CLINICAL STUDY PROTOCOL

Protocol title: Omission of surgery and sentinel lymph node dissection in clinically low-risk HER2positive breast cancer with high HER2 addiction and a complete response following standard anti- HER2-based neoadjuvant therapy (ELPIS trial)

Protocol code: HCB-ONC001 ELPIS (ML41519)

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Sponsor: Fundació Clínic per a la Recerca Biomèdica (FCRB)

Study Principal Investigators: PPD

CONFIDENTIAL

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SPONSOR'S SIGNATURES PROTOCOL TITLE: "Omission of surgery and sentinel lymph node dissectio in clinically low-risk HER2-positive breast cancer with high HER2 addiction and a complete response following standard anti-HER2-based neoadjuvant therapy (ELPIS trial)"

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PROTOCOL ACCEPTANCE FORM – SITE PRINCIPAL INVESTIGATOR

ELPIS: "Omission of surgery and sentinel lymph node dissection in clinically low-risk HER2-positive breast cancer with high HER2 addiction and a complete response following standard anti-HER2-based neoadjuvant therapy (ELPIS trial)"

Protocol ELPIS

I have read the protocol and agree that it contains all necessary details for conducting this study. I will conduct the study as outlined in this protocol and in compliance with GCP. I will provide copies of the protocol and all drug information related to preclinical and prior clinical experience furnished to me by the Sponsor, to all physicians and medical personnel under my supervision that collaborate with me in the conduction of this study. I will discuss these materials with them to ensure that they are fully informed regarding the study medication and the conduct of the study. I agree to keep all records and information collected during the study for the period of time as required by the applicable regulatory requirements.

Site Principal Investigator

_____

Site

_____

Name

_____ _____

Signature **Date**

INDEX

Abbreviated Title	ELPIS Trial
Trial Phase	*II*
Clinical Indication	HER2-positive HER2-enriched and ERBB2-high early breast cancer
Trial Type	Single arm
Type of control	-
Route of administration	Intravenous and subcutaneous
Trial Blinding	No
Treatment Groups	Paclitaxel/trastuzumab/pertuzumab (TDM-1 if residual disease)
Number of trial participants	17 evaluable patients (~27 patients included)
Estimated enrollment period	Approximately 24 months
Estimated duration of trial	Approximately 60 months
Duration of Participation	60 months – 5 years
Estimated average length of treatment per patient	12 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a prospective, single arm, open-label, unicenter, exploratory study in women with primary operable HER2-positive, HER2-enriched(HER2-E)/ERBB2-high breast cancer according to PAM50 intrinsic subtype and a ERBB2 pre-defined cutoff (high vs low ERBB2 expression), to evaluate the omission of surgery and sentinel lymph node dissection in patients with HER2-E and ERBB2 high breast cancer who achieving a complete response following standard anti-HER2-based neoadjuvant therapy with paclitaxel/trastuzumab/pertuzumab.

The primary trial objective is to estimate the loco-regional invasive disease-free survival(LR-IDFS) at 3-year of patients who achieve a complete response based on imaging (i.e. Magnetic resonance imaging [MRI]) and a stereotactic-guided vacuum-assisted breast biopsy (VAB), and omit loco-regional surgery.

Screening and allocation

After being informed, agreeing to participate in the study and signing the informed consent form, patients will start the screening procedures. All patients must have known estrogen receptor (ER), progesterone receptor (PgR) and HER2 status locally assessed by immunohistochemistry (IHC) and/or in situ hybridization (ISH), according to ASCO/CAP guidelines(1, 2). An Archived Formalin-Fixed Paraffin-Embedded (FFPE) specimen with adequate quantity and quality of tumor tissue must be provided. If not available, the patient

must agree to re-biopsy. Breast MRI and breast and axillar ultrasound (US), performed shortly prior to Day 1 of treatment as per standard of care (≤42 days), should be available for confirmation of baseline tumor ≤ 2cm and a negative ipsilateral axilla.

PAM50 test and ERBB2 levels will be determined in a central laboratory. Patients with a subtype other than HER2-E and/or low ERBB2 levels will not be allocated (screening failures). Remaining tissue will be kept for additional translational studies for those patients randomized in the study.

Neoadjuvant period

HER2-enriched/ERBB2-high patients will be eligible for the trial. After confirmation of all eligibility criteria, eligible patients will receive paclitaxel IV 80mg/m^2 every week for 12 weeks with trastuzumab and pertuzumab Subcutaneous Fixed-Dose Combination (FDC) (a loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by a maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab once every 3 weeks) for 5 cycles. In total, neoadjuvant therapy will last for 13 weeks.

After 13 weeks of neoadjuvant treatment, a breast MRI will be performed. If a complete response is observed on breast MRI, patients will undergo a stereotactic-guided VAB of the marker area to obtain 12 cylinders of breast parenchyma, which is equivalent to 2 grams of tissue.

Omission of surgery

If no invasive tumor cells and no *in situ* disease are identified in the stereotactic-guided VAB, patients will be eligible to omit loco-regional surgery. Whole breast radiotherapy without nodal radiotherapy will then be performed. Trastuzumab and pertuzumab FDC will be continued to complete 1 year of treatment and adjuvant endocrine therapy will be indicated according to hormonal receptor status by IHC.

Surgery

If invasive tumor cells and/or *in situ* disease are identified, patients will undergo surgery. Breast and axillary surgery will be done according to local practice procedures. The type of surgery performed will be recorded. Surgery samples of the residual tumor tissue will be collected regardless of whether they completed full neoadjuvant treatment. All patients will continue with Trastuzumab-emtansine (TDM1) completing 1 year of treatment (14 cycles) and adjuvant endocrine therapy will be indicated according to hormonal receptor status by IHC. Patients who have undergone surgery will receive radiotherapy treatment according to standard clinical practice. Adjuvant TDM-1 will be administered concurrently with radiotherapy.

Treatment follow-up

The first safety follow-up visit for the study treatment will be scheduled for all patients 28 days (+/- 7 days) after the last dose of any Investigational Medicinal Product (IMP) and it will be

called as end of treatment visit.

Afterwards, patients will be followed as scheduled in Section 6, up to end of study or the patient withdraws consent or until death, whichever occurs first. During these follow-up contacts survival status, post-study anticancer therapy evaluation, and clinical data will be collected as needed. Telephone contact is acceptable.

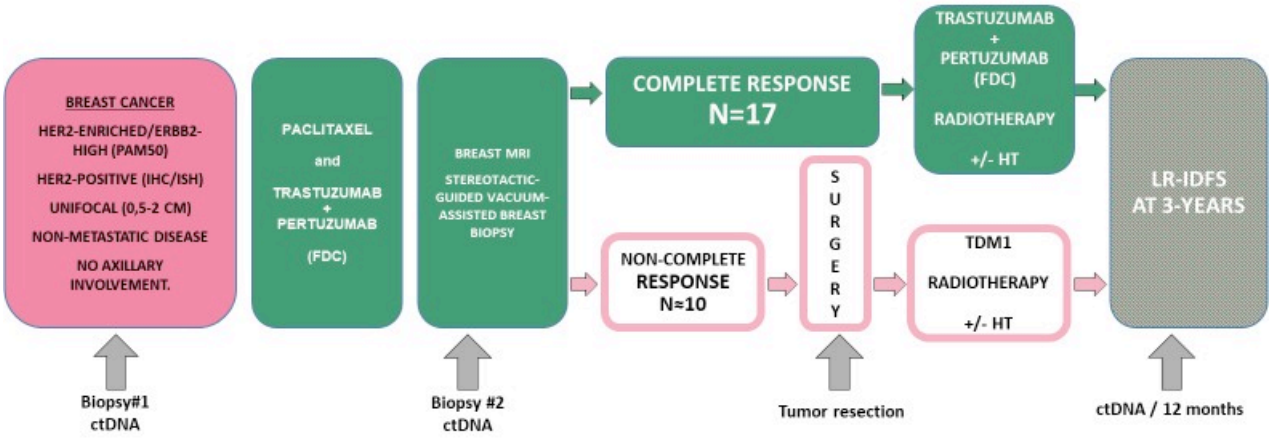
All ≥ grade 2 AEs will be followed up until improvement to baseline levels, grade 1 or complete recovery, the patient withdraws consent, patient's death or lost to follow-up. Patients who discontinue study drugs for any reason will be followed up to end of study (as defined in Section 6) or up to study termination, whichever occurs first. A summary of the study assessments is reported in Section 6: Schedule of assessments and study procedures.

End of study

The end of study will be 3 years from surgery of the last patient (if surgery is performed), up to 3 years from stereotactic-guided VAB of the last patient (if surgery is not performed), or the trial is terminated by the sponsor, whichever occurs first. The end of the trial is defined as the date of the last visit of last subject undergoing the trial. This data point will be considered LPLV (Last Patient Last Visit).

2.2 Trial Diagram

Omission of surgery and sentinel lymph node dissection in clinically low-risk HER2positive breast cancer with high HER2 addiction and a complete response following standard anti-HER2-based neoadjuvant therapy.



*After surgery, the addition of an adjuvant chemotherapy regimen based on anthracyclines can be administered at the researcher's choice. Adjuvant chemotherapy will be administered concurrently with trastuzumab and pertuzumab and prior to treatment with radiotherapy.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective	Endpoint
To evaluate the possibility of omission of surgery and sentinel lymph node dissection in clinically low-risk HER2-positive breast cancer with high HER2 addiction and a complete response following standard neoadjuvant chemotherapy and dual HER2 blockade.	To estimate the loco-regional invasive disease-free survival (LR-IDFS) at 3-year of patients who achieve a complete response based on imaging and a stereotactic-guided vacuum-assisted breast biopsy, and omit loco-regional surgery. 3-years LR-IDFS rate defined as time from the first date of no disease (i.e., date of stereotaxic guided biopsy) to loco-regional recurrence. Loco-regional recurrence is defined as recurrence of breast cancer in the same breast parenchyma as the original primary lesion, the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast.

3.2 Secondary Objective(s) & Hypothesis(es)

Objectives	Endpoints
1. To assess measures of clinical benefit of both arms	1.1 To estimate the disease-free survival at 3years and 5-years of patients who achieve a complete response based on imaging (i.e. MRI) and a stereotaxic guided biopsy and omit loco-regional surgery following neoadjuvant chemotherapy and dual HER2 blockade. 1.2 To estimate the disease-free survival at 3years and 5-years of patients who do not achieve a complete response based on imaging (i.e. MRI) following neoadjuvant chemotherapy and dual HER2 blockade. 1.3 To compare the rate of pathological complete response (pCR) between the treatment groups by HR status.

2. Analyze the financial impact of the omission of breast cancer surgery.	2.1 To compare the cost in patients with and without breast cancer surgery, not only direct cost for hospitals/public health system, but also indirect cost for public system
3. To assess the effect of investigational treatment and standard treatment on patient reported outcomes (PROs).	3.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), version 3. 3.2 EORTC QLQ-BR23 (breast cancer-specific questionnaire).
4. To evaluate the safety and tolerability of investigational treatment and their corresponding standard treatment.	4.1 Incidence, duration and severity of Adverse Events (AEs) assessed by the NCI Common Terminology for Classification of Adverse Events (CTCAE) version 5, including dose reductions, delays and treatment discontinuations.

3.3 Exploratory Objective

Mandatory tumor and blood samples collected during the pre-screening, treatment and follow up of the study will be used to investigate potential value of current and future RNA- and DNA-based biomarkers to predict response to the study drug(s).

4.0 BACKGROUND & RATIONALE

4.1 Background

HER2-positive early breast cancer

Overexpression and gene amplification of HER2-positive occurs in approximately 20% of invasive breast cancer and is associated with aggressive disease and poor prognosis (3). However, since the introduction of anti-HER2 therapies, such as trastuzumab, lapatinib, neratinib or pertuzumab, in combination with chemotherapy, the course of HER2-positive early breast cancer has dramatically changed and today a large proportion of patients with this disease are cured (4-7).

The neoadjuvant approach in early breast cancer

Systemic therapy delivered before definitive breast cancer surgery was once reserved to reduce the size and extent of locally advanced tumors. Today, however, is being used and

recommended more widely (8). The reasons are: 1) it increases the likelihood of tumor control and the potential for curability, 2) the surgical outcomes are improved, 3) it allows a rapid assessment of drug efficacy and 4) if no invasive tumor cells are identified after neoadjuvant therapy, the so-called pathological complete response (pCR), the long-term outcome is excellent (9, 10).

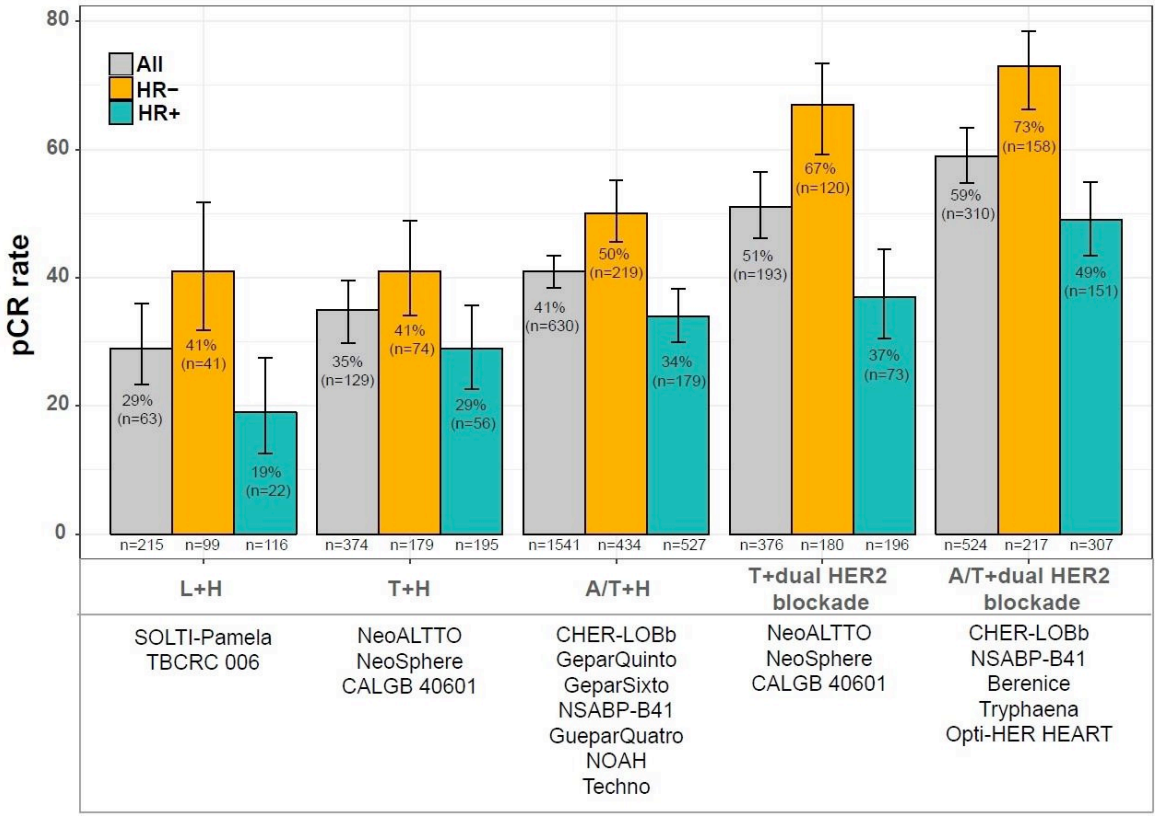
Efficacy of neoadjuvant treatment in HER2-positive early breast cancer

Among the different breast cancer subtypes, HER2-positive disease is today one of the most sensitive to systemic treatments. In Figure 1, we have reviewed the literature and combined the results of 16 neoadjuvant trials (n=2,923) (11-22) according to the type of chemotherapy treatment (taxane-only or anthracycline/taxane-based) and anti-HER2 treatment (trastuzumab-only or dual HER2 blockade). The results reveal that the range of pCR rates ranges from ~29% with dual HER2 blockade without chemotherapy to 60% with dual HER2 blockade with multi-agent chemotherapy. Today, current guidelines recommend dual HER2 blockade with pertuzumab and trastuzumab in combination with multi-agent chemotherapy (anthracycline/taxane or taxane/platinum) in patients with HER2-positive tumors above 2 cm or node-positive (23-25). In patients with tumors less than 2 cm and node-negative, the standard of care is trastuzumab in combination with chemotherapy.

Of note, dual HER2 blockade in combination with chemotherapy has been recently explored in the adjuvant setting of early-stage breast cancer in the APHINITY Trial (7). The addition of pertuzumab to trastuzumab lowered the chance of developing invasive breast cancer by 19% compared to trastuzumab alone. At a median follow-up of almost 4 years, 171 (7.1%) patients in the pertuzumab group had developed invasive breast cancer, compared to 210 (8.7%) patients in the placebo group. At 3 years, an estimated 94.1% of patients in the pertuzumab group were free of invasive breast cancer, compared to 93.2% of patients in the placebo group. Based on this data, dual HER2-blockade in combination with chemotherapy is the standard of care in first-line advanced disease (26) and neoadjuvant setting (21, 27) and will become more widely used in adjuvant early HER2-positive breast cancer.

The prognostic value of pCR has been confirmed in a large meta-analysis by Cortazar and colleagues (9). In this study, the authors obtained data from 12 international neoadjuvant trials and 11,955 patients. The results confirmed that pCR is associated with long-term outcome in the HER2-positive subgroup irrespective of hormone-receptor status (event-free survival: Hazard Ratio = 0.39, 95% CI 0.31-0.50; overall survival: 0.34, 0.24-0.47), although the most favourable outcomes after pCR were recorded in patients with HER2-positive hormone receptor-negative tumors who received trastuzumab (event-free survival: Hazard Ratio = 0.15, 0.09-0.27; OS: 0.08, 0.03-0.22).

