TITLE: Phase I/IIa Trial of Gemcitabine Plus Trastuzumab and Pertuzumab in Previously Treated Metastatic HER2+ Breast Cancer

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PROTOCOL

STUDY TITLE: Phase I/IIa trial of gemcitabine plus trastuzumab and pertuzumab in previously treated metastatic HER2+ breast cancer

STUDY DRUGS:	HERCEPTIN (trastuzumab) PERJETA (pertuzumab) gemcitabine
SUPPORT PROVIDED BY:	Genentech, Inc.
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STUDY NUMBER:	[redacted]
PROTOCOL VERSION/DATE:	1.1 11/14/2013

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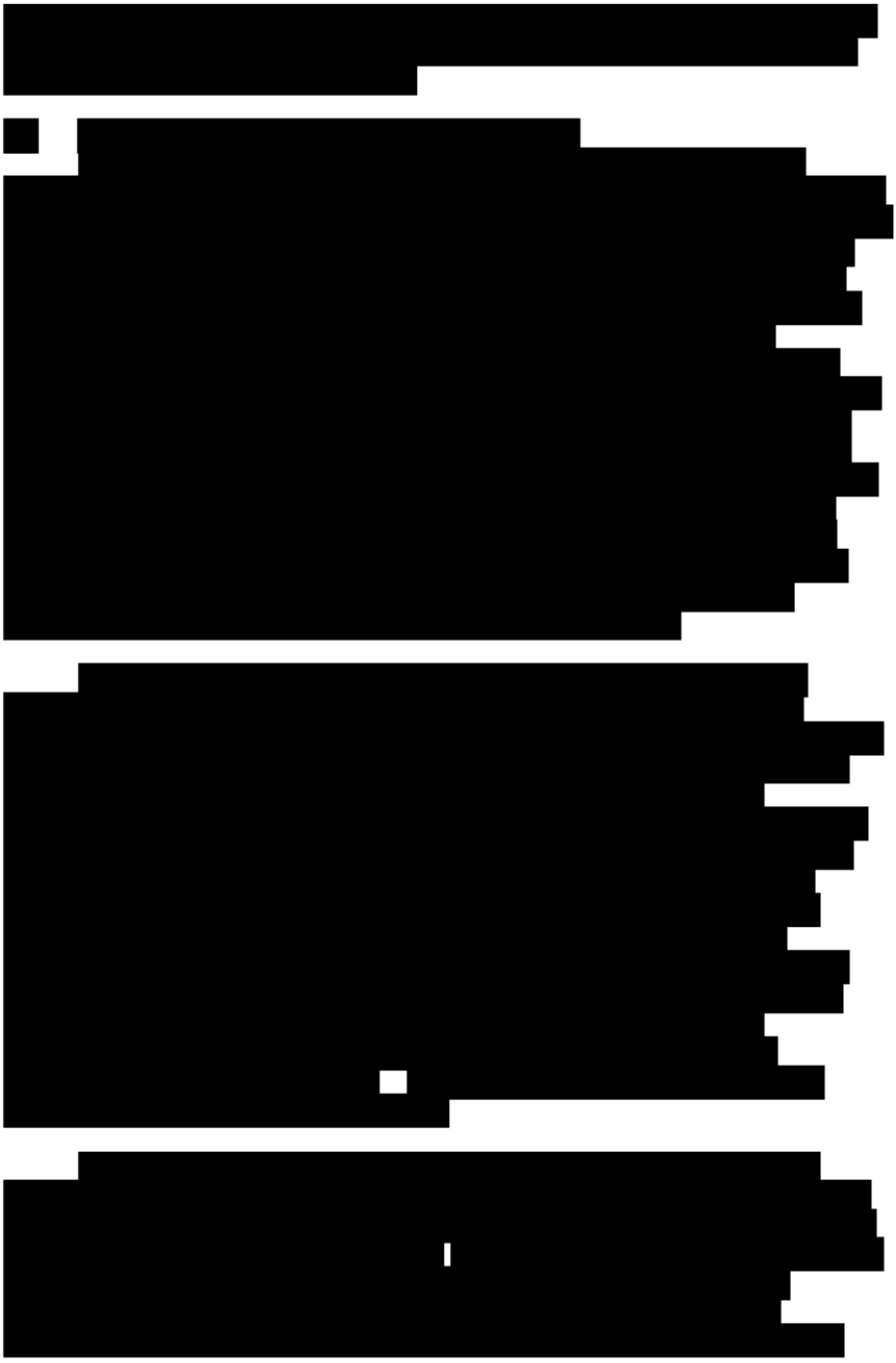

2. OBJECTIVES

The objective of the study is to evaluate the safety and activity of gemcitabine plus trastuzumab and pertuzumab in patients with metastatic HER2+ breast cancer who have progressed on at least one prior line of chemotherapy plus HER2 targeted agent.

