than 1 cm distant or clearly a separate tumor. Even then, sections for histopathologic analysis should be taken from the intervening tissues to rule out extension of the main tumor.

Images of the macroscopic findings (radiographs, digital photographs, or detailed diagrams) provide important documentation of the macroscopic findings and the accuracy and extent of sampling for histopathologic assessment, and can be very helpful for the pathologist when they are used as "a map" for the macroscopic description and the site of each section that is prepared for histopathologic examination. Furthermore, accurate mapping leads to more precise examination for the presence of residual disease, more accurate measurement of the pathologic tumor size for pathologic staging and more precise estimation of the residual tumor bed for assessment of cancer cellularity.

See Section 9 and Section 10 for specific details.

6 SELECTION OF SAMPLES FOR BIOMARKER STUDIES

Biomarker studies of residual tumor or tumor bed are optional in this study. Pathology assessment of the presence/extent of residual disease must take priority over collection of samples for biomarker studies. Therefore, procedures for biomarker sample collection in this trial are described below according to whether or not there is obviously residual macroscopic tumor.

If grossly identifiable tumor is clearly present, we suggest that three cores (suggest 18 gauge) or three punch biopsies (suggest 4 mm), should be obtained from the sliced tumor. *These three samples should be formalin-fixed and paraffin-embedded (FFPE) for the biomarker studies.*

If no grossly identifiable tumor is present but microscopic disease is subsequently identified, a representative block that would be comparable with the volume of three FFPE core biopsies can be submitted for the biomarker studies (optional consent required).

If the final interpretation is pCR, then a representative block from the fibrous tumor bed can be submitted for the biomarker studies (optional consent required).

7 EVALUATION OF THE TUMOR BED WHEN THERE HAS BEEN A SIGNIFICANT CLINICAL RESPONSE

The key information to be obtained after careful macroscopic and microscopic evaluation is accurate measurement of the three-dimensional extent of residual invasive cancer, the extent and proportion of in situ cancer component, presence of any lymphatic/vascular invasion, the status of surgical margins, and the presence and measurement of additional tumors in the breast.

Section 5 describes the important steps for imaging of the specimen and identification and description of the tumor bed. The specimen should be carefully oriented and the surgical margins should be inked.

The specimen should be cut as thinly as possible, into 3 – 5 mm slices. The sliced specimen should then be radiographed with radiologist review of the films to determine presence/extent of residual disease. The pathologist should examine the gross specimen (visually and by gentle palpation) to identify suspicious areas and proximity to margins, and correlate those findings with the radiologic findings. Review of the pathologic and radiographic examination should be discussed with the surgeon regarding adequacy of tissue removal and possible need for additional surgical resection. Preferably, this should be performed in the intra-operative setting to facilitate a single surgery.

The macroscopic dimensions of the residual fibrous tumor bed must be measured and reported in the three largest dimensions (see Section 5).

Images of the macroscopic findings (radiographs, digital photographs, or detailed diagrams) provide "a map" for the macroscopic description and the site of each section that is prepared for histopathologic examination. Furthermore, accurate mapping leads to more precise examination for the presence of residual disease, more accurate measurement of the pathologic tumor size for pathologic staging and more precise estimation of the residual tumor bed for assessment of cancer cellularity.

It is strongly recommended that a map be prepared for the pathologist and annotated with relevant measurements and the site of every tissue section obtained for histopathologic evaluation.

FFPE sections should be obtained from the suspicious areas as well as margins. The largest cross-sectional area of the residual tumor bed should be submitted for FFPE sections, and the pathology report should describe those sections and their relative

orientation. A hypothetical example of the section code would be: "slides A1 – A10; slice 4, largest tumor bed area, starting from anterior to posterior, from superior row (A1 – A3) to inferior row (A8 – A10)." This will allow accurate correlation of histopathologic findings with macroscropic findings and lead to more accurate assessment of final tumor size and pathologic stage. Also note that an annotated map (radiograph, digital image, or detailed diagram) makes this much easier for the pathologist.