Fig 1. Rates of pathological complete response (pCR) reported across 13 published neoadjuvant clinical trials in HER2-positive breast cancer. Bars denote 95% CIs. T, taxane; L, lapatinib; H, Herceptin (trastuzumab); A/T, anthracycline/taxane-based(28).



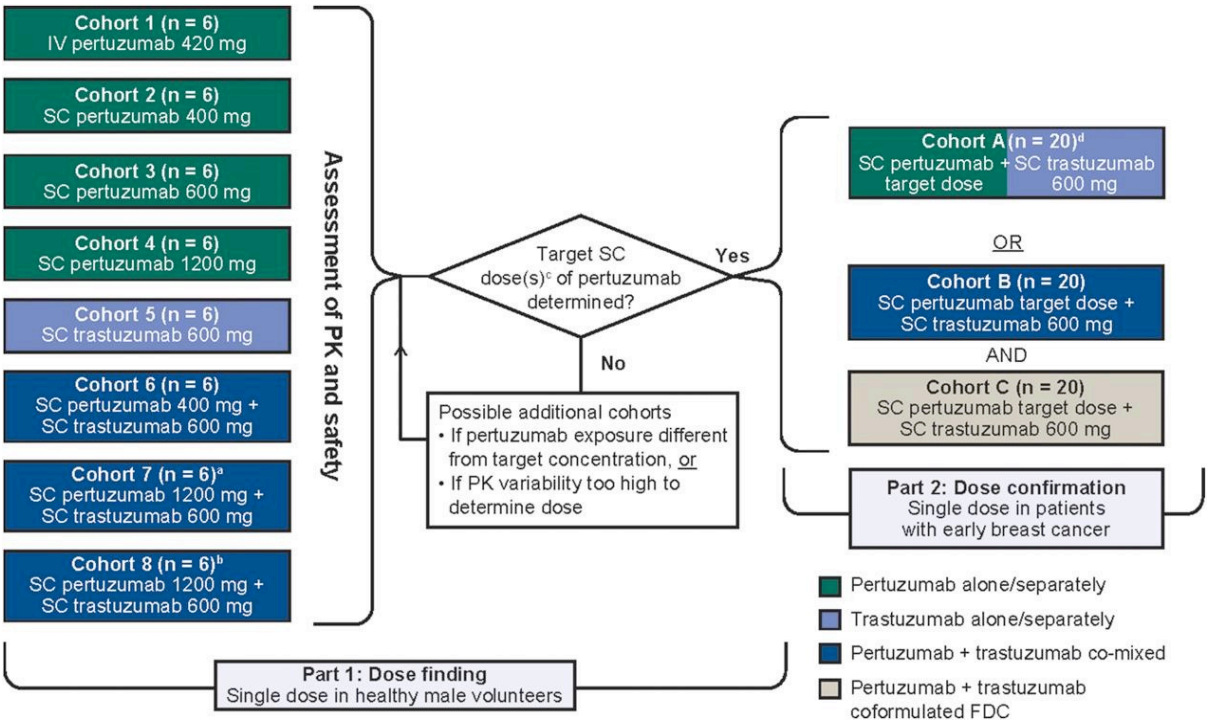
TDM1, a drug-antibody conjugate formed by a monoclonal antibody against HER2 combined with the anti-microtubule chemotherapy agent DM1, has demonstrated activity in metastatic and early BC patients. To evaluate the activity of TDM1 in the post-neoadjuvant scenario, the KATHERINE phase III trial randomized 1486 patients with HER2-positive BC and residual disease after neoadjuvant therapy to receive 14 cycles of TDM1 or to maintain trastuzumab for 14 cycles. In the interim analysis with a median follow up of 41.4 months, the 3-year invasive DFS rates were 88.3% in the TDM1 *versus* 77% in the trastuzumab group (HR 0.50; 95% CI 0.39–0.64, $p < 0.001$). The rate of distant recurrences was 10.5% with TDM1 *versus* 15.9% with trastuzumab, and all subgroups benefited from TDM1. Around 18% of the patients included in the study received neoadjuvant therapy with trastuzumab and pertuzumab, the current standard of care for most HER2-positive patients (40). Given the impressive results observed in the KATHERINE trial, post-neoadjuvant TDM1 represents the new standard of care treatment for HER2-positive patients with residual disease after neoadjuvant therapy.

Clinical Studies with Trasttumab and Pertuzumab fixed doses combination 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 fixed doses combination (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 2**.

Figure 2 Study BO30185 Schema



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 trastuzumab 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 pertuzumab SC had been established in Part 1. The overall schema for Part 2 was Cohort A only (co-administration of v SC [with rHuPH20] and trastuzumab SC [with rHuPH20], each agent administered separately) or otherwise Cohort B (pertuzumab and trastuzumab SC co-mixed product) and Cohort C (the FDC). Cohort A was only to be enrolled if there was a PK interaction between pertuzumab and trastuzumab observed in Part 1, or if the development of the FDC was not feasible. The pertuzumab and trastuzumab SC comixed 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 pharmacokinetic (PK) results from Part 1 and Part 2 (Cohort B) of the study showed that pertuzumab SC, given as a loading dose of 1200 mg and maintenance dose of 600 mg provides similar steady-state concentration at the end of a dosing interval (C_{trough}) and area under the concentration-time curve (AUC) as pertuzumab IV 840 mg and 420 mg, respectively, as

determined in healthy male volunteer (HMVs). Pertuzumab SC 600-mg dose in early breast cancer patients provides similar C_{trough} and AUC to the 420 mg IV and 600 mg SC cohorts in HMVs in Part 1 and dose proportionality through PK linearity confirms a pertuzumab SC 1200 mg loading dose. The safety profile of pertuzumab SC in the study was consistent with the known safety profile of pertuzumab IV and is well tolerated when given in combination with trastuzumab SC. There were no new safety signals identified. There were no serious adverse events, deaths, or adverse events leading to withdrawals during the study.

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: pertuzumab 1200 mg + Trastuzumab 600 mg, with rHuPH20 2,000 U/mL
- Maintenance dose SC: pertuzumab 600 mg + Trastuzumab 600 mg, with rHuPH20 2,000 U/mL

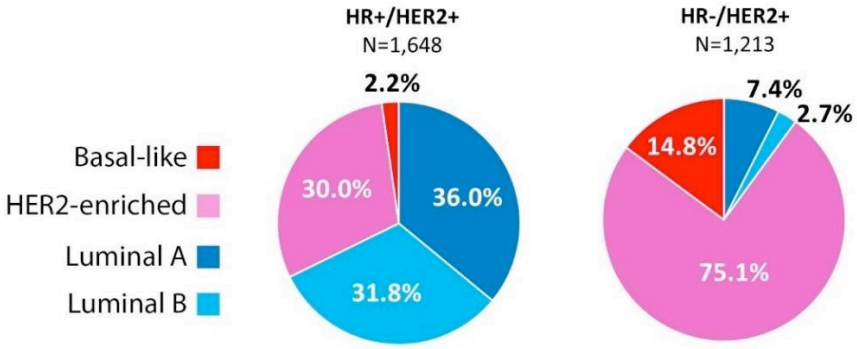
Recently, Roche has announced the phase III FeDeriCa study met its primary endpoint. The study showed a new investigational FDC of pertuzumab and trastuzumab, administered by SC injection in combination with IV chemotherapy, demonstrated non-inferior levels of pertuzumab in the blood (pharmacokinetics) compared to standard IV infusion of pertuzumab plus trastuzumab and chemotherapy in people with HER2-positive early breast cancer. The safety profile of the FDC of pertuzumab and trastuzumab was consistent with that of petuzumab and trastuzumab administered intravenously.[1,2]

Currently, there are several trials in recruitment in HER2-positive breast cancer testing Trastuzumab and pertuzumab FDC: NCT03674112; NCT04024462 and NCT03493854.

Biological heterogeneity within HER2-positive disease

We and others have shown that HER2-positive disease has a huge biological heterogeneity where all intrinsic molecular subtypes (Luminal A, Luminal B, HER2-Enriched, and Basal-like) can be identified by using gene expression analyses (**Fig. 3**). Among them, the HER2-E is characterized by high expression of growth factor receptor-related genes or proteins, such as EGFR/HER2 and/or FGFR4, and of cell cycle-related genes, and low expression of estrogen-related genes such as estrogen and progesterone receptors, as well as low expression of basal-related genes (e.g. keratin 5 and FOXC1). Thus, the HER2-E subtype is likely to have the highest activation of the EGFR/HER2 pathway and probably the one to benefit the most from anti-HER2 blockade. Importantly, HER2-E is not fully recapitulated by hormonal receptor (HR) status (29).

Figure 3. Distribution of the intrinsic subtypes within HER2-positive disease based on HR status. Combined cohort of various published studies(30).



Prognostic and predictive ability of the intrinsic subtypes within HER2-positive disease

Regarding prognostic implications, we have evaluated the prognostic value of these entities in a large retrospective cohort of 1,730 patients from the UK and Canada with and without HER2-positive disease treated in the adjuvant setting with different treatments except trastuzumab. The results revealed that intrinsic subtypes are an independent prognostic variable beyond tumour size and nodal status, and HER2-positive/Luminal A tumours showed a similar outcome compared to HER2-negative/Luminal A tumours(31).

In relation with the benefit of trastuzumab in early breast cancer, two randomised neoadjuvant clinical trials tested trastuzumab versus not in combination with chemotherapy in HER2-positive breast cancer. In the NOAH study, HR status was found predictive of pCR (48% for HR-negative vs. 18% for HR-positive; p = 0.002). Overall, pCR was found predictive of DFS and overall survival; concordant with this, patients with HR-negative tumors benefited more from trastuzumab than HR-positive patients (hazard ratio for DFS = 0.58 in HR-negative vs. 0.74 in HR-positive disease)(32). When intrinsic subtyping was evaluated in a subset of patients (46.7%) of the NOAH study, patients with HER2-E disease showed a higher benefit of adding trastuzumab in terms of pCR and EFS compared to nonHER2-E disease(33).

Although the NOAH results make a lot of sense from a biological perspective, the larger benefit from trastuzumab in HR-negative disease compared to HR-positive disease has not been observed in three large adjuvant clinical trials evaluating 1-year of trastuzumab vs. placebo and both HR groups seem to benefit similarly(6, 34). Concordant with this, in the first of these studies, the NSABPB31 trial, all the intrinsic subtypes benefit similarly from trastuzumab(35). Somewhat surprising, intrinsic subtyping in this study was not found to be prognostic. One main difference between the NOAH and the adjuvant trials is that the former was a poorer outcome population (e.g. OS at 5 years with trastuzumab: ~75% in the NOAH trial vs. ~90% in the combined N9831 and NSABP-B31 dataset). Although risk by itself should not be a predictor of therapeutic benefit, it might reflect differences in underlying biology which should be the ultimate responsible for the differentially response.

In the second of these studies, the N9831 trial(36), the intrinsic subtype has been evaluated in the majority of clinically defined HER2-positive tumors were classified as HER2-E (72.1%) or luminal (20.9%) using the Prosigna algorithm. All patients were node-positive or high-risk node-negative. The patients with HER2-E tumors received statistically significant benefit from trastuzumab (HR = 0.68, P = 0.005), as did the patients with luminal-type tumors (HR = 0.52, P = 0.01). Patients with basal-like tumors (6.9%) did not have statistically significantly better DFS when treated with trastuzumab and chemotherapy compared with chemotherapy alone (HR = 1.06, P = 0.87).

Efficacy of neoadjuvant treatment in HER2-positive early breast cancer based on intrinsic molecular subtype

A major challenge today is to discover a biomarker that can help identify patients who benefit the most from single and dual HER2 blockade. Fortunately, the biological heterogeneity of HER2-positive disease is being intensively studied. For example, we and others have shown that all of the main intrinsic molecular subtypes of breast cancer (Luminal A, Luminal B, HER2-E, and Basal-like) can be identified within HER2-positive disease using gene expression analyses (31, 37-39). Among them, the HER2-E subtype is characterized by higher expression of HER2-regulated genes together with lower expression of luminal-related genes compared with the Luminal A and B subtypes (31, 40). Concordant with this, The Cancer Genome Atlas breast cancer project revealed that HER2-positive tumours of the HER2-E subtype have the highest expression of phosphor-HER2 and phosphor-EGFR compared to the other subtypes(40). Thus, the HER2-E subtype is likely to have the highest activation of the EGFR/HER2 pathway and the one to benefit the most from the trastuzumab and lapatinib combination.

In the neoadyuvant setting, the HER2-E subtype has consistently been associated with a higher likelihood of pCR following anti-HER2 blockade with lapatinib, trastuzumab, both or trastuzumab/pertuzumab with or without chemotherapy (**Table 1 and 2**). Over the years, intrinsic subtyping has been explored in retrospective samples from prospective trials evaluating anti-HER2-based chemotherapy in the neoadjuvant (i.e. NeoALTTO(41), CALGB40601(19), NOAH(33), KRISTINE(42), CHER-LOB(43), SOLTI-OPTIHERHEART(44), BERENICE(45)) and adjuvant (i.e. NSABP-B31(35) and N9831(36)) settings. In the neoadjuvant setting, the HER2-E is associated with a higher pCR rate compared to non-HER2-E following either trastuzumab plus chemotherapy or dual HER2 blockade (i.e. trastuzumab+lapatinib or trastuzumab+pertuzumab) plus chemotherapy. Of note, dual HER2 blockade with chemotherapy in HER2-E disease (without taking into account HR status) achieves pCR rates of 70-80% **(Table 1)** (19). Interestingly, this association has been found independently of HR status and other clinical-pathological variables. Thus, it is expected that the pCR rates of the HER2-E subtype do not differ based on HR status. Indeed, in the KRISTINE trial the pCR rates within HR-positive/HER2-positive/HER2-E disease were similar as in HR-negative/HER2-positive/HER2-E disease(42) (64.9% vs 75.%).

Table 1. HER2-E based on PAM50 and pCR across HER2-positive neoadjuvant trials with antiHER2 therapy in combination with chemotherapy. AT, anthracycline/taxane; C,

carboplatin; D, docetaxel; H, herceptin; L, lapatinib; P, pertuzumab; T, paclitaxel;

	NeoALTTO (20)	CALGB 40601(19)	CherLOB (43)	SOLTI-OPTIHER (28)	KRISTINE (42)	KRISTINE (42)	BERENICE (45)	B41 (46)
Therapy	**T** +L/H/LH	**T** +L/H/LH	**AT** +L/H/LH	**AT** +H+P	**T-DM1** +P	**DC** +H+P	**AT** +H+P	**AT** +L/H/LH
N	254	265	64	58	183	171	294	276
Variable	pCR_B	pCR_B	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}
pCR in HER2-E	**52.0%**	**65.8%**	**50.0%**	**83.3%**	**62.2%**	**72.1%**	**74.2%**	**60.9%**
pCR in non-HER2E	**21.5%**	**31.1%**	**17.0%**	**46.43%**	**26.9%**	**32.8%**	**26.9%**	**25.7%**
P-value	<0.001	<0.001	0.008	0.003	<0.001	<0.001	<0.001	<0.001

Table 2. HER2-E based on PAM50 and pCR across HER2-positive neoadjuvant trials with dual HER2-blockade without chemotherpy. H, herceptin; L, lapatinib; P, pertuzumab; Le, letrozole; Tam, tamoxifen.

	SOLTI-PAMELA (47)	TBCRC 006/023 (48)	PER-ELISA (49)
Therapy	**L+H+/-Le or Tam**	**L+H+/-Le**	**H+P+Le**
N	151	114	40
Variable	pCR_B	pCR_B	pCR_{BA}
pCR in HER2-E	**41%**	**27.4%**	**45.5%**
pCR in non-HER2-E	**10%**	**9.8%**	**13.8%**
p	<0.001	0.034	0.042

We have completed a translational prospective clinical trial, called PAMELA where 151 patients were treated for 18 weeks with dual HER2 blockade (lapatinib with trastuzumab) without chemotherapy in the neoadjuvant setting(47). This study was designed specifically to test whether a particular genomic biomarker (i.e. intrinsic molecular subtype), measured at baseline using gene expression data, predicted the occurrence of pCR within HER2-positive disease. Our primary objective was met, and our results showed that the HER2-E subtype provides

independent information beyond HR status and identifies patients with a 40% change of achieving a pCR after dual anti-HER2 blockade without chemotherapy. Thus, the HER2-E intrinsic subtype can identify a group of patients with HER2-positive early breast cancer exquisitely sensitive to dual anti-HER2 therapy only, or anti-HER2-based chemotherapy.

4.2 Predictive value of ERBB2 mRNA levels within early HER2-positive disease

Previous studies have revealed that, within HER2-positive disease, ERBB2 mRNA levels alone are associated with pathological response following anti-HER2-based chemotherapy or dual HER2 blockade-only (**Table 3**) indicating that patients with high levels of this biomarker had a better response than those with low levels.

Table 3. ERBB2-high based on mRNA levels and pCR across HER2-positivve neoadjuvant cohorts.

	SOLTI-OPTIHER(28)	ICO/HCB (50)	SOLTI-PAMELA(47)	NeoSphere(51)	NeoSphere(51)	CALGB 40601(19)
Treatment	AT+H+P	AT+H	151	D + anti-HER2	H+P	T+antiHER2
N	58	90	151	285	102	265
pCR ERBB2_high*	78.8%	66.0%	50.6%	41.9%	23.4%	57.6%
pCR ERBB2_low*	48.0%	40.0%	10.5%	25.5%	10.9%	33.8%
p-value	0.0248	0.019	<0.001	0.004	0.113	<0.001

*ERBB2-high defined as percentile50. OPTIHER, ICO/H. CLINIC BARCELONA and PAMELA where evaluated by nCounter and use the same exact ERBB2 cutpoint to define high or low; NeoSphere uses qRTPCR and uses "median ERBB2 levels" to define high or low; CALGB40601 used RNAseq and "median ERBB2 levels were used". ICO/H. CLINIC BARCELONA (in-house dataset) have not been published.