2.1 PRIMARY OBJECTIVES

Phase I: Safety/feasibility of the recommended phase II dosing for gemcitabine plus trastuzumab and pertuzumab.

Phase II: Overall response rate (CR+PR) using RECIST 1.1 with the combination of gemcitabine plus trastuzumab and pertuzumab.

2.2 SECONDARY OBJECTIVES

Phase I and II: Progression free survival (PFS), biomarker and immune based correlates as it relates to clinical benefit from the combination

Phase II: Safety/toxicity of the combination using CTCAE 4.0

3. STUDY DESIGN

Single arm, non-randomized, open label phase I/II multisite Simon two stage minimax trial.

3.1 DESCRIPTION OF THE STUDY

Patients with metastatic HER2+ breast cancer who have progressed on at least one prior line of chemotherapy in combination with a HER2 targeting agent (i.e. T-DM1, trastuzumab, pertuzumab, or lapatinib) will be enrolled in this phase I/II single arm study.

Screening/baseline testing following consent:

- Review of clinical records for eligibility criteria
- History and physical exam
- Diagnostic quality CT scan of the thorax/abdomen/pelvis
- Nuclear medicine bone scan should be performed for those with known or suspected bone metastases
- Echocardiogram or MUGA scan
- Complete metabolic panel and complete blood count with differential

Patients should have all baseline evaluations completed and initiate study treatment within 28 days of signing consent. Routine CT scans that were done prior to consent but still fall within the 28 day window prior to the anticipated treatment start date may be used provided they are of adequate quality and can be reviewed by study site radiologists for measurable disease. Patients should have measurable disease on baseline scans and have target lesions selected as per RECIST 1.1 criteria (http://www.eortc.be/recist/). Qualified patients will then undergo central registration in Moffitt's Oncore system, the study coordinator will be sent a confirmation with treatment assignment via fax or email, and then treatment is initiated.

Phase I portion:

The phase I trial will start at the recommended phase 2 dose (RP2D) for gemcitabine but will have a de-escalation dose levels in the event that an unacceptable toxicity requires dose reduction.

Dose level 0 = gemcitabine (1200mg/m2) IV D1,8 q21 days

Dose level -1 = gemcitabine (1000mg/m2) IV D1,8 q21 days

Dose level -2 = gemcitabine (850mg/m2) IV D1,8 q21 days

Trastuzumab will be given using an 8mg/kg loading dose on C1D1, followed by 6mg/kg IV on subsequent cycles q21 days.

Pertuzumab will be given using an 840mg IV loading dose on C1D1, followed by 420mg IV on subsequent cycles q21 days.

There will be no dose adjustments or reductions for either trastuzumab or pertuzumab. A sample order sheet is included in Appendix A for each of the agents along with the supportive premedications given during administration.

The phase I trial will use a typical 3+3 design. The RP2D will be the dose level where 0-1 dose limiting toxicities (DLTs) in six patients occur. Six patients should be treated at the RP2D to acquire sufficient safety data to proceed with the phase II portion of the study. If 2 or more DLTs occur at a given dose level then accrual to that dose level is stopped and subsequent patients will be enrolled at the dose level below. In the event 2 DLTs occur at the -2 dose level then accrual to the trial will be held and discussions with the sponsor will take place to determine if there is a feasible protocol amendment that would allow the trial to continue or if the trial should be permanently closed. During the phase I portion of the study patients should be treated at least 1 week (+/- 2 days) apart to allow for a margin of safety.

Phase I DLT definition:

The definition of a DLT is any 1st cycle toxicity which meets the following criteria: ≥G3 non-hematologic toxicity or ≥G4 hematologic toxicity that is not expected with gemcitabine plus trastuzumab and not manageable with routine supportive care causing a delay of treatment greater than 3 weeks.