The number of sections taken is based upon gross inspection of the specimen, radiographic features, and overall size of the surgical specimen. Some pathologists employ cytologic evaluation of the freshly sliced tumor bed (touch imprint or gentle scrape preparation and smear) to confirm the presence of cancer cells at the time of gross examination, although that is optional.

The largest cross section of presumed tumor bed should be submitted for histologic evaluation, including any firm/suspicious appearing tissue. It is expected that a minimum of 10 – 15 blocks will be needed in cases where there is macroscopic complete response, to rule out residual microscopic disease. If the original tumor and/or resected specimen was/is large, it is recommended that at least one block should be taken per 10 mm of the pretreatment tumor size with additional samples to represent the specimen margins. If these blocks do not show tumor, further sampling should be carried out. If the residual tumor bed is small (< 3 cm) but not macroscopically malignant, then it should be completely submitted for histopathologic study. If larger than 3 cm, then at least 15 blocks from the tumor bed should be submitted.

Two points to note to avoid missing residual invasive cancer. First, clips are indicators and are not the actual lesion. Sometimes metallic clips migrate in the breast. Also, clips are placed as only focal indicators of a more extensive tumor. So it is important to carefully study the macroscopic and radiographic findings of surrounding tissues and not solely focus on the metallic indicator. Second, microcalcifications tend to remain stable in the treated breast, but might only represent the in situ component of the tumor. Therefore, microcalcifications are a helpful indicator for the tumor bed but are not necessarily the best indicator of the invasive component of the tumor. Since HER2-positive breast cancers can have extensive and distant in situ components, the microcalcifications should be sampled but not assumed to represent the site and extent of all residual invasive disease.

8 EVALUATION OF TUMOR BED WHEN THIS IS A RESIDUAL PALPABLE MASS

The key information to be obtained after careful macroscopic and microscopic evaluation is accurate measurement of the three-dimensional extent of residual

invasive cancer, the extent and proportion of in situ cancer component, presence of any lymphatic/vascular invasion, the status of surgical margins, and the presence and measurement of additional tumors in the breast.

For specimens with residual palpable mass, the resection specimen is inked and sectioned into 3 – 5 mm slices. On the basis of gross evaluation of the slices, the pathologist determines the tumor size and confirms with microscopic evaluation. Macroscopic tumor size should be reported in three dimensions, and distance from the resection margins within 10 mm should be reported in the macroscropic description. For tumors measuring up to 20 mm, the entire tumor should be submitted (after any biomarker sampling). For larger tumors, the largest cross-sectional area of the tumor should either be submitted entirely, or submitted as at least five representative tumor blocks.

9 EVALUATION OF AXILLARY LYMPH NODES

The key information to be obtained is the number of nodes containing metastases, the size of the largest metastasis, and the largest dimension of any extranodal extension.

If sentinel lymph nodes are biopsied by the surgeon, these should be evaluated as usual. There should be thin slices of the sentinel node (2–3 mm) submitted entirely. At minimum, an H&E stain or an H&E stain and deeper level, should be examined. Note that the literature for micrometastases and isolated tumor cells has not addressed their prognostic relevance in the post-neoadjuvant treatment setting. Therefore, all positive findings should be described and accurately reported. Use of molecular assays to assess sentinel lymph node status after neoadjuvant therapy is not allowed, because these assays are not designed to detect isolated tumor cells or very tiny micrometastases.

Lymph nodes may be difficult to recognize after neoadjuvant chemotherapy secondary to fibrosis and atrophy. In the case that lymph nodes are difficult to identify, fibrotic areas of the axillay fat and sections surrounding vessels should be submitted.

All lymph nodes removed should be examined histologically by serial gross sectioning. For lymph nodes with macroscopic evidence of malignancy, examination should be done by representative cross section, to represent the largest metastatic area. For lymph nodes without clearly identifiable malignancy upon macroscopic review, the lymph nodes should be completely submitted for FFPE sections for histological examination. If possible, these lymph nodes should be bisected along the longitudinal axis or cut into slices with a thickness of 2 – 3 mm. At least one representative histologic section should

be evaluated by hematoxylin and eosin (H&E) per paraffin block. Immunohistochemical staining for cytokeratin is not routinely performed on negative non-sentinel nodes.