Predictive value of ERBB2 mRNA levels beyond HER2-E subtype within HER2positive disease

In a recent study (Prat et al, JNCI, 2019, in press), we evaluated the value of HER2-E subtype to predict anti-HER2 sensitivity beyond single ERBB2 mRNA expression in tumor samples from PAMELA and TBCRC006/023 trials. All patients had HER2-positive early breast cancer and were treated with neoadjuvant lapatinib and trastuzumab. Patients with hormone receptor-positive tumors were treated with letrozole or tamoxifen. PAMELA (NCT01973660) treated 151 patients for 18 weeks. TBCRC006 (NCT00548184) treated 66 patients for 12 weeks. TBCRC023 (NCT00999804) randomized 97 patients to 12 vs. 24 weeks of treatment. Outcome was pCR, defined as no residual invasive carcinoma in the breast. Baseline intrinsic subtypes and ERBB2 mRNA expression were determined using the nCounter-based PAM50 predictor.

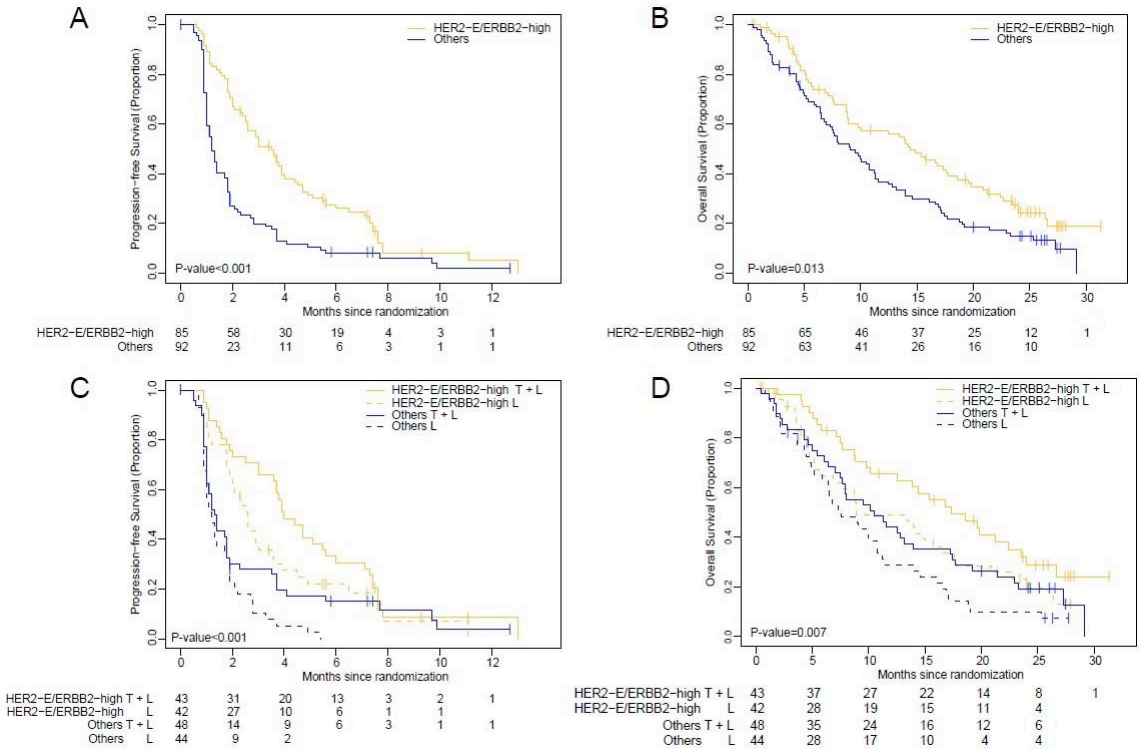
Two-hundred and sixty-five tumors (84.4%) were profiled. HER2-E subtype, which represented 65.7% of the cases, was found significantly associated with pCR compared to non-HER2-E (35.1% vs. 9.9%; odds ratio [OR]=4.92; 95% CI 2.31-10.50; P<0.001). At the same time, ERBB2-high group (defined as ERBB2 expression above 33rd percentile in PAMELA)

was found significantly associated with pCR compared to ERBB2-low group (36.1% vs. 8.2%; OR=6.51; 95% CI 2.96-14.31; P<0.001). HER2-E subtype represented 84.0% and 46.0% of ERBB2-high and ERBB2-low groups, respectively. The rates of pCR in HER2-E/ERBB2-high, nonHER2-E/ERBB2-high, HER2-E/ERBB2-low, and nonHER2E/ERBB2-low groups were 45.0%, 16.1%, 10.8%, and 6.7%, respectively. Finally, the HER2-E/ERBB2-high group independently predicted pCR (adjusted OR = 6.0; 95% CI [3.111.8]; P<0.001). Thus, we concluded that combining HER2-E subtype and ERBB2 mRNA levels better identifies anti-HER2 sensitivity than each variable alone in HER2-positive breast cancer.

To further test the ability of the combined biomarker to predict pCR, 40 of 44 (91.0%) HER2-positive/HR-positive tumor samples treated with pertuzumab, trastuzumab and letrozole in the PER-ELISA trial were profiled blinded using the same exact assay and ERBB2 cut-point. PER-ELISA (NCT02411344) was a single-arm phase II study of 64 patients with Stage I-III HER2-positive/HR-positive disease[53]. After diagnostic core biopsy including baseline Ki67 evaluation, the patients started letrozole for 2 weeks followed by a core-biopsy for Ki67 central evaluation. Patients defined as molecular responders (Ki67 relative reduction >20% from baseline) started therapy with the combination of letrozole, trastuzumab and pertuzumab. Trastuzumab and pertuzumab were administered for 5 courses, letrozole was continued until surgery. Patients defined as molecular non-responders discontinued letrozole and received weekly paclitaxel combined with pertuzumab and trastuzumab. In this study, we only selected patients whose tumor responded to letrozole. The pCR rate of HER2-E/ERBB2-high was 66.7% (4/6) and the pCR rate of the others group was 14.7% (5/34). The OR of the HER2-E/ERBB2-high group for achieving a pCR was 11.60 (95%CI 1.66-81.10; p=0.014) compared to the other group. No other clinical-pathological variable was significantly associated with pCR, although the study was not powered for this purpose.

Finally, to test the ability of the combined biomarker to predict survival outcome, 117 (40%) of tumor samples from the EGF104900 trial were profiled using the same exact assay and ERBB2 cut-point as in the previous studies. EGF104900 (NCT00320385) was a randomized phase III clinical trial of 296 women with HER2-positive advanced disease, who experienced progression on prior trastuzumab-containing regimens, to receive either lapatinib alone or lapatinib and trastuzumab[6]. The HER2-E/ERBB2-high group represented 48% of all samples. The adjusted PFS hazard ratio of the HER2-E/ERBB2-high group vs. others was 0.52 (95% CI 0.35-0.79; p<0.001). Median PFS of the HER2-E/ERBB2-high group was 3.5 months (95% CI 2.6-5.4) compared to 1.2 months (95% CI 1.0-1.7) in others. The ORR of the HER2-E/ERBB2-high group was significantly higher compared to others (ORR 16.3% vs. 3.7%; p=0.017). For OS, the adjusted hazard ratio for HER2-E/ERBB2-high vs. others was 0.66 (95% CI 0.44-0.97; p=0.034). Median OS was higher in the HER2-E/ERBB2-high group (14.4 months [95% CI 8.9-17.8]) compared to others (9.1 months [95% CI 7-11.3]). (**Fig. 4**)

Fig. 4: HER2-E/ERBB2-high biomarker in the EGF104900 trial of advanced HER2-positive breast cancer. (A) Progression-free survival (PFS). (B) Overall survival (OS). (C) PFS according to treatment arm. (D) OS according to treatment arm.



Breast MRI as an imaging biomarker of pCR

Magnetic resonance imaging (MRI) appears to provide the best agreement with pathology compared to physical examination, mammography, and sonography(52, 53) even though in some cases, dynamic MRI may tend to slightly overestimate pathologic tumour size measurements(54) or underestimate residual disease(52). In this regard, the combined use of diffusion-weighted imaging and dynamic MRI has shown to have the potential to improve the diagnostic performance in monitoring the response to neoadjuvant treatment(55). Recently, our group found that absence of late enhancement on MRI after neoadjuvant therapy in triple-negative and Her2-positive breast tumours was associated with pCR(56).

Loco-regional treatment after neoadjuvant therapy

The current loco-regional treatment after neoadjuvant systemic therapy (NST) is surgical resection of the tumor or mastectomy irrespective of the type of response **a**nd adjuvant radiotherapy is performed irrespective of treatment response after tumorectomy or in high risk patients that undergo mastectomy (57). Regarding the management of the axilla, the status of the axillary nodes before NST dictates the approach. If the axilla is negative before NST, sentinel node-biopsy is performed at surgery and, if it is negative, no further dissection is

performed or nodal radiotherapy is needed. If the axilla is positive before NST, axillary node dissection is performed in general, although strategies to lower the surgical aggressiveness and/ or nodal radiotherapy in the axilla in those patients that achieved a pCR are being explored**,** for example NSABP B-51/RTOG 1304 or Alliance A011202(58-60).

Selective Elimination of Breast Cancer Surgery After Neoadjuvant Systemic Therapy

The therapeutic value of surgery is questionable if the patient achieves a pCR to NST. NST can eliminate both invasive and in situ carcinoma in up to 50% of patients, particularly in triple-negative disease or HER2-positive cancers. Determining which patients have achieved a pCR without surgical resection has been problematic because breast imaging alone lacks sufficient sensitivity and specificity to be effective (61, 62). Attempting to identify patients with a pCR without surgical intervention, Heil et al. (63, 64) analyzed a multicenter pooled analysis comparing percutaneous core cut to percutaneous vacuum-assisted core biopsy VAB in patients with a clinical response to NST. Image-guided VAB and the existence of a marker clip improved the negative predictive value (NPV) and decreased the false-negative rate (FNR) when compared with the partial mastectomy specimen. Further investigation of image-guided VAB with a marker clip demonstrated an improved NPV of 94.4% and reduced FNR of 4.8%.

Kuerer et al. conducted a feasibility trial in triple-negative breast cancer or HER2-positive patients comparing fine-needle aspiration (FNA) with VAB following NST. Individually, FNA and VAB had an NPV of 63 and 90%, respectively, and FNR of 52 and 10%, respectively. Combined FNA/VAB had an NPV of 95% and FNR of 5%.37 The pathologic response in the VAB was concordant with the pathologic status of the partial mastectomy in approximately 98% of cases(65, 66). False-negative cases had < 12 cores taken and/or a very large initial tumor size. This feasibility study demonstrates that VAB is superior to FNA, and a follow-up study of image-guided VAB following NST requires a minimum of 12 cores of the original tumor bed and < 5 cm disease by initial breast imaging prior to NST. Based on these results, the same group has started a prospective clinical trial (NCT02945579) similar to ELPIS, where 50 patients with HER2-positive or triple negative breast cancer, without biomarker selection, when image-guided biopsy shows no residual cancer.

Selective Omission of a Sentinel Node Biopsy

A patient with invasive breast cancer may only derive a therapeutic benefit from the sentinel node biopsy if the lymph node results actually change the therapy that the patient would have received. Older breast cancer patients tend to have more comorbidities and die of causes unrelated to their breast cancer regardless of their axillary node status(67). Previously published clinical trials give us insight into which older breast cancer patients may not need a sentinel node. The Cancer and Leukemia Group B (CALGB) 9343 trial(68) investigated patients who were ≥ 70 years of age with estrogen receptor (ER)-positive and predominantly progesterone receptor (PR)-positive breast cancers, randomizing them to whole-breast radiation therapy plus tamoxifen or tamoxifen alone. The primary endpoint, i.e. overall survival, demonstrated no difference between the two study arms(68). Interestingly, twothirds of these women had no axillary surgery at all, again with no differences in breast cancer-specific

mortality. Moreover, patients who had no axillary surgery had very few axillary recurrences (6/204, 3%)(68). The explanation for omitting both radiation and sentinel node biopsy and having equivalent outcomes is understanding the biology of the patients enrolled on the trial. Hughes et al. chose to investigate the two most favorable breast cancer phenotypes by gene expression patterns—Luminal A and Luminal B(69). These are both richly ER-positive with the most favorable prognosis of the known breast cancer phenotypes to date, and are exquisitely sensitive to anti-estrogen therapy.

Two additional studies, the International Breast Cancer Study Group (IBCSG) (70) and the Milano Group(71, 72) randomized older ER-positive breast cancerpatients undergoing partial mastectomy to axillary clearance (IBCSG)/axillary dissection (Milan) plus tamoxifen versus no axillary surgery alone. In both trials, the no axillary surgery arms had a slightly higher loco-regional recurrence rate (IBCSG: 1 vs. 3%; Milan 0 vs. 6%). However, this locoregional recurrence difference did not translate into a difference in breast cancer-specific mortality or overall survival between the two arms. Both of these trials enrolled the most favorable phenotypes—older patients with richly ER-positive, Luminal A, and possibly some Luminal B, breast cancers. Thus, the fact that there is no difference in overall survival in a patient with ER-positive breast cancer receiving tamoxifen should not be unexpected. Collectively, the three trials (CALGB 9343, IBCG, and the Milan trial) strongly suggest that no axillary surgery is necessary in Luminal A, and possibly some Luminal B, phenotypes.
The Early Breast Cancer Trialist's Collaborative Group (EBCTCG) overview demonstrated that a recurrence did not influence survival in this subgroup of patients (59).

Regarding the management of the axilla when no breast surgery occurs, data from MD Anderson among 290 patients with TN/HER2-positive breast cancer with T1–2 N0 disease and normal findings on nodal sonography at initial diagnosis showed that those with a pCR in the breast after NST demonstrated that none (0%) had evidence of axillary lymph node metastases after NST(66). Among 237 patients with fine-needle aspiration/core biopsydocumented N1 disease, 89.6% of patients with a breast pCR after NST had no evidence of axillary metastases, and 57.5% of patients without a breast pCR had residual axillary metastases. Thus, those with initial N0 disease will not have any nodal surgery. Patients with initial ultrasound biopsy-confirmed N1 disease are also eligible to participate in the study if biopsy does not demonstrate residual breast disease. However, these patients will require targeted axillary dissection to confirm no residual disease prior to radiotherapy.

Survival outcomes in patients with HER2-positive early breast cancer who achieve a pCR following neoadjuvant anti-HER2-based therapy

We have evaluated the survival outcomes of 144 consecutive patients with HER2-positive disease treated with neoadjuvant anti-HER2-based chemotherapy at Hospital Clínic and Hospital 12 de Octubre. The median follow-up of this population was 5.1 years. A total of 57 patients (39.6%) achieved a pCR. Patients with a pCR showed a non-significant statistical trend towards better outcome. Among those that achieved a pCR, 7 patients relapsed (12.2%). Of note, all these relapses occurred in patients with lymph node involvement disease despite

achieving a pCR.

Next, we evaluated the subset of 51 patients with low-risk disease (i.e. we excluded cT3-4 and cN positive disease). The median follow-up of this population was 4.7 years. A total of 19 patients (37.2%) achieved a pCR. Among those who achieved pCR, no patient relapsed. The DFS at 3 years was 100%. Overall, this data suggests that patients with HER2-positive disease with low tumor burden before neoadjuvant therapy who achieve a pCR after neoadjuvant therapy, their long-term outcome is excellent.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Female participants who are at least 40 years of age on the day of signing the informed consent form with histologically confirmed diagnosis of breast cancer.

2. A participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 7 months after the last dose of study treatment.

3. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

4. Histologically confirmed invasive adenocarcinoma of the breast, with all of the following characteristics:
   - HER2-positive status by local determination according to 2018 ASCO/CAP guidelines(1).
   - PAM50 HER2-enriched subtype and ERBB2-high as predefined cutoff as per central determination.
   - Unifocal invasive carcinoma: only 1 invasive focus can be observed (the tumor focus containing or not containing an in situ component)
   - Tumor largest diameter ≤2 cm as defined by breast MRI.
   - No nodal involvement (i.e. cN0). Any suspicious axillary node by ultrasound

must be biopsied. If the biopsy or the FNA is negative of tumor cells, patient is eligible.

– No evidence of distant metastasis (M0) by routine clinical assessment.

5. Patient must have known ER and PR status locally determined prior to study entry (2).
6. Eligible for taxane therapy.
7. Willingness of the patient to omit surgery if all criteria are met following neoadjuvant therapy.
8. Estimated life expectancy of at least 5 years irrespective of the diagnosis of breast cancer.
9. Breast cancer eligible for primary surgery
10. Have provided archival tumor tissue sample or newly obtained core. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are mandatory. Available pre-treatment FFPE core biopsy evaluable for PAM50 or possibility to obtain one.
11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation (Appendix 1).
12. Ability and willingness to comply with study visits, treatment, testing and to comply with the protocol.
13. Have adequate organ function as defined in the following table (**Table 4**). Specimens must be collected within 10 days prior to the start of study treatment.

Table 4. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	

Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN with the following exception:
	Patients with known Gilbert disease: serum bilirubin level ≤3 x ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. [b] Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to allocation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has received prior anti-cancer therapy, including investigational agents, or treatment for primary invasive breast cancer.
3. Known hypersensitivity to any of the excipients of trastuzumab, pertuzumab, TDM1 or paclitaxel.
4. Clinical stage II, III or IV.
5. History of radiotherapy in the ipsilateral breast or axilla.
6. History of surgery of the ipsilateral axilla.
7. Bilateral invasive breast cancer.