Phase II Portion:

The phase II portion of the study can commence as soon as the last patient on the phase I completes one cycle of therapy. It will be a single arm, open label, non randomized, Simon two stage minimax phase IIa. The first stage of the trial will enroll 20 patients. If there are 8 or fewer objective responses out of the first 20 evaluable patients enrolled then the trial will stop early for futility. If 9 or more objective responses are seen in the first 20 evaluable patients, then the second stage of the trial consisting of 17 additional evaluable patients will commence.

Patients will undergo consent, screening, central registration as previously described, and start treatment at the RP2D. Patients in the phase II can be initiated on treatment concurrently with no delay required between individual patients.

Evaluability of patients for endpoints:

Any patient who receives any dose of the study treatment will be evaluated for the safety/toxicity endpoints in the trial. To be considered evaluable for the primary efficacy endpoint (ORR) the patient must undergo two treatment cycles followed by a response scan. Those un-evaluable for the efficacy endpoint may be replaced with approval from the study sponsor.

3.2 RATIONALE FOR STUDY DESIGN

The study population is patients with previously treated, metastatic HER2+ breast cancer. The compelling reason for studying this particular population is that there is ample evidence that continued targeting of HER2 signaling through progression on prior HER2 directed therapy confers clinical benefit (i.e. Trastuzumab Beyond Progression study). With the inclusion of newer HER2 targeted therapies such as first line pertuzumab combination therapy and T-DM1, there is little data regarding the efficacy of pertuzumab/trastuzumab combined with salvage chemotherapy in previously treated patients. This trial seeks to provide some clinical information regarding safety and efficacy for gemcitabine/pertuzumab/trastuzumab in this patient population.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure:

Phase I: Establishing the recommended phase 2 dose for the combination of gemcitabine+trastuzumab+pertuzumab with safety data described using CTCAE 4.0 terminology.

Phase II: Objective response rate (CR+PR) using RECIST 1.1 criteria for the combination of gemcitabine+trastuzumab+pertuzumab at the recommended phase 2 dose.

3.3.2 Secondary Outcome Measures:

- Stable disease > 6 months, median progression free survival (in months) for all patients evaluable for response
- Safety/toxicity using CTCAE 4.0 frequency data
- Exploratory analysis for correlation between clinical outcomes (ORR, PFS) and levels of circulating MDSCs (HLA-DR-CD33+), NK cells (CD56+), and ratio of CD4+/CD14+HLA-DRlow using multiparametric flow cytometry at baseline, weeks 4,7, and 10
- Exploratory analysis for correlation between clinical outcomes (ORR, PFS) and the level of HER2-HER3 dimerization as measured by a proximity ligation assay on isolated circulating tumor cells

3.3.3 Ancillary Safety Outcome Measures

Cardiac safety monitoring by measuring ejection fraction via serial MUGA scans during treatment q3 months

3.4 SAFETY PLAN

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 4.5).

[redacted]

[redacted]

[redacted]

3.4.2.1 Metastatic Breast Cancer Protocols (Refer to Appendix F)

Refer to Appendix F for Algorithm for Continuation and Discontinuation of HER2 Targeted Study Medication for MBC Trials

If LVEF is <40% or is 40-50% with a 10% or greater absolute decrease below the pretreatment value, withhold pertuzumab and trastuzumab and repeat LVEF assessment within approximately 3 weeks.

If after a repeat assessment, the LVEF has not improved, or has declined further, discontinuation of pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

For delayed or missed doses, if the time between 2 sequential infusions is less than 6 weeks, the 420 mg IV dose of Perjeta should be administered. Do not wait until the next planned dose. If the time between 2 sequential infusions is 6 weeks or more, the initial dose of 840 mg Perjeta should be re-administered as a 60 minute IV infusion followed every 3 weeks thereafter by a dose of 420 mg IV administered over 30-60minutes.

Pertuzumab should be withheld or discontinued if trastuzumab treatment is withheld or discontinued.

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

4.0 MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Subject Selection

Metastatic HER2+ breast cancer patients who present for treatment at participating Southeast Phase 2 Consortium study sites would be selected for consent and treatment on this study protocol.