10 REPORTING RESULTS

10.1 PRIMARY TUMOR

Neoadjuvant systemic therapy can result in a range of responses from no identifiable response to complete absence of tumor. The tumor bed must be identified to reliably diagnose pCR. Characteristic changes include edematous fibrous tissue with residual vascularity and scattered mast cells and lymphocytic infiltrate, histiocytic cells with cytopathic degenerative vacuolization, hyalinized vascular stroma, fat necrosis, hemosiderin-laden macrophages, and absence of glandular tissue can indicate the tumor bed. However, there is no doubt that accurate clinical-pathologic correlation at the time of macroscopic examination and sectioning remains the most precise method to identify the tumor bed.

Standard pathology reporting of tumor bed size, residual tumor size, type of cancer, DCIS status, vascular invasion status, excision status, and distance to margin should be reported where applicable.

In the absence of gross tumor, significant residual disease may still be present microscopically. Extensive sampling must be done to confirm that there is no residual invasive disease.

The postneoadjuvant therapy pathological T category (ypT) is based on the largest focus of residual tumor, if present. Treatment-related fibrosis adjacent to residual invasive carcinoma is not included in the ypT maximum dimension. When multiple foci of residual tumor are present, the (m) modifier is included. The pathology report should include a description of the extent of residual tumor explaining the basis for the ypT categorization and, when possible, also should document the pretreatment cT category.

Residual cancer cells can have an unexpected, unusual bizarre appearance, or might have subtle signet ring, plasmacytoid, or histiocytoid apppearance. On occasion, immunochistochemical stains to distinguish between histiocytes (CD68) and epithelial cells (cytokeratins AE1/AE3 or cytokeratin 7) might be necessary to detect residual tumor cells in the tumor bed, surgical margins and/or lymphatics.

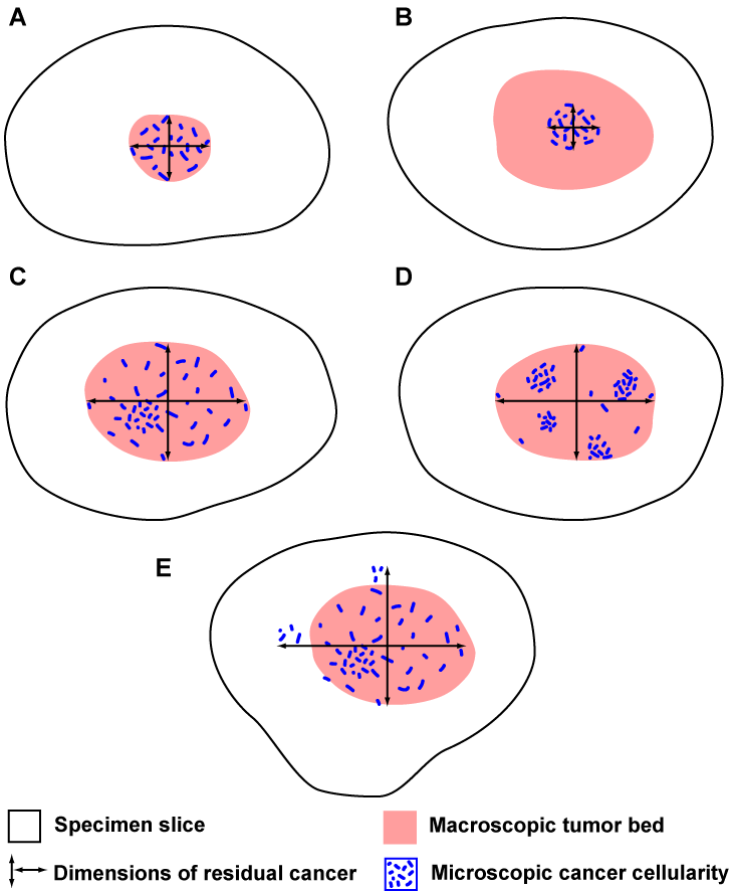
If residual disease is noted, standard histolopathologic parameters such as type, size, vascular invasion, and margin status should be recorded. Grade is affected by treatment changes and has not been validated as independently prognostic in residual disease. Refer to the electronic case report form to ensure information needed for all data fields is recorded.