8. Infiltrating lobular carcinoma.

9. Multicentric or multifocal breast cancer, defined as the presence of two or more foci of cancer in the same or different quadrants of the same breast.

10. Patients who have undergone sentinel lymph node biopsy prior to study treatment.

11. Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) or symptomatic pericarditis within 12 months prior to screening.
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV).
    - Documented cardiomyopathy.
    - Patient has a Left Ventricular Ejection Fraction (LVEF) < 55% at baseline as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO).
    - Clinical significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
    - Long QT Syndrome or family history of idiopathic sudden death or congenital long QT syndrome or any of the following: ○ Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure or history of clinically significant/symptomatic bradycardia ○ QTc> 500 msec or conduction abnormality in the previous 12 months.

12. Has an active infection requiring systemic therapy.

13. Patients with a history of previous breast cancer are excluded. Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix), unless in complete remission with no therapy for a minimum of 5 years are excluded. For patients with a history of other non-breast cancers within 5 years and considered of very low risk of recurrence per investigator's judgment (for example, papillary thyroid cancer treated with surgery), eligibility is to be discussed with Study Medical Monitor.

14. Has a known history of Human Immunodeficiency Virus (HIV). Note: No HIV testing is required.

15. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg]

reactive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required.

16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

18. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 7 months after the last dose of trial treatment.

19. Patients unable or unwilling to undergo MRI scans

20. Patients currently on following medications, which cannot be interrupted 7 days prior treatment start:
    - Any prohibited medication as per trastuzumab, pertuzumab or paclitaxel Summary product characteristics.
    - Herbal preparations/medications, dietary supplements.
    - Antineoplastic systemic chemotherapy or biological therapy
    - Immunotherapy not specified in this protocol
    - Any oral, injected, or implanted hormonal methods of contraception.
    - Radiation therapy (except for adjuvant radiotherapy).
    - High-doses of systemic steroids [> 20 mg of dexamethasone a day (or equivalent) for > seven consecutive days] and other immunosuppressive agents should be avoided. Standard premedication for chemotherapy and local applications are allowed.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.1.3.2 Contraception

Paclitaxel, trastuzumab, pertuzumab and TDM1 may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pertuzumab, TDM1 or

trastuzumab or up to 7 months after the end of treatment, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Sponsor within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) and followed as described in Section 7.2.1.

5.1.5 Use in Nursing Women

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

It is not known whether trastuzumab, pertuzumab and TDM-1 are secreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrolment and women should not breast-feed during study therapy and for 7 months after the last dose.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 5
Table 5. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pertuzumab and trastuzumab FDC SC	A loading dose of 1200 mg pertuzumab and 600 mg trastuzumab followed by a maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab	Q3W	SC infusion	Day 1 of each 3 week cycle during 5 neoadjuvant cycles and 13 adjuvant cycles if complete response	Experimental
Paclitaxel	80 mg/m^2	Q1W	IV infusion	Day 1,8,15 of each 3 week cycle during 4 cycles	Standard of care (non-IMP)

TDM1	3,6 mg/kg	Q3W	IV infusion	14 adjuvant cycles if not complete response	Experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 2 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

The medicinal products should be administered sequentially on Day 1 of each cycle (every three weeks) as follows: Trastuzumab/pertuzumab FDC SC at day 1. Paclitaxel IV will be administered after Trastzumab/Pertuzumab FDC SC. All trial treatments will be administered on an outpatient basis.

Investigational Medicinal Products

Pertuzumab/Trastuzumab FCD SC

All patients will receive Pertuzumab/Trastuzumab FDC SC on Day 1 of the first treatment cycle as a loading dose of 1200 mg of pertuzumab and 600mg of trastuzumab, followed by 600 mg of pertuzumab and 600mg of trastuzuamb on Day 1 of each subsequent 3-week cycle. Pertuzumab/Trastuzumab FDC SC will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy if complete response, inclusive of therapy given both in the neoadjuvant and adjuvant setting. In the case of non-complete response, the patient will receive TDM1 as adjuvant treatment.

New injections should be given at least 2.5 cm from the old injection site(s) and never into areas where the skin is red, bruised, tender, or hard. During the course of treatmt with Pertuzumab/Trastuzumab FDC SC, other medicinal products for SC administration should preferably be injected at different sites. If it is considered as necessary by the investigator in some cases an observation period it may be followed, but it will not be mandatory. On these cases, patients may be observed for at least six hours after the start of the first dose of Pertuzumab/Trastuzumab FDC SC for administration-associated symptoms such as fever, chills, etc. If no administration reactions occur with the first administration, the observation period for subsequent administrations may be shortened to two hours.

TDM1

TDM-1 will be administered on Day 1 of a 3-week cycle q3w at a doce of 3.6 mg/kg IV as

adjuvant treatment in patients with non-complete response. The total dose will be calculated based on the patient's weight on Day 1 of (or up to 3 days before) each cycle with no upper limit. Changes in weight of < 10% from baseline do not require dose recalculation.

The first infusion of trastuzumab emtansine will be administered over 90 minutes (± 10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of trastuzumab emtansine may be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period after infusion. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable. Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, antihistamines such as diphenhydramine, or corticosteroids) may be given at the investigator's discretion

Non-Investigational Medicinal Products

Paclitaxel IV

Paclitaxel will be administered in line with the respective product information and/or recognized clinical practice guidelines.

Paclitaxel will be administered at the 80 mg/m^2 dose via 1-hour IV infusion on Days 1, 8, and 15 of every 21-day cycle. On days of scheduled infusions of Trastuzumab SC and Pertuzumab IV and paclitaxel (i.e., Day 1 of every cycle), paclitaxel is to be administered after Trastuzumab SC and Pertuzumab IV. Doses of paclitaxel should not be administered more frequently than every 7 days.

To reduce the risk of severe hypersensitivity reactions, all patients should be premedicated prior to paclitaxel administration. Prior to receiving the first two study infusions of paclitaxel, all patients will receive corticosteroids (8-10 mg dexamethasone or equivalent) as part of either the institutional standard of care or the following premedication:

- Dexamethasone 8-10 mg (or equivalent) administered orally approximately 12 and 6 hours prior to the paclitaxel infusion. Patients may be treated with dexamethasone ≤10 mg IV within 1 hour prior to the paclitaxel infusion if the patient did not take the oral dexamethasone.

- Diphenhydramine 50 mg IV (or equivalent) 30-60 minutes prior to the paclitaxel infusion

- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30-60 minutes prior to paclitaxel infusion.

Endocrine therapy

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

5.2.2 Dose Modification and toxicity management

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

When several toxicities with different grades of severity occur at the same time, the dose interruptions or modifications should be according to the highest grade observed. If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., trastuzumab, pertuzumab, TDM1 or paclitaxel) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

Treatment administration may be delayed to assess or treat AEs such as cardiac AEs myelosuppression, or other events. Overall, the following recommendations must be accomplished:

- When treatment is temporarily interrupted because of toxicity caused by trastuzumab/pertuzumab FCD SC or paclitaxel, the treatment cycles will be restarted such that the trastuzumab/pertuzumab FCD SC and paclitaxel infusions remain synchronized.

- If it is anticipated that paclitaxel will be delayed by >1 week, then trastzumab/pertuzumab FCD SC should be given without the chemotherapy, as long as there is no contraindication.

- In general, the start of a cycle may be delayed to allow recovery from toxicities, but there should be no delays within cycles. Cycle length is fixed at 21 days, and dosing on Days 8 and 15 of a cycle may be skipped but should not be delayed outside of the +1 day window.

- If a dose of trastuzumab/pertuzumab FDC is delayed (i.e., the time between two sequential infusions is < six weeks), the 600 mg dose of trastuzumab/pertuzumab FDC SC should be administered as soon as possible. If a dose is missed (i.e., the time between two sequential infusions is ≥ six weeks), a reloading dose of trastuzumab/pertuzumab FDC SC should be given as described in the product labeling.

- The treating physician may use discretion in accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient.

Dose modification of the amount of study drug administered due to changes in patient´s weigh

Trastuzumab/pertuzumab FDC SC are administered as a fixed dose irrespective of the patient´s body weight. Dose reductions of trastuzumab/pertuzumab FDC SC will not be allowed.

The amount of paclitaxel is calculated according to the patient's body surface area (BSA). Weight and height should be recorded at baseline and the BSA calculated, thereafter at every scheduled visit for all patients should be re-weighed. The amount to be administered must be recalculated if the patient's body weight has changed by > 10% (increased or decreased) from baseline. Recalculation based upon smaller changes in body weight or BSA are at investigators' discretion.

During study treatment, some toxicity may be attributable to paclitaxel or trastuzumab/pertuzumab FDC SC . It is important to evaluate the possible cause of toxicity and weigh risk versus benefit for each agent to determine the schema of dose modifications (e.g., which agent to prioritize for maintaining dose level and the sequence of dose modifications).

General guidelines are provided in the following subsections based on the known safety profile of study drugs.

Dose Modification and toxicity management for AEs associated with trastuzumab/pertuzumab FDC SC

The safety plan for patients in this study is based on the known nonclinical toxicities of trastuzumab and pertuzumab, clinical experience with this molecule in completed and ongoing studies, and clinical toxicities related to its components (trastuzumab and pertuzumab). The anticipated important safety risks and potential safety risks of trastuzumab/pertuzumab FDC SC are outlined below and detailed in the IB. Please refer to the IB for a complete summary of safety.
Patients should not hold or discontinue anti-HER2 therapy for side effects potentially or likely related to concomitant paclitaxel as per the investigator's judgment. If anti-HER2 therapy is discontinued, patients may continue on paclitaxel or endocrine therapy as per the investigator's judgment.

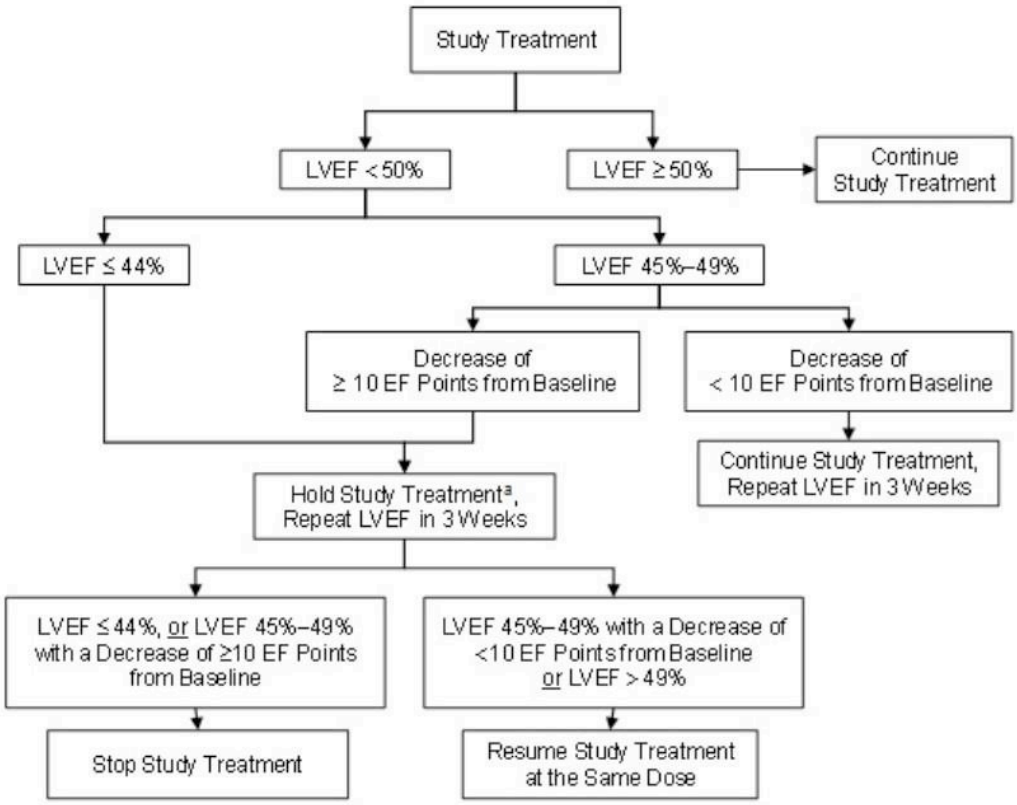
Cardiac toxicity

Anti-HER2 therapies are associated with cardiac toxicity. All patients must have a baseline LVEF ≥ 55% assessed by ECHO or MUGA scan. The same method should be used throughout the study for each patient, and preferably performed and assessed by the same assessor. LVEF will be monitored regularly according to the schedule of study assessments and procedures

The results of the LVEF assessments will be used to determine if trastuzumab and pertuzumab administration can be continued. Refer to **Figure 5** for the algorithm for continuation and discontinuation of study treatment on the basis of asymptomatic LVEF assessment.

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

Figure 5. Study algorithm for continuation and discontinuation of anti-HER2 therapy based on asymptomatic drop in LVEF



LVEF = left ventricular ejection fraction; EF = ejection fraction % points; Note: Baseline refers to the screening LVEF. Three intermittent holds of study treatment will lead to discontinuation.

Administration-related reactions

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

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

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

Significant injection-related symptoms must have been resolved before any subsequent study treatment administration. Patients who experience infusion reaction symptoms may be premedicated with paracetamol and antihistamines for subsequent injections or may be treated using desensitization protocols according to institutional practices.

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

Patients who experience the following events will be discontinued from the study treatment that is considered responsible for the event:

- Grade 4 hypersensitivity reaction.
- Acute respiratory distress syndrome.
- Bronchospasm.

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

Dose Modification and toxicity management for AEs associated with paclitaxel

Paclitaxel infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria; these events should be treated with aggressive symptomatic therapy. Pulseoximetry and pulmonary function tests to confirm respiratory and ventilation compromise in patients with suspected pneumonitis.

Other events that required discontinuation of paclitaxel in clinical trials include cases of severe neurotoxicity, such as peripheral neuropathies. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.

Refer to the local paclitaxel prescribing information for further details

Hematologic Toxicities

Absolute neutrophil count (ANC) must be ≥1000/μL (≥1000 cells/mm3) and platelet count

must be ≥75,000/μL (≥75,000 cells/mm3) for the patient to receive paclitaxel 80mg/m^2 on any treatment day (Day 1, 8, 15 of any 21-day cycle).

Dose modifications should be made according to the following **table 6:**

Table 6. Hematological dose modifications

ANC		Platelets	Paclitaxel Dose
≥1,000/μL (≥1,000 cells/mm3)	and	≥75,000/μL (≥75,000 cells/mm3)	80 mg/m^2
<1,000/μL (<1,000 cells/mm3)	or	<75,000/μL (<75,000 cells/mm3)	Hold(1)

(1) If treatment is held, the CBC should be repeated until ANC ≥1000/μL (≥1000 cells/mm3) and platelets ≥75,000/μL (≥75,000 cells/mm3). If paclitaxel therapy must be held for > 3 weeks to allow for resolution of haematologic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving pertuzumab and trastuzumab.

For any patient experiencing any of the following haematologic toxicities, the paclitaxel dose should be reduced to 65 mg/m² for all subsequent cycles:

- Fever (>38.5°C) associated with ANC <1,000/μL (<1,000 cells/mm3)
- Absolute granulocyte count <500/μL (<500 cells/mm3) for > 5 days
- Significant bleeding associated with a platelet count <40,000/μL (<40,000 cells/mm3)
- Any platelet count <20,000/μL (<20,000 cells/mm3).

If these severe hematologic toxicities recur in subsequent cycles despite dose reduction, paclitaxel should be discontinued, however the patient may continue receiving pertuzumab and trastuzuamab.

If the start of a cycle is delayed (i.e. pertuzumab, trastuzuamab and paclitaxel are held) for low counts, Day 1 will be postponed, and dosing resumed when ANC recovers to ≥1500/μl (≥1500 cells/mm3) and platelet count returns to ≥100,000/μl (≥100,000 cells/mm3).

In certain situations, a cycle may begin with the administration of pertuzumab and trastuzuamab alone (without paclitaxel on Day 1). If paclitaxel cannot be administered on Day 8 of the cycle, it may be administered on Day 15 if counts have recovered to permissible levels.

If paclitaxel cannot be administered on Day 15 of the cycle, the next dose of paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels.

Hepatic Toxicities

In case of hepatic toxicities, dose modifications should be made according to the following table:

Table 7: Hepatic dose modifications

AST and/or ALT		Bilirubin	Paclitaxel dose
≤ 5 x ULN	And	≤ 1.5 mg/dL (≤ 25.65 µmol/L)	80mg/m2
> 5 but ≤ 10 x ULN	Or	1.6 - 2.5 mg/dL (27.36 - 42.75 µmol/L)	65mg/m2
> 10 x ULN	Or	≥ 2.6 mg/dL (≥ 44.46 µmol/L)	Hold(1)

AST: aspartate aminotransferase; ALT: Alanine Aminotransferase; ULN: upper limit of normal

(1) Hold therapy until AST and or ALT < 10 x ULN and bilirubin < 2.5 mg/dL. If paclitaxel must be held for > 3 weeks to allow for resolution of hepatic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving pertuzumab and trastuzumab.

Peripheral Neuropathy

If grade 3 toxicity develops, paclitaxel treatment should be withheld until the neuropathy recovers to < grade 2 (pertuzumab and trastuzumab treatment should continue as scheduled). When treatment is resumed, the paclitaxel dose should be reduced permanently to 65 mg/m². If grade 3 neuropathy persists for > 3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel treatment but may continue receiving pertuzumab and trastuzumab.

Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with standard antiemetics and will not result in dose modification.

Anaphylaxis/Hypersensitivity

- Mild symptoms (e.g., mild flushing, rash pruritus): No treatment needed. Supervise at

bedside and complete paclitaxel infusion.