4.1.2 Inclusion Criteria

- Adult males or females (aged 18 or older) with histologically confirmed, metastatic HER2+ (by IHC 3+ or FISH ratio ≥ 2.0) breast cancer
- Have progressed on at least one prior line of chemotherapy plus HER2 directed therapy such as trastuzumab and/or pertuzumab in the metastatic setting. T-DM1 would count as a line of therapy and patients previously treated with T-DM1 are eligible

- Have not been treated with gemcitabine in the metastatic setting
- Measurable disease per RECIST 1.1 criteria
- ECOG performance status ≤ 2
- Left Ventricular Ejection Fraction (LVEF) $\geq$ 50% at baseline as determined by either ECHO or MUGA
- Adequate bone marrow function as indicated by the following:
  ANC >1500/μL

  Platelets ≥100,000/μL

  Hemoglobin >10 g/dL
- Adequate renal function, as indicated by creatinine ≤1.5× upper limit of normal (ULN)
- Adequate liver function, as indicated by bilirubin ≤1.5× ULN, AST or ALT <2× ULN unless related to metastatic breast cancer to the liver (in which case AST/ALT < 5x ULN is allowed).
- Signed informed consent
- Adequate birth control in sexually active women of childbearing potential

4.1.3 Exclusion Criteria

- Active uncontrolled infection or major concurrent illness which in the opinion of the investigator would render the patient unsafe to proceed with the study
- Uncontrolled central nervous system metastases. Treated, non-progressing CNS disease (documented by brain MRI) off corticosteroids for at least 1 month are eligible
- Pregnant or lactating women
- Prior chemotherapy within the last 3 weeks (last 6 weeks for nitrosureas/mitomycin)
- Prior radiation therapy within the last 4 weeks; prior radiation therapy to indicator lesion (unless objective disease recurrence or progression within the radiation portal has been documented since completion of radiation).
- Other concomitant active malignancies
- History of significant cardiac disease, cardiac risk factors or uncontrolled arrhythmias
- Ejection fraction <50% or below the lower limit of the institutional normal range, whichever is lower
- Hypersensitivity to any of the study medications

- Untreated psychiatric conditions preventing informed consent

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open label, single arm study. All patients enrolled will receive the combination of gemcitabine/pertuzumab/trastuzumab.

[redacted]

4.3.3 Trastuzumab Dosage, Preparation, and Storage

a. Dosage

The recommended initial loading dose is 8 mg/kg trastuzumab administered as a 90-minute infusion. The recommended maintenance trastuzumab dose is 6 mg/kg q3wk and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. Trastuzumab may be administered in an outpatient setting. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION). If different from above the specific dose and regimen of trastuzumab to be used should be described here.

[redacted]

[redacted]

[redacted]

4.3.4 Pertuzumab Dosage, Preparation, Administration, and Storage

a. Dosage

The initial dose of pertuzumab is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 - 60 minutes

When administered with pertuzumab the recommended initial dose of trastuzumab is 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg.

[redacted]

c. Administration

Treatment may be administered in an outpatient setting by administration of a 840 mg pertuzumab loading dose by intravenous (IV) infusion over 60 minutes, followed every 3 weeks thereafter by a dose of 420 mg administered over a

period of 30 - 60 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.**

When administered with pertuzumab, the recommended initial dose of trastuzumab is 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg.

If pertuzumab and trastuzumab are being administered concomitantly with chemotherapy, monoclonal antibody administration should precede chemotherapy administration. Patients should be observed for fever and chills or other infusion-associated symptoms. If chemotherapy is discontinued during the treatment phase, either because of completing a planned number of cycles of chemotherapy, or because of chemotherapy related toxicity.

Trastuzumab and Pertuzumab Infusion Time and Post-Infusion Observation Period			
		Infusion Time (minutes)	Post-Infusion Observation Period (minutes)
HP Loading Doses (8 mg/kg and 840mg)	First Infusion	60	60
HP (6mg/kg and 420mg) q3w	Subsequent Infusions	30-60 [a]	30 [a]
[a] Only if previous dose was well tolerated.			

4.3.5 Trastuzumab and Pertuzumab Dosage Modification

Dose modification of trastuzumab and pertuzumab is not permitted.

4.3.6 Trastuzumab and Pertuzumab Overdosage

There is no experience with overdosage in human clinical trials.

4.3.7 GEMCITABINE PREPARATION AND DOSING

Refer to the full prescribing information for gemcitabine to obtain formulation and preparation information at [redacted] The initial dosing of the gemcitabine will be the recommended phase 2 dose identified in the phase 1 portion of the study.