For the purposes of pathologic response, intralymphatic or intravascular cancer alone (without invasive cancer) must be distinguished from in situ carcinoma, and should be considered to be residual invasive disease.

Alterations of cellularity may lead to a false impression of multifocality. IHC examination can often demonstrate altered tumor cells in fibrosis. If multifocality is suspected, then sampling of the intervening tissues is advised to look for subtle extension of the main tumor. Also, representative sections of the tissues adjacent to the tumor bed are helpful to look for residual invasive cancer and to ensure accurate tumor measurement.

Residual invasive cancer is not necessarily contiguous because treatment can eliminate some regions of the tumor. Therefore, residual tumor size should be based upon the total histopathological extent of tumor after macroscopic and microscopic correlatioin, and not the size of the largest individual lesion. Diagrammatic mapping of sections to macroscopic findings is the most accurate method to measure, stage, and evaluate the residual disease. Therefore, the macroscopic dimensions of the residual tumor bed (in three dimensions) might be adjusted up or down after the histopathologic evaluation of the corresponding tissue sections from the tumor bed and representative surrounding tissues. The postneoadjuvant therapy pathological T category (ypT) is based on the largest focus of residual tumor, if present. Treatment-related fibrosis adjacent to residual invasive carcinoma is not included in the ypT maximum dimension. When multiple foci of residual tumor are present, the (m) modifier is included. The pathology report should include a description of the extent of residual tumor explaining the basis for the ypT categorization and, when possible, also should document the pretreatment cT category.

Figure 1 Illustration of Macroscopic-Microscopic Correlations to Define Final Dimensions of Residual Cancer



In Figure 1, the macroscopic tumor bed dimensions in Examples A, C, D also define the final dimensions of the residual tumor bed after microscopic review. However, the macroscopic tumor bed dimensions in Example B overestimate the extent of residual cancer, and so the dimensions of the residual tumor bed (d1 and d2) would be revised after microscopic evaluation of the extent of residual cancer in the corresponding slides from the gross tumor bed. In a different example (E), microscopic residual cancer extends beyond the confines of the macroscopic tumor bed. Again, the dimensions of the residual tumor bed (d1 and d2) would be revised after microscopic evaluation of the recognizable extent of residual cancer beyond the macroscopic tumor bed.

10.2 LYMPH NODES

Response to neoadjuvant systemic therapy may cause lymph node metastases to be replaced by hyaline stromal scars, mucin pools, and/or aggregates of histocytes without any visible tumor cells. The presence of a large scar in a lymph node without identifiable tumor cells is indicative of complete response to therapy. Furthermore, the appearance

of a metastatic focus is often altered by prior neoadjuvant therapy. Cells may be scattered, rather than in a discrete mass. The measurement of the metastasis should represent the extent of the metastasis (from one end to the opposite) and does not require that tumor cells be confluent in their distribution. Also, the tumor cells can have bizarre appearance, or might have subtle signet ring, plasmacytoid, or histiocytoid apppearance. In difficult cases regarding determination of residual invasive disease, immunochistochemical stains to distinguish between histiocytes (CD68) and epithelial cells (cytokeratins, suggest AE1/AE3 or cytokeratin 7) may be used to detect residual tumor cells. AJCC definition and classification for node-positivity, including isolated tumor cell clusters (ITC), by immunohistochemistry must be followed in order to render the appropriate nodal status (i.e., positive or negative). [Table 1]. The largest focus of residual tumor in the lymph nodes, if present, is used for ypN categorization. Treatment-related fibrosis adjacent to residual lymph node tumor deposits is not included in the ypN dimension and classification.