- Moderate symptoms (moderate flushing, rash, mild dyspnea, chest discomfort): Stop paclitaxel infusion. Administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). After recovery of symptoms, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. If symptoms recur, the reaction should be reported as an adverse event and the patient will discontinue paclitaxel treatment but may continue pertuzumab and trastuzumab.

- Severe life-threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilators, generalized urticaria): Stop the infusion and administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). Add epinephrine or bronchodilators if needed. The reaction should be reported as an adverse event and the patient will discontinue paclitaxel treatment but may continue pertuzumab and trastuzuamab.

Other Toxicity

If the patient develops any other grade 3 or 4 toxicity considered related to paclitaxel, paclitaxel should be held until symptoms resolve to grade 1 or less (pertuzumab and trastuzumab treatment should continue as scheduled). When treatment is resumed, the paclitaxel dose should be reduced permanently to 65 mg/m². If grade 3 toxicity persists for >3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel treatment but may continue trastuzumab and pertuzumab.

Refer to the local paclitaxel prescribing information for further details.

Dose Modification and toxicity management for AEs associated with TDM1

The safety plan for patients in this study is based on the known nonclinical toxicities of trastuzumab emtansine, clinical experience with this molecule in completed and ongoing studies, and clinical toxicities related to its components (trastuzumab and maytansine, the parent drug of DM1). The anticipated important safety risks and potential safety risks of trastuzumab emtansine are outlined below and detailed in the IB. Please refer to the IB for a complete summary of safety. Risk management guidance to avoid or minimize such anticipated toxicities, is detailed herein (**Table 8**) as well as in the IB.

Table 8: Dose Reduction for Trastuzumab Emtansine

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

Guidelines for managing specific AEs are provided in **Table 9**. For AEs not listed in **Table 9**, the following guidance should be used: for Grade 3 non-hematologic AEs not adequately managed by standard medical intervention or for any Grade 4 nonhematologic AE, study treatment should be held until recovery to Grade≤ 1. A maximum dose delay of 42 days from the last administered dose of study drug will be allowed for recovery. After appropriate recovery, trastuzumab emtansine may be resumed with one dose level reduction (e.g., trastuzumab emtansine reduced from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg). Dose reduction levels for trastuzumab emtansine are shown in **Table 8**. For patients who have an event while being treated with trastuzumab emtansine 2.4 mg/kg, study treatment will be discontinued. The dose of trastuzumab emtansine, once reduced, may not be re-escalated.

Patients who discontinue trastuzumab emtansine may complete the duration of their intended study treatment up to 14 cycles of HER2-directed therapy with trastuzumab if appropriate based on toxicity considerations and investigator discretion. Patients who discontinue trastuzumab emtansine for cardiac toxicity, or other toxicity that may be attributed to the trastuzumab component (e.g., hypersensitivity, pneumonitis) may not continue on trastuzumab/pertuzumab FCD SC after discontinuation of trastuzumab emtansine.

Cardiotoxicity

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. LVEF<40% has been observed in patients treated with trastuzumab emtansine. Patients without significant cardiac history and with an LVEF≥55% determined by ECHO or MUGA scan are eligible for study participation. LVEF will be monitored at screening and regularly throughout the study until the assessment at the safety follow-up visit. Patients with symptomatic cardiac dysfunction will be discontinued from study treatment. Asymptomatic declines in LVEF will be handled as per the algorithm shown in **Figure 5**.

Hematologic Toxicity (Thrombocytopenia and Hemorrhage)

Thrombocytopenia, or decreased platelet count, was reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (≥ 50,000/mm3),

with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (≥ 75,000/mm3) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients. Cases of bleeding events with a fatal outcome have been observed. Severe cases of hemorrhagic events, including CNS hemorrhage, have been reported in clinical trials with trastuzumab emtansine; these events were independent of ethnicity. In some of the cases, the patients were also receiving anti-coagulation therapy. There was no clear correlation between the severity of thrombocytopenia and severe hemorrhagic events; however, the need for use of platelet transfusions has been reported.

Patients on anti-coagulant treatment have to be monitored closely during treatment with trastuzumab emtansine. Platelet counts will be monitored prior to each trastuzumab emtansine dose.

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1− 4 transaminitis), has been observed in patients while on treatment with trastuzumab emtansine in clinical trials.

Transaminase elevations were generally transient. The incidence of increased AST was substantially higher than that for ALT. A cumulative effect of trastuzumab emtansine on transaminases has been observed; the majority of patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine.

Rare cases of severe hepatotoxicity, including death due to drug-induced liver injury and associated hepatic encephalopathy, have been observed in patients treated with trastuzumab emtansine. Although there is evidence of drug-induced liver toxicity in patients treated with trastuzumab emtansine, its potential to cause acute severe liver injury with clinically meaningful changes in liver function is unclear as the observed cases were confounded by concomitant medications with known hepatotoxic potential and/or underlying conditions. Nevertheless, a contributory role of trastuzumab emtansine in these cases cannot be excluded. Therefore, acute severe liver injury (Hy's law) remains an important potential risk with trastuzumab emtansine. A Hy's law case has the following components:

- Aminotransferase enzymes are greater than 3 ×ULN with concurrent elevation of serum total bilirubin to>2 ×ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
- No other reason can be found to explain the combination of increased aminotransferases and serum total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.
- The finding should be serious as shown by gross jaundice, clinical disability, or need for hospital care and should be at least probably drug-induced (by trastuzumab emtansine).

Trastuzumab emtansine treatment in patients with serum transaminases >3 ×ULN and concomitant total bilirubin > 2×ULN should be permanently discontinued.

Patients must have adequate and stable liver function: hepatic transaminases (AST/ALT) and total bilirubin must be within acceptable range, as defined in the protocol, within 4 weeks prior to the first dose of trastuzumab emtansine. Liver function will be monitored prior to each trastuzumab emtansine dose. Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine and presenting with signs and symptoms of portal hypertension. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension and also may be fatal. NRH should be considered in patients who develop clinical symptoms of portal hypertension and/or a cirrhosis-like pattern seen on CT scan of the liver but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with trastuzumab emtansine. Diagnosis of NRH can only be confirmed by histopathology.

Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.
Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome, have been reported in clinical trials with trastuzumab emtansine. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. Patients with dyspnea at rest as a result of complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Treatment has included administration of steroids and oxygen, as well as study drug discontinuation. Upon diagnosis of drug-related ILD/pneumonitis, trastuzumab emtansine treatment has to be permanently discontinued.

Infusion-Related Reactions/Hypersensitivity

Infusion-related reactions ([IRR] anaphylactoid/cytokine release reactions) and hypersensitivity (anaphylactic/allergic reactions) may occur with the administration of monoclonal antibodies and have been reported with trastuzumab emtansine. Treatment with trastuzumab emtansine has not been studied in patients who had trastuzumab permanently discontinued due to an IRR/hypersensitivity; treatment with trastuzumab emtansine is not recommended for these patients.

IRRs, characterized by one or more of the following symptoms: flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia-have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Trastuzumab emtansine treatment should be interrupted in patients with severe IRRs. Trastuzumab emtansine treatment should be permanently discontinued in the event of a life-threatening IRR. Patients should be observed closely for hypersensitivity. Serious, allergic/anaphylactic-like reactions have been observed in clinical trials with treatment of

trastuzumab emtansine. Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients will be observed closely for infusion-related/hypersensitivity reactions during and after each trastuzumab emtansine infusion for a minimum of 90 minutes after the first infusion and for a minimum of 30 minutes after subsequent infusions in the absence of infusion-related AEs. Pre-medication is allowed according to standard practice guidelines. In the event of a true hypersensitivity reaction (where severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.

Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine. Treatment with trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤ Grade 2. Patients should be examined for signs of peripheral neuropathy prior to each dose of trastuzumab emtansine. Patients who experience Grade≥ 3 neurotoxicity in the form of peripheral neuropathy that does not resolve to Grade≤ 2 within 42 days after last dose received will be discontinued from study treatment.

Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Rare reports of more severe events, such as cellulitis, pain (tenderness and burning sensation), and skin irritation, have been received as part of the continuing surveillance of trastuzumab emtansine safety. These reactions have been observed more frequently within 24 hours of infusion. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

Table 9: Guidelines for Managing Specific Adverse Events of Trastuzumab Entamsine

Event	Action to Be Taken
Infusion reactions (caused by cytokine release)/Hypersensitivity (allergic reactions)	
Life threatening infusion-related reaction/Hypersensitivity (allergic reaction)	Stop infusion, study treatment permanently discontinued. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used, as appropriate, at the investigator's discretion. Patients should be monitored until complete resolution of symptoms.

Infusion-related or clinically significant hypotension	Stop infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patients until complete resolution of symptoms. May re-treat at investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.
Infusion-related symptoms (e.g., chills, fever)	Decrease infusion rate by 50% or interrupt infusion for patients who experience any other infusion-related symptoms (e.g., chills, fever). When symptoms have completely resolved, infusion may be restarted at ≤ 50% of prior rate and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate at the next cycle, with appropriate monitoring. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used as appropriate at the investigator's discretion. Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent infusions at the investigator's discretion. Patients should be monitored until complete resolution of symptoms.
Hematologic toxicity	
Grade ≥ 3 hematologic toxicity (other than thrombocytopenia)	Withhold study treatment until recovery to ≤ Grade 1. Weekly CBC assessments should be done until recovery, or as medically indicated. A maximum dose delay of 42 days from the last administered dose to Grade ≤ 1 or baseline will be allowed; otherwise, patients must be discontinued from study treatment.
Grade 4 thrombocytopenia at any time	Assess platelet counts weekly or as medically indicated until recovery. Hold trastuzumab emtansine until Grade ≤ 1, then resume with one dose level reduction (i.e., from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg) in subsequent cycles. If event occurs with 2.4 mg/kg dose, discontinue study treatment.
Hepatotoxicity	
ALT	For a Grade 2-3 ALT increase that occurs on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until ALT recovers to Grade ≤1. Resume with dose reduction by one level for Grade 2 or 3 elevations. Grade 2-3 ALT elevations that are noted between cycles do not require dose delay or reduction unless ALT remains elevated (Grade 2) at the time of planned dosing. For Grade 4 ALT increase, discontinue trastuzumab emtansine. Repeat lab evaluation (within 24 hours) may be done to exclude lab error prior to discontinuing study treatment.

AST	For Grade 2 AST increase on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until AST recovers to ≤ Grade 1. Resume without dose reduction when recovered. For Grade 3 AST increase on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until AST recovers to ≤ Grade 1. Resume with dose reduction by one level when recovered. For Grade 4 AST increase, discontinue trastuzumab emtansine. Repeat lab evaluation (within 24 hours) may be done to exclude lab error prior to discontinuing study treatment.
TBILI	For TBILI > 1.0 x ULN to < 2.0 x ULN that occurs on the laboratory evaluation for cycle Day 1 or the day of planned dosing, hold trastuzumab emtansine until TBILI recovers to≤ 1.0 x ULN (or direct bilirubin recovers to ≤ 1.0 x ULN for patients with Gilbert's syndrome). For TBILI elevations> 1.0 x ULN to≤ 2.0 x ULN, resume when recovered with a one level dose reduction. For TBILI> 2 x ULN at any time (or direct bilirubin> 2 x ULN for Gilbert's syndrome), discontinue trastuzumab emtansine and report the event as an SAE (if applicable) or non-serious expedited AE (ifapplicable). Assess AST, ALT, and TBILI weekly or as medically indicated until recovery. Allow a maximum dose delay of 42 days from the last administered dose to recovery as described above or otherwise discontinue study treatment.
Nodular Regenerative Hyperplasia	For any clinical signs of liver dysfunction, discontinue trastuzumab emtansine and have the patient evaluated by a hepatologist. If there are signs of portal hypertension (e.g., ascites and/or varices) and a cirrhosis-like pattern is seen on CT scan of the liver, the possibility of NRH should be considered. For liver biopsy guidelines, please see Appendix 8. Trastuzumab emtansine should be discontinued in the event of a diagnosis of NRH.
Neurotoxicity	
Grade ≥ 3 peripheral neuropathy	Discontinue trastuzumab emtansine if event does not resolve to Grade 2 or baseline value within 42 days after the last administered dose.
Cardiotoxicity	
LVSD	Refer to Figure 5 for the algorithm for continuation and discontinuation of study treatment on the basis of asymptomatic LVEF assessment.
Grade 3-4 LVSD or Grade 3-4 heart failure	Discontinue study treatment.
Grade 2 heart failure accompanied by LVEF < 45%	Discontinue study treatment.
Interstitial lung disease	
Grade 3-4 pneumonitis	Discontinue study treatment regardless of attribution

Grade 1-2 pneumonitis	Discontinue study treatment if not radiotherapy-related. For symptomatic (Grade 2) radiotherapy-related pneumonitis, discontinue if not resolving with standard treatment (e.g., steroids). Relationship to radiotherapy should be determined on the basis of timing and location of radiographic abnormalities relative to the radiation treatment. Upon diagnosis of drug-related ILD/pneumonitis, trastuzumab emtansine treatment has to be permanently discontinued. Patients discontinued from trastuzumab emtansine for pneumonitis may not continue study treatment with trastuzumab.
Radiotherapy-related skin toxicity	
Grade 3-4	Do not administer study treatment until recovery to Grade ≤ 1.

AE, adverse event; CBC, complete blood count; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NRH, nodular regenerative hyperplasia; SAE, serious adverse event; ULN, upper limit of normal.

Dose Modifications/Toxicity Management – Endocrine Therapy

Patients should not hold or discontinue endocrine therapy for side effects potentially or likely related to concomitant anti-HER2 therapy as per the investigator's judgment. If a patient finds oneself not able to tolerate endocrine therapy, an attempt to change to an alternative endocrine therapy is a priority, while continuing treatment with anti-HER2 therapy. If a patient is considering stopping endocrine medication altogether, anti-HER2 therapy must continue.

5.2.3 Labeling of investigational products.

Roche is responsible for manufacturing all the IMPs and will be manufactured according to GMP.
All the IMPs will be packaged, labeled and supplied by Roche in accordance with European Regulation.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from trial therapy may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participants's primary physician.

Note: Seasonal influenza vaccines for injection are generally killed virus vaccine and are allowed.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be

administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs/AESIs/Special Situations as defined in Section 7.2.

The following concomitant treatments are permitted during the study:

- Endocrine therapy (e.g. tamoxifen and letrozole), and other adjuvant endocrine therapy drugs according to institutional practices.
- Erythropoiesis-stimulating agents (ESA) are allowed (such as Procrit®, Aranesp®, Epogen®) for the supportive treatment of anemia. Blood transfusions are permitted during the study.
- The prophylactic use of granulocyte-colony stimulating factors (G-CSF; GM-CSF) is allowed during the first treatment cycle, and can be used for cases of neutropenia arising during treatment, as primary and secondary treatment, in accordance with the National Comprehensive Cancer Network (NCCN) guidelines.
- The use of medication for the treatment of diarrhea, nausea, or vomiting is permitted.
- Any medications deemed necessary to ensure patient safety and well-being may be administered at the discretion of the investigator with the exception of prohibited therapies contained in the next section.

5.3.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pertuzumab
- Any oral, injected, or implanted hormonal methods of contraception.
- Radiation therapy (except for adjuvant radiotherapy).
- High-doses of systemic steroids [> 20 mg of dexamethasone a day (or equivalent) for >

seven consecutive days] and other immunosuppressive agents should be avoided. Standard premedication for chemotherapy and local applications are allowed.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.3.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with are outlined along with the dose modification guidelines in Section 5.2.2.

5.4 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Noncompliance with study treatment or procedure requirements.
- The participant is lost to follow-up.
- Completion of 18 treatments (approximately 1 year) with trastuzumab and pertuzumab.
- The subject fails to comply with the protocol requirements or fails to cooperate with investigator

5.5 Participant Replacement Strategy

Patients will be replaced if they are considered to be non-evaluable. An evaluable patient is one that has received at least one combination dose, and IRM + BAV has been made diagnosing pCR according to the Investigator site assessment.

Patients who have failed screening (usually because they have failed one or more of the inclusion or exclusion criteria) will not receive study treatments and are considered not to be evaluable.