Table 1 American Joint Committee on Cancer (AJCC, 8th edition): Pathologic Nodal Staging Classification

Pathologic Nodal Stage*	Definition
pNx	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed at all)
pN0	No regional lymph node metastasis histologically
(i-)	• No regional lymph node metastases histologically • Negative IHC
(i+)	Malignant cells in reginal lymph node(s) no greater then 0.2 mm (detected by H&E or IHC, including ITCs)
(mol-)	• No regional lymph node metastases histologically • Negative molecular findings (RT-PCR)
(mol+)	• No regional lymph node metastases detected by histological or IHC • Positive molecular findings (RT-PCR)
pN1	• Micrometastases or metastases in 1 – 3 axillary lymph nodes, and/or • Clinically negative internal mammary lymph nodes with micrometastases, or • Macrometastases by sentinel lymph node biopsy
mi	Micrometastases > 0.2 mm and/or > 200 cells, but none > 2.0 mm
a	Metastases in 1 – 3 axillary lymph nodes, at least 1 metastasis > 2.0 mm
b	• Metastases in internal mammary nodes with micrometastases, or • Macrometastases detected by sentinel lymph node biopsy but not clinically detected

Appendix 9: Pathology Manual (cont.)

Pathologic Nodal Stage*	Definition
c	Metastases in 1 – 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	• Metastases in 4 – 9 axillary lymph nodes, or • Clinically detected*** internal mammary lymph nodes in the absence of axillary lymph node metastases
a	Metastases in 4 – 9 axillary lymph nodes (at least 1 tumor deposit > 2.0mm)
b	Metastases in clinically detected*** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	• Metastases in 10 or more axillary lymph nodes, or • Metastases in infraclavicular (Level III axillary) lymph nodes, or • Clinically detected*** ipsilateral internal mammary lymph nodes in the presence of one or more positive Level I and II axillary lymph nodes, or • Metastses in more than 3 axillary lymph nodes and ipsilateral internal mammary lymph nodes with micrometastases, or • Macrometastases detected by sentinel lymph node biopsy but not clinically detected***, or • Macrometastases in ipsilateral supraclavicular lymph node
a	• Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit > 2.0mm), or • Metastases to the infraclavicular (Level III axillary) lymph nodes
b	• Metastases in clinically detected*** ipsilateral internal mammary lymph nodes in the presence of ≥ 1 positive Level I, II axillary lymph nodes, or • Metastases in > 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
c	Metastases in ipsilateral supraclavicular lymph nodes

*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification is based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection and is designated (sn) for "sentinel node" (e.g., pN0[sn])

**Isolated Tumor Cell Clusters (ITCs) are detected by routine H&E or by IHC and defined as:

Small clusters of cells ≤ 0.2mm, or

A single tumor cell, or

A cluster of < 200 cells in a single histological cross-section

***Clinically detected is defined by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on the FNA biopsy with cytologic examination.

10.3 EVALUATION OF MARGINS

Special attention should be paid to margins, which may be more difficult to evaluate after neoadjuvant therapy.

Discontinuous fibrous lesions in close relationship to the resected margin should be carefully examined to rule out residual disease. Also, the tumor cells can have an unexpected, unusual bizarre appearance, or might have subtle signet ring, plasmacytoid, or histiocytoid apppearance. On occasion, immunochistochemical stains to distinguish between histiocytes (CD68) and epithelial cells (cytokeratins AE1/AE3 or cytokeratin 7) might be necessary to detect residual tumor cells. However, one must also recognize that treatment changes in proliferative fibrocystic tissues can mimic in situ or even invasive disease.

11 REFERENCES AND SUGGESTED READING

Giuliano AE, Connolly JL, Edge SB et al. Breast Cancer—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. Ca Cancer J Clin 2017;67:290 – 303.

Hennessy BT, Hortobagyi GN, Rouzier R, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 2005;23:9304 – 11.

Loi S, Symmans WF, Bartlett JM, et al. Proposals for uniform collection of biosamples from neoadjuvant breast cancer clincial trials: timing and specimen types. Lancet Oncol, 2011;12:1162 – 68.

Mauri D, Pavlidis N, Ioannidis J. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97:188 – 94.

Mauriac L, Durand M, Avril A, et al. Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. Results of a randomized trial in a single centre. Ann Oncol 1991;2:347 – 54.

Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. J Clin Oncol 2007;125:2650 – 5.

Provenzano E, Bossuyt V, Viale G, et al: Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. Mod Pathol 2015;28:1185 – 201.

Rastogi P, Anderson S, Bear H, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778–85.

Semiglazov VF, Topuzov EE, Bavli JL, et al. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer. Ann Oncol, 1994;5:591–5.

von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796–804.

Hortobagyi GN et al. AJCC Cancer Staging Manaul, Eighth Edition. Breast. The American Colleague or surgeons (ACS), Chicago, Illinois.

Appendix 10 Radiotherapy Guidelines

I. BREAST CONSERVING THERAPY

MANDATORY: Breast Radiotherapy after Complete Local Excision

Breast radiotherapy (RT) may be contraindicated in patients with significant comorbidity (for example, scleroderma and systemic lupus erythematosus). Reasons for not delivering breast RT after complete local excision of the primary breast cancer should be documented in the electronic case report form (eCRF).

Target Volume

- Whole breast including the primary tumor bed
- Primary tumor bed boost in conjunction with whole breast RT may be used as per local policy declared by the center prior to local activation.
- Partial breast RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: Refer to Item III below.

Dose Fractionation

- Whole breast - recommended schedules:

a) 50 Gy in 25 fractions, 5 fractions per week; or

b) 42.5 Gy in 16 fractions, 5 fractions per week; or

c) 40 Gy in 15 fractions, 5 fractions per week.

Other schedules may be used as per local policy declared by the center prior to local activation.

- Primary tumor bed boost in conjunction with whole breast RT: As per local policy declared by the center prior to local activation.
- Partial breast RT: As per local policy declared by the center prior to local activation.

Treatment planning

- Computed tomography (CT)-based treatment planning is strongly recommended for whole breast RT and tumor bed boost.
- CT-based treatment planning is mandatory for partial breast irradiation delivered using external beam RT.

II. POST-MASTECTOMY RADIOTHERAPY

MANDATORY:

a) 4 or more positive axillary nodes or

b) Pathologic T4 disease.

c) 'Non-resectable' microscopic positive deep margin (invasive carcinoma or ductal carcinoma in situ [DCIS])

OPTIONAL:

d) 1–3 positive axillary nodes or

e) Higher risk node negative disease (for example T3 primary in the presence of high histologic grade and/or lymphovascular invasion)

Target Volume

- Whole chest wall
- Primary tumor bed boost in conjunction with chest wall RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: Refer to Item III below.

Dose Fractionation

- Whole breast: Recommended schedule is 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation.
- Primary tumor bed boost in conjunction with chest wall RT: As per local policy declared by the center prior to local activation.

Treatment planning

- CT-based treatment planning is strongly recommended for chest wall RT.

III. REGIONAL NODAL RADIOTHERAPY

For patients who have completed sentinel node biopsy (SNB) alone or axillary lymph node dissection (ALND) as per protocol

RECOMMENDED:

Any breast surgery, 4 or more positive axillary nodes

OPTIONAL:

Any breast surgery, 0–3 positive axillary nodes, pathological T4 (pT4) disease

Target volume

- Required:

a) Supraclavicular fossa if there are 4 or more positive axillary nodes;

b) Internal mammary nodes if tumor involvement is biopsy confirmed.

- Optional:

c) Supraclavicular fossa if there are 0–3 positive axillary nodes;

d) Axilla as per local policy declared by the center prior to local activation (for example, known or high risk of residual axillary disease postsurgery);

e) Internal mammary nodes if there is a high risk of tumor involvement as per local policy declared by the center prior to local activation.