5.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of Roche decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Study procedures	Screening	Neoadjuvant chemotherapy + Trastu/pertu					Pre surg [l].	Surg[m].	Radio therapy treatment	Adjuvant Trastuzumab pertuzumab or TDM1	Visit follow up	Visit follow up
	Day -42 to Day -1	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1			During the next 3 months.	Every 3 months	Every 3 months	Every 12months
Year		0	0	0	0	0	0	0	0	0	1,2,3	4-5
Visit window		+/- 2d	+/- 2d	+/- 2d	+/- 2d	+/- 2d				+/-3d	+/- 2 weeks	+/- 4 weeks
Informed consent [a]	X											
Medical history and demographic data [b]	X											
Anamnesis	X	X	X	X	X	X	X		X	X	X	X
Concomitant medication	X	X	X	X	X	X	X			X	X	X

Complete physical examination [c]	**X**											
Targeted physical[c]		**X**	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Breast and regional lymph node examination[c]		**X**	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Weight	**X**	**X**	**X**	**X**	**X**	**X**						
Height	**X**											
Vital Sign	**X**	**X**	**X**	**X**	**X**	**X**				**X**		
ECOG Performance Status	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Mandatory tumor samples [d]	**X**						**X**	**X**				
Recording of HER2, ER, PR and ki67 per local laboratory.	**X**											

CBC with differential and platelet count [e]	**X**	**X**	**X**	**X**	**X**					**X**	**X**	**X**
Fasting serum chemistry [f]	**X**	**X**	**X**	**X**	**X**					**X**	**X**	**X**
Pregnancy test	**X**	**x (urine) (only every 4 cycles) (serum if any positive urine pregnancy to confirm it)**									**Until 7 m post discontinuation**	
INR, PT, and aPTT/PTT	**X**									**Every 3 weeks if TDM1 adjuvant**		
Review of eligibility criteria	**X**											
LVEF (ECHO or MUGA scan)	**X**	**x (only every 12 weeks +/- 1 week)**										
Mammogram	**X**										**Every year**	**X**
Breast MRI	**X**					**X**					**Every year[n]**	
Axillary ECO	**X**					**X**					**Every year**	

Confirmation of PAM50 & ERBB2 levels eligibility	**X**											
Paclitaxel administration		**X**	**X**	**X**	**X**							
Trastuzumab/ pertuzumab FCD administration[h]		**X**	**X**	**X**	**X**	**X**				**Trastuzumab and pertuzumab every 3 weeks if complete response**		
TDM1 administration[h]										**TDM1 every 3 weeks if not-complete response**		
Stereotacticguided vacum assisted breast biopsy							**X**					
CR determination[g]							**X**					
Surgery								**X**				
Radiotherapy administration[i]									**X**			
AEs/SAEs other reportable safety events assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Survival followup											**X**	**X**
Plasma Sample for biomarkers[j]	**X**		**X**				**X**				**Every 12 months**	
Patient-reported outcomes[k]		**X**					**X**			**C1 and C10 post BAV/SURG**		

a) Signed informed consent must be provided prior to any study-specific evaluations. Assessments performed as standard of care within the timeframe may be used.

b) Medical history includes clinically significant diseases that are currently active or that were active within the last 5 years, surgeries, cancer history (including date of diagnosis, primary tumor histology, grade, staging, prior cancer therapies, and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse. Demographic data include age, sex, and self-reported race/ethnicity.

c) A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, breast and regional lymph node and neurological systems as well as weight (in kilograms) and height (in centimeters; height is measured at the screening visit only). BHreast and regional lymph node and symptom-directed physical exam after baseline assessment.

d) All patients must consent to the collection of tumor biopsies (FFPE). Tumor tissue should be of good quality based on total and viable tumor. An FFPE block should be provided. Fine-needle aspiration, brushing, and lavage samples are not acceptable. Retrieval of archival tumor sample can occur outside the screening period (centrally perform PAM50 test and ERBB2 levels). The histological samples will also be collected after the biopsy performed by stereotactic-guided vacuum-assisted breastbiopsy and the surgery in those patients who proceed to operate

e) Complete blood count includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

f) Fasting serum chemistry: creatinine, sodium, potassium, calcium, total protein, serum bilirubin (with direct bilirubin if total bilirubin>ULN), alkaline phosphatase, glucose, AST, and ALT. Screening results may be valid for Week 1, Day 1 if performed within 7 days prior to Week 1, Day 1.

g) If a complete response is observed on breast MRI, patients will undergo a stereotactic-guided vacuum-assisted breast biopsy of the marker area to obtain 12 cylinders of breast parenchyma, which is equivalent to 2 g of tissue, to confirm a pCR.

h) If complete response, trastuzumab/pertuzumab FCD will be continued to complete 18 cycles. If not-complete response, TDM1 will be administer up to 14 cycles. Adjuvant endocrine therapy will be indicated according to hormonal receptor status by IHC.

i) Whole breast irradiation was delivered daily to 50 Gy in 25 fractions using tangential fields. An additional boost irradiation of 16 Gy in 8 daily fractions after WBI was planned.

j) Plasma from 30 ml of blood will be collected and banked at C1D1, C2D1, before surgery, C1 after surgery and every 12 months during first 12 months.

k) The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) will be completed by the patients at the investigational site. All PRO questionnaires must be administered prior to any other study assessment(s) and prior to administration of study drug.

l) Pre-surgery / End of Treatment visit must occur between completion of 13 weeks and surgery. If feasible by institutional logistics and timing, these windows should be maintained for patients proceeding to curative surgery after early treatment interruption.

m) Surgery will take place after 13 weeks treatment period and 1 weeks (+ 3 weeks) after the last dose of chemotherapy.

n) IRM during follow-up will be performed every 12 months for patients who have omitted the surgery.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about the trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

After signing the consent, tumor tissue (archival or newly obtained) will be sent to a central laboratory to either analyze or confirm HER2-E subtype and ERBB2 high levels. This will be conducted during the screening phase prior to enrolling into the trial (≥ Day 1). For eligibility into the study, patients **must** be HER2-enriched/ERBB2 high confirmed by a designed laboratory. Tumor tissue requirements, along with shipping requirements, will be detailed in the laboratory manual provided by the central laboratory.

To perform the PAM50 test, investigator judgement of patient's potential eligibility to the study should be assessed as per inclusion/exclusion criteria (section 5.1) and TRIAL FLOW CHART (section 6).

7.1.1.1.2 Consent and collection of specimens for future biomedical research

The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research subtrial. A copy of the informed consent will be given to the participant.

If the participant signs the Future Biomedical Research consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research. All residual samples after protocol-defined studies are completed will be stored in a central sample repository as a collection (Section 9.3).

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol- specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number and will be done centrally through the eCRF that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of Randomization Number

Not applicable

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Administration of trial medication(s) will be witnessed by the investigator and/or trial staff. The total volume of trial medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol specified treatment plan for greater than 4 weeks between

treatment infusion for nondrug-related or administrative reasons require consultation between the investigator and FCRB and written documentation of the collaborative decision on participant management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 42 days prior to the date of allocation. The site study team must review screening images to confirm the participant has breast tumor ≤ 2cm. The tumor site may be marked with a radiopaque clip or marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy. Metastatic disease will be excluded as per institutional standards.

Breast MRI MRI Technique:

Three MR scanners will be used: a) 1.5-T MR imaging system (Signa, GE medical Systems, Milwaukee, WI) with a dedicated bilateral four-channel breast surface coil and, b) 1.5-T MR imaging system (Aera, Siemens, Erlangen, Germany) with a dedicated bilateral sixteenchannel breast surface coil, and c) 3-T MR imaging system (Vida, Siemens, Erlangen, Germany) with a dedicated bilateral sicteen-channel breast surface coil. Table 2 shows the summary of sequence parameters.

All patients will be imaged in prone position and the study protocol will consist of the following: a) positioning acquisition, b) DWI in the axial plane with two b values according to recommendations optimised for a magnetic field strength of 1.5 T, c) axial T2-weighted FSE sequence without fat suppression and, c) dynamic axial 3D, fat-suppressed, T1-weighted gradient-echo sequence. Images will be obtained prior to a rapid bolus injection and five times after injection of contrast. The bolus injection will consist of 0.1 mmol/kg gadoteric acid (Clariscan, GE Healthcare, Milwaukee, WI) and 20 mL saline flush, delivered through an intravenous cannula inserted in an antecubital vein. d) automated subtraction of the appropriate pre-contrast and post-contrast images and multiplanar reconstruction of data sets.

MRI Interpretation:

Breast MRI will be performed prior to the start of chemotherapy and after completion of treatment. Tumour response will be assessed using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) classification. Likewise, change in tumour vascularity between both MR exams will be also evaluated. In this regard, two types of tumour enhancement will be defined: a) early enhancement: that observed in the first post-contrast sequence, b) late enhancement: that observed in the last post-contrast sequence. According to these, two groups will be identified:

1. MRI complete response: complete absence of both early and late enhancement in the second breast MRI.

2. Radiologic partial response or no response:

a) partial disappearance of early enhancement in the lesion or,

b) complete absence of early enhancement but persistence of late enhancement.

Table 8. The summary of sequence parameters of breast MRI.

	SIGNA	**AERA**	**VIDA**
DWI sequence			
TR (ms)	8000	6500	6500
TE (ms)	65	66	75
Slice thickness (mm)	4	4	4
FoV (mm)	320 x 320	360 x 270	360 x 360
Matrix (mm)	132 x 132	192 x 115	190 x 190
b values (s/mm^2)	0/700	50/700	50/700
T2 FSE sequence			
TR	3800	1200	1500
TE	120	253	255
Slice thickness	2	2	1,5
FoV	330 x 330	340 x 340	360 x 360
Matrix	416 x 416	512 x 476	448 X 448
3D T1-weighted sequence			
Flip angle	15º	10º	10
TR	4.7	4.65	4,54
TE	2.3	1.78	1,68
Slice thickness	2	2	1,6
FoV	330 x 330	340 x 340	360 x 360
Matrix	416 x 416	416 x 416	448 x 336
In-plane resolution (mm)	0.8 x 0.8	0.8 x 0.8	0.8 x 0.8

Axillar lymph nodes US

Baseline evaluation of axillary lymph nodes assessed with ultrasound**.** Ultrasound-guided FNA or core biopsy is only required to confirm nodal status in case of suspicious axillary lymph nodes.

7.1.2.6.1 Tumor Imaging before surgery

Following neoadjuvant therapy, a breast MRI, with the same characteristics as those previously explained, will be performed. If a complete response is observed on breast MRI, patients will undergo a stereotactic-guided VAB.

7.1.2.6.2 Stereotactic-guided vacuum-assisted breast biopsy

Once imaging exams have confirmed a complete response, a stereotactic-guided BAV will be performed with a dedicated device (EnCor, Bard, Tempe, AZ) and needles (EnCor Biopsy Probe, 10G, Bard, Tempe, AZ). The biopsy will obtain breast tissue from the area containing the metallic marker, which identifies the place where the tumor was before treatment, and around to obtain 12 cylinders of breast parenchyma, which is equivalent to 2 grams of tissue.

7.1.2.7 Histological evaluation of biopsy

All tissue fragments will be paraffin-embedded, sectioned, H/E- stained and microscopically analyzed. Pathological complete response will be considered when no residual infiltrating neoplasm is present. This will be immunohistochemically confirmed whenever necessary. If no invasive tumor cells and no in situ disease are identified, patients will be eligible to omit loco-regional surgery. Although presence of residual in situ carcinoma is accepted within pCR, such event will invalidate an expectant conduct for the patient and surgical removal will be performed following current institutional guidelines. Samples from stereotacticguided VAB will be collected for translational purposes.

7.1.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tissue for PAM50 analysis should be obtained from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion. Informed consent for the study must be taken prior to collection of a new biopsy. If the participant signs the Future Biomedical Research consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research. Include a copy of the local pathology

report with the tissue for PAM50 analysis. For a tumor biopsy to be considered newly obtained (fresh biopsy) the sample from a core biopsy must be obtained from the subject during the screening period.

Plasma sampling will be obtained from all participants. All baseline plasma samples should

be drawn in screening period, at Cycle 2 and at before surgery.

Sample collection, storage, and shipment instructions for serum samples will be provided in the Samples Manual. The leftovers samples of those patients who have not signed Future Biomedical Research consent will be returned to the service of the Hospital of origin.

7.1.3 Cardiac function monitoring

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

At baseline, LVEF must be done within 42 days prior to randomization. During study treatment, all assessments will be performed between days 15-21 of the previous cycle to allow evaluation of the results before the indicated cycle (please note that the LVEF should be done as close to the assigned week as possible but prior to the next infusion). Subsequent scheduled LVEF assessments must be performed every four cycles after randomization during neoadjuvant therapy. After surgery, LVEF assessments must be performed every four cycles until the end of study treatment as stated in Section 6. If an investigator is concerned that an AE may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Any patient who develops clinical signs or symptoms of cardiac failure should undergo an LVEF assessment, a standard 12-lead ECG, and cardiac enzyme assessment. See Figure 5 for study algorithm for continuation and discontinuation of anti-HER2 therapy based on interval LVEF assessments.

7.1.4 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 11**.

Table 11 Laboratory Tests

Hematology	Chemistry	Urinalysis (as clinical indicated)	Other
Hematocrit	Alkaline phosphatase	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alanine aminotransferase (ALT)	Glucose	(β-hCG)†
Platelet count	Aspartate aminotransferase (AST)	Protein	PT (INR)
WBC (total and differential)	Lactate dehydrogenase (LDH)	Specific gravity	aPTT
Red Blood Cell Count	Calcium	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count	Glucose	results are noted	
Absolute Lymphocyte Count	Potassium	Urine pregnancy test †	
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		Blood for correlative studies
	Total protein		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. ‡ If considered standard of care in your region.			

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.5 Surgery

In case of not objectifying complete response on IMR +/- VAB, definitive breast surgery will be performed no more than 21 days weeks after completion of preoperative treatment (21 days since day 1 of last preoperative treatment). Tumor samples from breast cancer surgery will be collected for translational purposes.

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

Surgical staging of the axilla should also be performed by:

- SNLB will be performed in patients without axillary involvement at the time of diagnosis. All patients should undergo level I and level II axillary dissections if the sentinel node(s) are reported positive for malignancy. One Step Nucleic Acid amplification (OSNA) techniques will be allowed, where microlesions with size ≤ 250 cCP/μL will be considered as a negative result of SNBL.

After the neoadjuvant treatment period, the investigator will report if patient undergoes breast surgery, and the type of surgery performed.

7.1.6 Radiotherapy

Radiotherapy was planned using computed tomography scans acquired supine with the both arms elevated above the head. Whole breast irradiation (WBI) was delivered daily to 50 Gy in 25 fractions using tangential fields. An additional boost irradiation of 16 Gy in 8 daily fractions after WBI was planned. The clinical target volume (CTV) was the breast tissue in the WBI and metallic marker plus a 1.5 cm margin inside the breast tissue in the boost irradiation. The planning target volumes were generated as an additional 0.5 cm margin applied on the CTVs to allow for minor variations in patient positioning.

7.1.7 Patient-reported Outcomes

Patient-reported Outcome (PRO) data will be elicited from the patients in this study to more fully characterize the clinical profile of omission of surgery when compared to standard treatment. The PRO questionnaires, translated as required in the local language, will be distributed by the investigator staff and completed by the patient at the investigational site. PRO questionnaires must be administered prior to any other study assessments and prior the administration of study treatment.

The EORTC QLQ-C30 and the Modified Breast Cancer module QLQ-BR23 questionnaires will be used to assess Health-Related Quality of Life (QoL), including side-effects of systemic therapy (e.g., sore mouth/tongue, difficulty swallowing, diarrhea, skin problems) and patient functioning during the neoadjuvant period and post-surgery follow-up (refer to schedule of assessments in Section 6 for a detailed description of timepoints).

The EORTC QLQ-C30 is a widely used Health-Related QoL measure in oncology trials with excellent psychometric properties demonstrating both reliability and validity. The measure consists of "five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-oflife scale" with a recall period of "the past week"(73). Scale scores can be obtained for each of the multi-item scales, global health status/QoL scale, and six single items by using a liner transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of "the past week," and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment). As this trial will include patients in the neoadjuvant setting, the last seven items of the original BR23 questionnaire, items numbered 47−53 that deal with symptoms and side effects not relevant to the population under study, will be removed. These seven items addressed symptoms experienced by patients with metastatic breast cancer and those undergoing radiation. Therefore, in consultation with the EORTC, these items were deleted, as the validity of the measure would not be compromised by their removal. In addition, as "oral mucositis" and "skin problems" are key symptoms of this therapy not assessed by currently available tools, validated items from the EORTC item bank were added to assess the presence and bothersomeness of oral mucositis (two items: sore mouth/tongue, difficulty swallowing) and skin problems (two items). Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

Refer to Appendix 4 for the EORTC QLQ-C30 and the modified QLQ-BR23.

7.1.8 Cost analysis

In order to estimate the costs associated with all patients, whether they are undergoing surgery or only pharmacological treatment, outpatient and inpatient costs will be analyzed (74-78).

a.Costs directly attributable to each patient

i. Cost of unit dose drugs and outpatient hospital medication

ii. Cost of blood bank

iii. Cost of prostheses

iv. Cost of other materials used and imputable directly to the patient's episode

v. Imputation of the cost of the requested diagnostic tests (image and laboratory) via the internal billing rate of each test requested

b. Imputable costs based on standards

i. For the days of conventional hospitalization, he will impute:

1. Cost of stay in the room (including nurses and sanitary assistants of the room, administration staff of the room, consumption of warehouse material not directly attributable to the patient, pharmacy plant (not unit) and indirect costs of the room (supplies, laundry and closet, cleaning, repairs, depreciation, etc.) It is necessary to take into account that each room has a different stay cost, therefore it will allocate the stay cost depending on the room where the patient has been each day

2. Day cost of medical care (imputation to patient of the cost of the costs of the medical service that attends to it based on the stays produced, differentiating between general, intermediate or intensive rooms)

3. Cost of the hospitality (attribution to patient of the cost of the kitchen and hospitality depending on the stays produced)

4. Cost of support (imputation to patient of the cost of admissions to apply for hospital discharge)

c. Costs attributable to the surgical intervention (both the primary intervention with the mastectomy and the second intervention related to the placement of the posterior mammary prosthesis)

1. Cost of the surgeon and anesthetist

2. Cost of the nursing, auxiliary, stretcher, cleaning and other staff related to the intervention

3. Cost of surgical material (Sutures, gauze, covers, pajamas, specific material related to mastectomy interventions, etc.)

4. Cost of the drugs used during the intervention (anesthetics, antibiotic prophylaxis, antihaemorrhagic and haemostatic, etc.)

d. Indirect non-healthcare costs Human capital method

The potential years of work life lost will be calculated and the expected annual salary will be applied as well as the expected employment rate specific to sex and age. Adjustments may

be applied such as a salary growth rate and a discount rate from the second year of the study.

The average costs will be the sum of the future salaries with growth and discounted all the year after the death by the expected occupation rate

The costs of absenteeism and presenteeism will also be analyzed

In this case, the level of absenteeism and presenteeism will be measured. The valuation of these costs will also be based on the previously estimated salary.

7.1.9 Other Procedures

7.1.9.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who complete 18 cycles of treatment with pertuzumab and trastuzumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Followup Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.9.2 Blinding/Unblinding

This is an open-label trial; therefore, FCRB, investigator and participant will know the treatment administered.