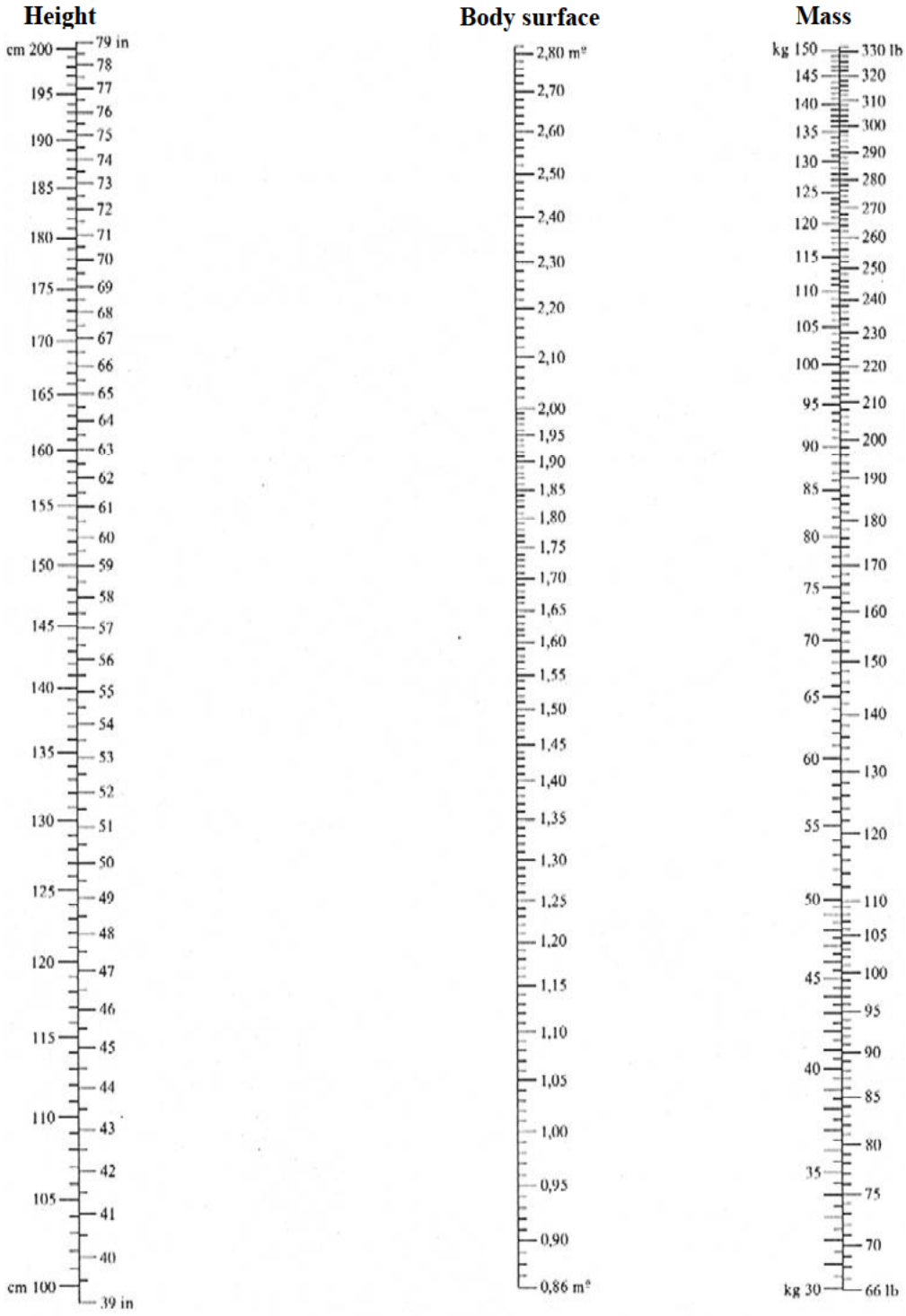
Dose fractionation

- Recommended schedule: 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation. Hypofractionated schedules are not recommended.

Treatment planning

- CT-based treatment planning is strongly recommended for supraclavicular fossa and/or axillary RT.
- CT-based treatment planning is mandatory for internal mammary nodal RT.

Appendix 11
Nomogram for Determination of Body Surface Area



Based on the Formula from Du Bois and Du Bois, Arch intern Med , 17, 863 (1916): $0 = M^{0,425} \times L^{0,725} + x71,84$ resp $\log 0 = \log M x 0,425 + \log L x 0,725 + 1,8564$
(0: Body surface [in cm2], M; Body mass [in kg]: L: Body length [in cm]