7.1.10 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.10.1 Screening

Within 42 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.0 Visit requirements are outlined in the Schedule of Activities (Flow Chart). Screening procedures may be repeated after consultation with the Sponsor.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol Flow Chart, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation if there are

Day -1 procedures planned per protocol.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the allocation for the following:

- Evaluation of ECOG is to be performed within 10 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

7.1.10.2 Treatment Period

Visit requirements are outlined in the Section 6 – Schedule of Activities. Specific procedure related details are provided in Section 7

7.1.10.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted 28 days (+/- 7 days) after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 14 days) the first 3 years and every 52 weeks (± 28 days). The imaging time point will occur every 52 weeks (± 14 days).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the treatment, is also an adverse event.

Roche product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational or marketed, manufactured by, licensed by, provided by or distributed by Roche for human use.

Adverse events may occur during the treatment in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.

- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization or within 7 months after last dose of her2 therapy (trastuzumab/pertuzumab/TMD1), or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. The Investigator will follow the female subject until completion of the pregnancy,

and must notify the Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome). The Investigator will follow the newborn until 12 months of the infant's life (follow up at 3, 6 and 12 months of the infant's life).

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the

event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Sponsor.

7.2.1 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol specified intervention, including but not limited to washout or discontinuation of usual therapy, diet or a procedure.

- Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization with in the 7 months after last dose of her2 therapy (trastuzumab/pertuzumab/TDM1), or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor

The investigator will follow the information on the outcome of the pregnancy, including premature termination should the case arise and on the infant until 12 months of life. Spontaneous miscarriage and congenital abnormalities will also be reported as SAEs. Follow- up queries may be sent, asking for further information, if required for a comprehensive assessment of the case. The follow-up period will be deemed to have ended when the health status of the child has been determined at 12 months of the infant's life. Additional follow-up information on any Trastuzumab/Pertuzumab/TDM1 -exposed pregnancy and infant will be requested at specific time points (i.e., after having received the initial report, at the end of the

second trimester, two weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

7.2.2 Immediate Reporting of Adverse Events to the Sponsor

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

7.2.2.1 AEs definitions

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

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

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

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

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

The descriptions and grading scales found in the revised CTCAE version 5.0 will be utilized for all toxicity reporting.

The intensity (severity) of an AE will be recorded as one of the following but also TCAE Grade will be recorded (Section 7.2.3)

7.2.2.2 Serious Adverse Events (SAEs)

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

- 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 National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Table 10 and Appendix 2); 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 7.2.2.5 for reporting instructions).

Refer to **Table 12** for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the treatment, must be reported within 24 hours to the Sponsor.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to treatment that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All participants with serious adverse events must be followed up for outcome.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Roche Investigational Compound Number (IND, CSA, etc.) at the time of submission.

Definition of life threatening

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

Definition of hospitalization

AEs requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject/patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment which would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious. Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not to be notified according to immediate reporting criteria. If anything untoward is reported during any procedure, this must be reported as an AE and either 'serious' or 'non-serious' attributed according to the usual criteria.

Definition of clinically/medically significant event

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

Clinically/medically significant events MUST be reported as SAEs.

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

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

7.2.2.3 Adverse Event of Special Interest (AESI)

Adverse events of special interest (serious and non-serious) 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 7.2.2.5 for reporting instructions). Adverse events of special interest for this study are as follows:

- trastuzumab: congestive heart failure
- pertuzumab: Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of monoclonal **antibody**

7.2.2.4 Special Situation Reports:

The following Special Situation should be collected even in the absence of an AE:

- Data related to overdose (accidental or intentional), medication error, drug misuse and drug abuse
- Data related to a Suspected Transmission of Infectious Agent by Medicinal Product (STIAMP)

7.2.2.5 Adverse event reporting and other safety related issues reporting

AEs will be collected from the first study-mandated procedure until the safety follow-up visit to be done 28 days (+/- 7 days) after the last day of study treatment. All study subjects/patients will be carefully monitored for the occurrence of AEs during this period. Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible. Any additional events that fall outside this definition should also be reported separately.

All AEs must be recorded in the CRF. SAE reporting and timeframe

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

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

• The full details of the SAE and/or AESI should be collected and fully documented using the SAE form and sent to Sponsor.

• Follow-up information, copies of the results of any tests, the outcome of the event plus the

investigator's opinion of IMP relationship to the SAE(s) and AESI(s), and other document when requested and applicable, will accompany the SAE form as available on the day of reporting or provided as soon as possible thereafter.

• The original SAE Report Form and the fax confirmation sheet from the Sponsor must be kept with the CRF documentation at the study site(s).

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

SAEs and AESIS will be followed until resolved, a stable outcome or baseline condition is reached, subject/patient is lost to follow-up or dies.

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

7.2.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 12 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during the trial product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the inclusion in the trial and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause treatment to be discontinued?	
Relationship to Roche Product	Did treatment cause the adverse event? The determination of the likelihood that tratment caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between treatment and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely treatment caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to treatment such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of treatment? Is the time of onset of the AE compatible with a drug-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Roche Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was treatment discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

	Rechallenge	Was the participant re-exposed to treatment in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY TREATMENT, OR IF REEXPOSURE TO TREATMENT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding treatment or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Roche product relationship).**
Yes, there is a reasonable possibility of treatment relationship.		There is evidence of exposure to treatment. The temporal sequence of the AE onset relative to the administration of Roche product is reasonable. The AE is more likely explained by treatment than by another cause.
No, there is not a reasonable possibility of treatment relationship		Participant did not receive the treatment OR temporal sequence of the AE onset relative to administration of treatment is not reasonable OR the AE is more likely explained by another cause than the treatment. (Also entered for a participant with overdose without an associated AE.)

7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All SUSARs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Sample size calculation

This is an exploratory study. No formal sample size calculations will be performed.

A maximum sample size of 17 patients with complete response and no surgery will be enrolled. This sample size has been chosen to balance the need to minimize exposure to patients with the need to provide adequate safety and efficacy information.

This trial will be positive as standard treatment if 0% of the patients need surgery within the first three years after completed radiation and chemotherapy.

8.2 Statistical Analysis Plan

This trial will be positive as standard treatment if 0% of the patients need surgery within the first three years after completed radiation and chemotherapy. If 1 or more need surgery within the first three year of observation, the chance of the true operation frequency being < 20% is less than 5%.

Results will be presented by study product with descriptive statistics appropriate to the nature of the variables and they will be calculated according to standard methods.

- Continuous variables: minimum, P25 (percentile 25), median, P75 (percentile 75), maximum and N.

- Categorical variables: total column %, each category N and 95% Confidence Intervals (95%CI) from Wilson Method for main variables as evaluation of response.

Where applicable, these summaries will be provided by visit.

The Kaplan-Meier method will be used to estimate the survival curves. As well to estimate the loco-regional and distant disease-free survival (LRD-IDFS) at 3-years of patients who achieve a complete response based on imaging (i.e. MRI) and VAB.

The detailed procedure will be included in the SAP and in the Final Report. The handling of missing data will follow the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP/ICH/363/96).

The analysis was performed using SAS version 9.1.3 software (SAS Institute Inc., Cary, NC, USA) and the level of significance was established at the 0.05 level (two-sided). Since this is a proof of concept clinical trial, all p-values will by considerer only for descriptive purposes.

An eCRF will be designed, validated and implemented with MACROTM and will provide electronic data capture functionality to the investigators. The system complies with the relevant international standards and provides the capability to perform all major data management activities within a consistent, auditable and integrated electronic environment (query management, data entry, data validation, report generation). MACROTM has been designed to support compliance with the requirements of relevant Competent Authorities of Europe and the rest of the world, including the internationally recognized ICH Good Clinical Practice and FDA 21 CFR Part 11. Any data transfer will be done using secure SSL connection with encryption.

The investigator will be provided with eCRFs, and will ensure all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign (e-sign) the eCRFs to verify the integrity of the recorded data.

In general, the investigator must maintain source documents such as radiological or laboratory reports and complete history and physical examination reports.

9.0 TRANSLATIONAL RESEARCH

Translational research data will be collected outside the clinical database; correlations with relevant clinical features will be performed by specialized scientists of PPD and reported in a separate ad-hoc report, which will integrate the results and findings described in the clinical study report.

All the data analyses of the study will be under the responsibility of the Sponsor and they will be based on a statistical plan according to the protocol specifications.

9.1 Biological specimens

The tissue samples collected will be used to identify biomarkers that may be predictive of response or toxicity to the proposed treatments and/or prognostic for breast cancer. Since the knowledge of new markers that may correlate with disease activity and the efficacy or safety of the treatment is evolving, the analyses may change during the course of the study and may include determination of additional markers of tumorigenesis pathways and mechanisms of treatment response. The collected tumor tissue samples may also be used to develop and validate diagnostic assays and allow the generation of statistically meaningful biomarker data.

Remaining sample materials after the completion of the initial biomarker assessments (e.g., aliquots of tumor RNA or DNA) may be used for further assessment of expanded marker panels.

Samples will be stored at the PPD for up to 15 years after database closure, with the additional option of further long-term storage in a sample collection. They will be stored under the responsibility of the PPD. All patients will be consented for the collection and use of research blood and tissue samples. All samples will be linked anonymized and only identified by the trial ID and unique sample number allocated.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data. Patients will be informed that the sample collection is composed by biological samples from patients with cancers and that these samples stored and their associated data may be used for biomedical research in the field of cancer diseases. These investigations must be previously approved by the Ethics Committe.

9.1.1 Tumor tissue samples

Collection of tumor biopsies is an essential part of this study. Paraffin-embedded and formalin-fixed tumor samples will be obtained from all patients. Quality of tumor samples even for pre-screening sample will be evaluated upon arrival to central laboratory. Pathological analysis includes hematoxylin and eosin (H&E) staining, identification of areas with greater amount of tumor cells and determination of their tumor cell percentage. Confirmation of eligibility criteria requires central assessment of an adequate quantity and quality of pre- screening sample. If not available, the patient must agree to re-biopsy.

9.2 Gene expression signatures

The study foresees the identification of the molecular intrinsic subtypes (Luminal A, Luminal B, HER2-E, basal-like) and the normal breast-like group using the PAM50 panel (non-commercial version). This panel measures the expression of 50 classifier genes and 5 control genes, which classify the tumors into 5 intrinsic subtypes (luminal A, luminal B, HER2- enriched and basal-like) and the normal breast-like group. ERBB2 high tumors will be determinate on base of a pre-definied cutoff.

9.2.1 The nCounter platform

The NanoString nCounter Analysis System (http://www.nanostring.com/) delivers direct, multiplexed measurements of gene expression through digital readouts of the relative abundance of hundreds of mRNA transcripts. It uses gene-specific probe pairs that hybridize directly to the mRNA sample in solution eliminating any enzymatic reactions that migh introduce bias in the results. After hybridization, all of the sample processing steps are automated.

9.2.2 RNA Extraction

The PAM50 assay uses RNA from FFPE breast tumor tissue. A section of the FFPE breast tissue will first be examined with a hematoxylin and eosin (H&E) staining to determine percent tumor nuclei, percent normal nuclei, and percent necrosis per standard pathology processing. The slide will then be reviewed by a pathologist, who will identify and mark the region of the tissue that contains an adequate percentage of tumor for the gene expression test on the slide. RNA will be extracted from the FFPE tissue sample using an RNA isolation kit. Additional general-purpose laboratory reagents are required for deparaffinization. The extraction process includes a step for removing genomic DNA from the sample. Following extraction of total RNA and removal of genomic DNA, the optical density is measured at wavelengths of 260 nm and 280 nm to determine both yield and purity using a low volume spectrophotometer. RNA will be stored at –80ºC until time of testing.

9.2.3 Technical procedures and data analysis

For each set of up to 10 RNA samples isolated from breast cancer tissue, the user will pipette a defined amount of RNA into separate tubes within a 12-reaction strip tube and add the CodeSet and hybridization buffer as specified within the assay protocol. A set concentration of reference sample is pipetted into the remaining two tubes with CodeSet and hybridization buffer. The CodeSet consists of probes for each gene that is targeted, additional probes for endogenous “housekeeping” normalization genes and positive and negative controls that are spiked into the assay. The reference sample consists of in vitro transcribed RNA for the targeted genes and housekeeping genes. Once the hybridization reagents are added to the respective tubes, the user transfers the strip tube into a specified heated-lid heat block and incubates for a defined period of time at a set temperature of 65ºC.

Upon completing hybridization, the user will then transfer the strip tube containing the set of 10 assays and two reference samples into the nCounter Prep Station. An automated purification process then removes excess capture and reporter probe through two successive hybridization-driven magnetic bead capture steps. The nCounter Prep Station then transfers the purified target/probe complexes into an nCounter cartridge for capture to a glass slide. Following completion of the run, the user removes the cartridge from the Prep Station and seals it with an adhesive film.

The cartridge is then sealed and inserted into the nCounter Digital Analyzer. The analyzer counts the number of probes captured on the slide for each gene, which corresponds to the

amount of target in solution. The signals of each sample will be normalized using the housekeeping genes to control for input sample quality. The signals are then normalized to the reference sample within each run to control for run-to-run variations. The resulting normalized data is input into the breast cancer-subtyping algorithm or gene signatures score algorithm.

9.2.4 DNA seq

DNA mutation analysis will be performed on tumor DNA samples to identify specific loci, genes, or gene pathways associated with sensitivity to the treatment combination in order to search for predictive biomarkers or response and also to evaluate the tumor mutational load

9.2.5 ctDNA seq

Evaluation of tumor load by Next Generation Sequencing will be evaluated through the study (ctDNA plasma samples).

9.3 Sample repository

All residual samples after protocol-defined studies are completed will be stored in a central sample repository as a collection. The samples in the study repository might be used for future biomarker research towards further understanding of treatment with study drugs, of breast cancer, related diseases, and adverse events, and for the development of potential, associated diagnostic assays, in accordance with the recommendations and approval of the Study Steering Committee. Samples will be stored up to 15 years or until they are exhausted, whatever happens first, in accordance with applicable local regulations (Law 14/2007 on Biomedical Research and the Royal Decree 1716/2011).

A separate, specific signature will be required to document a patient's agreement to allow future biomarker research and storage in repository of any remaining samples. Labels of biological samples will not contain any clinical information of patients.

Samples will be stored in the biorepository of the PPD. Responsible for the samples custody is PPD The repository is located in the PPD

Samples will be stored as a collection and registered in the National Registry of Biobanks, in agreement with article 37 of the Royal Decree 1716/2011.

Results derived from the analysis of biological samples of a patient will not be provided to the Site Investigators, unless patient explicitly requests this information, in compliance with local and national law. Patient must be informed that those results are for investigational use only and should not be used for treatment decision. The final results deriving from investigation with these biological samples will be published in accordance with the Steering Committee charter of this study. These investigations must be previously approved by the Ethics Committee.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

Pertuzumab/Trastuzumab FCD SC and Trastuzumab emtansine IV will be IMPs.

Paclitaxel will be prescribed by the investigator and will be obtained from the center's pharmacy as necessary. Consequently, conditioning and labeling will depend on locally marketed supplies of this drug. For further details, see the local prescribing information for paclitaxel and/or recognized clinical practice guidelines.

10.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pertuzumab/trastuzumab FCD and TDM1 will be provided by Roche as summarized in **Table 13.**

Table 13: Product Descriptions

Product Name & Potency	Dosage Form
Trastuzumab 600/Pertuzumab1200 FCD	Solution for Injection
Trastuzumab 600/Pertuzumab 600 FCD	Solution for Injection
Trastuzumab emtansine 20ml vial	Solution for Injection

10.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Roche or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Ethical and regulatory standards

11.1.1 Independent Ethics Committee

This protocol and any amendments will be submitted to a properly constituted Independent Ethics Committee (IEC), in accordance with the International Conference on Harmonization (ICH) guidelines, the applicable European Directives and local legal requirements, for approval of the study. Approval must be obtained in writing before the first subject can be recruited.

During the Clinical Trial, any amendment or modification to the Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety.

Principal Investigator will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor. Before study start, the investigator must sign the Protocol signature page to confirm that he/she agrees to conduct the study in compliance with these documents and with all instructions and procedures described in the Protocol and to permit access to all relevant data and records to the study monitors, the Sponsor auditors, representatives of FCRB 's clinical quality assurance department, designated the Sponsor agents, IECs and health authorities upon request.

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually DSUR and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

11.1.2 Ethical conduct of the study

The Clinical Trial will be conducted in compliance with the Protocol, regulatory requirements, the ICH guidelines for Good Clinical Practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

This Clinical Trial will be recorded in the public registry website clinicaltrials.gov and Registro Español de Estudios Clínicos before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients and their healthcare practitioners on how to enroll in the trial.

11.1.3 Subject information and consent

All potential participants will receive verbal and written information on the study in a previous interview with the study doctor in their hospital. In this information, special emphasis will be placed on the fact that participation in the study is voluntary and that the patient may withdraw herself from the study at any time and for any reason, without this affecting her medical care. All patients will have the opportunity to ask questions about the study and they will be given sufficient time to decide if they wish to participate.
The ICF must mention the specific data that will be recorded, collected, processed and that can be sent to countries pertaining to and outside of the European Economic Area (EEA). In accordance with the in accordance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and LOPD, the individuals participating in the study shall not be identified.

Personal data will be managed in accordance with the applicable legislation in force at the time, and in particular, in accordance with Regulation (EU) No 2016/679 of 27 April 2016 on the protection of individuals with regard to the processing of their personal data (hereinafter, "GDPR").The processing, communication and transfer of personal data of all participants will be adjusted to compliance with Regulation EU 2016/679 of the European Parliament and the Council of 27 April 2016 on the protection of natural persons as to the processing of personal data and the free circulation of data, being mandatory as of May 25, 2018. The legal basis that justifies the processing of your data is the consent given in this act, in accordance with the provisions of the Article 9 of the EU Regulation 2016/679.

The data collected for the study will be collected only identified by a code, so that no information will be included to identify the participants. Data will be processed with the only purpose of carry out all activities related to the clinical trial in compliance with pharmacovigillance regulations (for the drug safety control). The legal basis for the processing of the data is the participant consent and Article 9.2 of the Regulation. Only the study doctor and his collaborators have the right to access the source data (clinical history) and will be able to relate the data collected in the study with the patient's medical history.

The identity of the participants will not be available to any other person except for a medical

emergency or legal requirement. Health authorities, the Research Ethics Committee and personnel authorized by the Sponsor of the study, may have access to the personal data identified when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation.

Only encrypted data will be transferred to third parties and to other countries, which in no case will contain information that can identify the participant directly (such as name and surnames, initials, address, social security number, etc.). In the event that this assignment occurred, it would be for the same purpose of the study described and guaranteeing confidentiality. If a transfer of encrypted data is carried out outside the EU, either in entities related to the hospital where the patient participates, to service providers or to researchers who collaborate with them, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

The sponsor of the trial commits to carry out the data processing according to EU Regulation 2016/679 and, therefore, to keep a record of the processing activities to carry out and to make a risk assessment of the data processing, to establish what measures will be applied and how it will be done.

In addition to the rights already covered by the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation) participants can now limit the processing of data collected for the project that has to be rectified, request a copy or move to a third party (portability). To exercise these rights, the participant should be directed to the principal investigator of the study or the Data Protection Delegate of their site. The participant also has the right to contact the Data Protection Agency if not satisfied. The data cannot be deleted even if a patient discontinues the study, to guarantee the validity of the investigation and comply with the legal duties and the medication authorization requirements.

In accordance with the provisions of recital 33 of the regulations and the corresponding provisions of each country involved in the study regulations, the data may be preserved in such a way that the clinical data are kept separate from the identifiers, to be used in future investigations, applying all technical precautions necessary to avoid their re-identification, and in accordance with all ethical and legal requirements.

The patient will be given a copy of the Patient Information Sheet, including the signed ICF.

Eligible patients can only be included after granting their written informed consent (before witnesses, when required by laws or standards). The signature of the ICF must be obtained before performing any study-specific procedures (that is, any of the procedures described in the Protocol). The date on which the ICF is signed must be recorded in the eCRF.

The investigators will be given an ICF approved by the IEC that is considered to be appropriate for the study and that satisfies the ICH GCP standards and legal requirements.

Any modification to this ICF proposed by the investigator must be accepted by the Sponsor and approved by the local IEC. A copy of the approved version must be provided to the trial monitor after IEC approval is obtained.

11.2 Subject records and source data

A current copy of the Curriculum Vitae describing the experience, qualification, and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the Clinical Trial.

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the subject is in a clinical study
- The identity of the study, e.g., Study code
- Subject screening number and/or subject number
- That IC was obtained and the date
- Diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination
- Subject health service identification number

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data recorded on the e-CRFs. Data reported on the e-CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Signed sections of CRFs will be monitored on a regular basis.

11.2.1 Study documentation and storage of records

The investigator or the site must store the essential documents (as defined in Standard E6 of the ICH GCP, section 8) as required by the applicable administrative requirements. The investigator or the site will have to take measures to prevent the accidental or early destruction of said documents.

After the study is closed, the investigator or the designated individual from the site must store all study records in a secure, protected area of the site, except where, according to local legislation, they must be stored by another person or institution. The records must be stored to enable their easy, timely recovery as needed (for example, audit or inspection) and, whenever possible, to allow any subsequent analysis of the data together with the site's assessment, the support systems and the personnel. When so permitted by local standards or legislation or the

institution's policy, some or all of these records can be stored in a format other than hard copy (for example, microfile, scanned or electronic support); however, precaution must be exercised before adopting these measures. The investigator must make certain that all reproductions are legible, a true and exact copy of the original and that they comply with the standards for accessibility and recovery, including that of regenerating a printed copy if necessary. Moreover, the investigator must make certain that there is an acceptable backup copy of these reproductions and an acceptable quality control process for making said reproductions.

The Sponsor will inform the investigator of the period for storing these records for the purposes of complying with all current administrative requirements. The minimum storage period must comply with the strictest standard applicable to the study at this site, as dictated by the institutional requirements, laws or local standards or Sponsor 's procedures and standards; otherwise, the default storage period shall be at least 25 years after the finalization of the study.

The investigator must notify the Sponsor of any change in the availability of the files, for example: archived in an off-site facility or transfer of the ownership of the records in the event the investigator leaves the site.

11.3 Access to source data and documentation

For the purpose of ensuring compliance with the Clinical Trial Protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and, as such, will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection. The confidentiality of the data verified and the protection of the patients should be respected during these inspections. Any results and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator must take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

11.4 Study monitoring

11.4.1 Responsibilities of the investigators

The Investigators and delegated investigator staff undertakes to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for GCP, and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF], or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by FCRB representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint other individuals, as he/she may deem appropriate, as Sub-investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-investigators must be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

11.4.2 Responsibilities of sponsor and monitoring

The Sponsor of this Clinical Trial, FCRB, is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial the site will be contacted through monitoring visits, letters, or telephone calls by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements, and any emergent problems.

The Monitor will visit the study site on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements, and any study specific documents such as e-CRF completion guidelines.

Monitoring visits will be conducted to confirm that:

- The investigational team is adhering to the study protocol.
- IC has been obtained from all participants.
- AEs have been reported as required.
- Data are being accurately recorded on the e-CRFs.
- IMP is being stored correctly and drug accountability is being performed on an on-going basis.
- Facilities are, and remain, acceptable throughout the study.
- The Investigator and the site are receiving sufficient information and support throughout the study.

Moreover, during monitoring visits, the data recorded on the e-CRFs, source documents, and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the subject in the study, i.e., source data verification.

Detailed monitoring visit information will be provided separately in the Monitoring Plan (MP). The MP will be approved before the first patient is included.

11.4.3 Source document requirements

According to the ICH guidelines for GCP, the Monitoring Team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded on the e-CRF. The IC Form will include a statement by which the patient allows Sponsor´s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records, which support the data on the e- CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.).

These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

11.4.4 Use and completion of case report forms and additional requests

It is the responsibility of the Investigator to maintain adequate and accurate Case Report Forms, which for this trial will be of electronic nature. The electronic Case Report Form (eCRF) is designed by the Sponsor to record, according to Sponsor instructions, all observations and other data pertinent to the Study. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available to the Sponsor as soon as they are entered in the e-CRF system. The computerized handling of the data by the Sponsor when available in the e-CRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests along with their responses will be managed through the e-CRF.

11.4.5 Use of computerized systems

Procedures shall be employed and controls designed to ensure the confidentiality of electronic records. Such procedures and controls must include validation of systems to ensure accuracy and reliability, ability to generate accurate and complete copies of records, protection of records to enable retrieval, use of secure, computer-generated, timestamped entries, use of operational system checks, use of device checks to determine validity of source data input, determination

that those who develop, maintain, or use such systems have adequate education and training, the establishment and adherence of written policies to deter record falsification, the use of appropriate controls over systems documentation including the distribution or use of documentation for system operation and maintenance, and revision and change control procedures, which document timesequenced development and modifications of systems documentation. For data management activities, the e-CRF will be built using e- Clinical SQL Server.

11.5 Data management

Data management and handling will be conducted according to the study specific Data Management Plan in accordance with ICH guidelines and SAIL standard operating procedures (SOPs), which will be prepared and approved before the first patient is included.

Data entry, validation, and data queries will be handled by the SAIL The data will be subjected to validation according to SAIL SOPs in order to ensure accuracy in the collected e-CRF data.

Before database closure, reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e., discrepancies and additions from the process defined in the Data Management Plan, will be described in a study-specific Data Management Report.

11.6 Confidentiality

11.6.1 Patient records

The investigator shall ensure that the anonymity of the patients and protection of her identity from unauthorized individuals are maintained. In the eCRFs or other documents sent to the data management department, patients shall not be identified by name, but by an identification code. Subjects will be codified with a study code that prevents their identity from being deduced. The investigator must keep a patient inclusion log with their codes and full names. The investigator will have to store the documents that are not going to be sent to the data processing center, for example, original patient ICFs, in a strictly confidential manner. Only data collected for the study that does not bear any information that could directly identify the patient will be transferred to third parties or other countries. Should this transfer occur, it will be for the same purposes as the study and guarantee confidentiality with at least the level of protection afforded by applicable regulations in Spain. Patients will be informed that their clinical data will be incorporated into an automated study-specific file after and the results of the clinical trials and different studies conducted with samples can be communicated at scientific meetings, medical conferences or publications. However, patient's identity or identifiable data will never be disclosed.

11.6.2 Study documentation and related data

All information disclosed or provided by Sponsor (or any company/institution acting on its behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the e-CRFs, the Summary of Product Characteristics and the results obtained during the course of the Clinical Trial, is confidential prior to the publication of the Clinical Trial results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of Sponsor. However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators are bound by the same obligations as the Investigator. The Investigator must inform the Sub-investigators of the confidential nature of the Clinical Trial. The Investigator and the Sub-investigators should use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account. Furthermore, the Investigator and Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, the Investigator, and the collaborators involved in the study.

11.7 Property rights

All information supplied by the Sponsor in connection with this study will remain the sole property of FCRB and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from Sponsor and will not be used except in the performance of this Study. Sponsor will retain ownership of all data.

All information, documents, and intellectual property (IP) provided by Roche are and remain the sole property of Roche. The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

In terms of the results generated by the study, the Sponsor will maintain ownership of all data and will allow Roche to make scientific and commercial use of it, if it considers it pertinent. Any reports, documents, publications and inventions directly or indirectly arising from this study shall be the immediate and exclusive property of Sponsor. FCRB, as Sponsor, may use and exploit all the study results at its full discretion.
As the case may be, the Investigator and/or the Sub-investigators should provide all assistance required by Sponsor, at FCRB's expense, for obtaining and defending any patent, including signature of legal documents.

11.8 Clinical trial protocol amendments

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes to the Clinical Trial Protocol without agreement by Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to patients enrolled in the trial, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by Sponsor, and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the IC Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised IC form prior to implementation of the change and patient signature should be recollected if necessary.

11.9 Protocol deviations

Deviations to the study protocol will be documented in a Protocol Deviation Log. The classification of subjects into protocol violators will be made during a meeting before database lock. Listings will indicate the allocation of subjects by analysis set and the number of subjects per analysis set will be recorded in the Clinical Study Report.

11.10 Insurance

Sponsor should provide insurance or should indemnify (legal and financial coverage) the Investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence, or non-compliance with the protocol. The insurance will cover related injuries of the participants according to local regulatory requirements. Clinical trial participants will be provided on request with the conditions of insurance along with the patient information and consent form

11.11 Study committees

1.11.1 Steering Committee

A SC will be created comprising Sponsor investigators associated with the design or conduct of the study, as well as non-Sponsor investigators, provided the Principal Investigator of the study deems it appropriate. They will review the main safety and efficacy data.

The SC shall ensure that the management of the study is carried out in line with the Protocol and GCP guidelines. The SC may propose and must review and approve any necessary amendment to the Protocol. It will also make decisions regarding the publications generated

from the study data. Information on members, responsibilities and frequency of steering committee meetings are specified in the SC statutes.

The SC may be consulted for advice when needed, either in face-to-face meetings or via teleconference.

11.12 Premature discontinuation of the study or close- out of a site

Decided by Sponsor in the following cases:

- If new information on the product leads to doubt as to the benefit/risk ratio.
- If the Investigator has received from Sponsor all IP, means, and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon.
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including, but not limited to, breach of the Clinical Trial Protocol, breach of the applicable laws and regulations, or breach of the ICH guidelines for GCP.
- If the total number of patients are included earlier than expected.

In any case, Sponsor will notify the Investigator of its decision by written notice.

Decided by the Investigator

The Investigator must notify (30 days' prior notice) Sponsor of his/her decision and give the reason in writing. In all cases (decided by Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

11.13 Report and publication

All publications and presentations of the study results must comply with the approved scientific practice and academic standards and comply with Sponsor 's publication policy. This policy is available to all investigators and groups participating in the study. Every investigator who wishes to publish or present the study data must obtain the permission of the study SC. Sponsor must review and approve any article prior to it being submitted to journals, congresses or conferences. The authorship of the publications will be decided by the SC, which will follow the standard guidelines of peer-reviewed journals and will observe FCRB's publication policy.

Key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov prior to enrolment of the first patient.

Once the study has been completed, Sponsor will prepare a Clinical Study Report (CSR) in line

with the ICH guidelines on the structure and content of clinical study reports (ICH E3). All publications and presentations must be based on the CSR.

Sponsor agrees to communicate the results of the study, regardless of if they are positive or negative, in public access media, and shall particularly respect the dissemination of the results in scientific publications, assuming an active role in the preparation of articles or summaries, in line with the SC, and participating in its submission to the corresponding authors. All study communications must mention Roche's economic support and supply of the drugs. In order to guarantee the protection of the industrial property arising from the study, Roche will have the right to review all articles prior to submission.

Sponsor will have the right to use the results in internal presentations and for the external promotion of its interests.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from Sponsor in advance.

11.14 Funding

This study was supported by a grant from Roche. Roche had no role in the management of this trial. The decisions and responsibilities of this trial were all under the sponsor.

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13.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

For WOCBP: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of <1% per year, or 2 effective non-hormonal contraceptive methods during the study treatment periods and for 7 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

A WOCBP if she is post-menarchal, has not reached a post-menopausal state (post-menopausal defined as ≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

Examples of 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) and copper intrauterine devices.

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 post-ovulation methods) and withdrawal are not acceptable methods of contraception.

• A negative serum pregnancy test must be available prior to randomization for women of childbearing potential (defined as post-menarchal, has not had ≥ 12 continuous months of amenorrhea with no identified cause other than menopause, and has not undergone surgical sterilization [removal of ovaries and/or uterus])

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

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

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in **Table 14** .

Table 14 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: EORTC QLQ-Core 30 and Modified EORTC QLQ-BR23

SPANISH (SPAIN)

EORTC QLQ-C30 (versión 3)

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

Por favor ponga sus iniciales:
Su fecha de nacimiento (día, mes, año):
Fecha de hoy (día, mes, año): 31

		En absoluto	Un poco	Bastante	Mucho
1.	¿Tiene alguna dificultad para hacer actividades que requieran un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4.	¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

Durante la semana pasada:		En absoluto	Un poco	Bastante	Mucho
6.	¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4
8.	¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9.	¿Ha tenido dolor?	1	2	3	4
10.	¿Necesitó parar para descansar?	1	2	3	4
11.	¿Ha tenido dificultades para dormir?	1	2	3	4
12.	¿Se ha sentido débil?	1	2	3	4
13.	¿Le ha faltado el apetito?	1	2	3	4
14.	¿Ha tenido náuseas?	1	2	3	4
15.	¿Ha vomitado?	1	2	3	4
16.	¿Ha estado estreñido/a?	1	2	3	4

Por favor, continúe en la página siguiente

SPANISH (SPAIN)

Patient number: |__|__|__|__|__|__|__|__| Date of assessment: |__|__| DD|__|__|__| MMM|__|__|YY

SPANISH (SPAIN)

EORTC QLQ - BR23

Las pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada.

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
31. ¿Tuvo la boca seca?	1	2	3	4
32. ¿Tenían la comida y la bebida un sabor diferente al habitual?	1	2	3	4
33. ¿Le dolieron los ojos, se le irritaron o le lloraron?	1	2	3	4
34. ¿Se le cayó algo de pelo?	1	2	3	4
35. Conteste a esta pregunta sólo si le cayó algo de pelo: ¿Se sintió preocupada por la caída del pelo?	1	2	3	4
36. ¿Se sintió enferma o mal?	1	2	3	4
37. ¿Ha tenido subidas repentinas de calor en la cara o en otras partes del cuerpo?	1	2	3	4
38. ¿Tuvo dolores de cabeza?	1	2	3	4
39. ¿Se sintió menos atractiva físicamente a consecuencia de su enfermedad o tratamiento?	1	2	3	4
40. ¿Se sintió menos femenina a consecuencia de su enfermedad o tratamiento?	1	2	3	4
41. ¿Le resultó difícil verse desnuda?	1	2	3	4
42. ¿Se sintió desilusionada con su cuerpo?	1	2	3	4
43. ¿Estuvo preocupada por su salud en el futuro?	1	2	3	4

Durante las últimas <u>cuatro</u> semanas:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
44. ¿Hasta qué punto estuvo interesada en el sexo?	1	2	3	4
45. ¿Hasta qué punto tuvo una vida sexual activa? (con o sin coito)	1	2	3	4
46. Conteste a esta pregunta sólo si tuvo actividad sexual: ¿Hasta qué punto disfrutó del sexo?	1	2	3	4

Por favor, continúe en la página siguiente

Patient number: |__|__|__|__|__|__|__|__| Date of assessment: |__|__| DD|__|__|__| MMM|__|__|YY

SPANISH (SPAIN)

Durante la semana pasada:	En absoluto	Un poco	Bastante	Mucho
47. ¿Sintió algún dolor en el brazo o en el hombro?	1	2	3	4
48. ¿Se le hinchó el brazo o la mano?	1	2	3	4
49. ¿Tuvo dificultad para levantar el brazo o moverlo a los lados?	1	2	3	4
50. ¿Ha tenido algún dolor en la zona de su pecho afectado?	1	2	3	4
51. ¿Se le hinchó la zona de su pecho afectado?	1	2	3	4
52. ¿Sintió que la zona de su pecho afectado estaba más sensible de lo normal?	1	2	3	4
53. ¿Ha tenido problemas de piel en la zona de su pecho afectado (p.e. picor, sequedad, descamación)?	1	2	3	4