4.3.8 GEMCITABINE DOSE REDUCTIONS/DELAYS

The following dose reduction recommendations for subsequent day 1 dosing are described below. These dose reductions are permanent. Two dose reductions

are allowed while on study. The first table is for hematologic toxicity and the second table is for non-hematologic toxicity. Any grade 2 or greater pneumonitis due to gemcitabine warrants discontinuation of gemcitabine permanently and administration of steroids.

HEMATOLOGIC TOXICITIES

Situation	Gemcitabine
First episode of febrile neutropenia OR ANC ≤ 1000/mm^3 or platelets < 100 k by Day 1 of next cycle	Reduce by 20% of original starting dose
Second episode of febrile neutropenia OR ANC ≤ 1000/mm^3 by Day 1 or platelets < 100 k	Reduce by 40% of original starting dose
First episode of Grade 4 thrombocytopenia OR bleeding associated with thrombocytopenia	Reduce by 20% of original starting dose
Second episode of Grade 4 thrombocytopenia OR bleeding associated with thrombocytopenia	Reduce by 40% of original starting dose

NON-HEMATOLOGIC TOXICITIES

NCI CTC Grade	Gemcitabine
0 – 2 [1,2]	No change form original starting dose
3 (except nausea and vomiting or Grade 4[2]	Reduce by 20% of original starting dose
Second episode of Grade 3 or 4 toxicity[2]	Reduce by 40% of original starting dose
Third episode of Grade 3 or 4 toxicity[2]	Remove subject from trial

Gemcitabine dosage adjustment for hematological toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on day 8 of therapy. If marrow suppression is detected, gemcitabine dosage should be modified according to guidelines in the table below.

Day 8 Dosage Reduction Guidelines for Gemcitabine	Platelet count (x10^6/L)	% of full dose

Absolute granulocyte count (x 10^6/L)			
≥1000	And	≥100,000	100
999-750	And/Or	75,000-99,999	80
<750	And/Or	<75,000	Hold

If a day 8 gemcitabine dose is held due to toxicity then that dose will not be made up for the remainder of that cycle. With the exception of pneumonitis as described previously, dosing on d8 should be held for any G3-4 non-hematologic toxicity. Subsequent dosing should follow the same dose reductions shown in the table once the toxicity has resolved to a G0-1. In addition, physician judgment can be exercised in initiating subsequent cycle dose reductions for a grade 2 or less toxicity due to concerns over patient tolerance of the chemotherapy.

4.4 CONCOMITANT AND EXCLUDED THERAPY

All standard anti-emetics, supportive care medications, growth factors such as GCSF or pegylated GCSF are permitted while on study treatment. Concomitant bisphosphonates or denosumab for bone metastases are permitted if these agents were initiated prior to initiating the study therapy and patients are stable on these medications. Aspirin, platelet inhibiting agents, and anticoagulants are permitted only if they are absolutely medically necessary (i.e. treatment for DVTs/PEs or cardiac stents/CAD) and as long as they are held when medically indicated due to thrombocytopenia from gemcitabine. No other cytotoxic, targeted, or anti-hormonal agents intended to treat the underlying malignancy should be administered concurrently with the study treatment.

4.5 STUDY ASSESSMENTS

Study Calendar (Showing first 3 cycles):

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[c]
Trastuzumab and Pertuzumab		A			A			A			A			
Gemcitabine		B	B		B	B		B	B		B	B		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											X	
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Height	X													
Weight	X	X			X			X			X			X
Performance status	X	X			X			X			X			X
CBC w/diff, plts	X	X	X		X	X		X	X		X	X		X
Serum chemistry[a]	X	X			X			X			X	X		X
EKG (as indicated)	X													
Adverse event evaluation		X----------											X	X
Tumor measurements	X	Tumor measurements are repeated after every *6* weeks (+/- 3 days). Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic evaluation	X	Radiologic measurements should be performed every *6* weeks (+/- 3 days)												X
B-HCG	X[b]													
MUGA or echocardiogram (q3 months +/- 1 week)	X												X	X
CTCs, Immune response markers(1st 3 cycles only)	X				X			X			X			

A: *Trastuzumab and Pertuzumab* 6mg/kg and 420mg IV q21 days, following loading dose on CID1
B: *Gemcitabine at RP2D on days 1,8 IV q21 days*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum or urine pregnancy test (sexually active women of childbearing potential).
c: Off-study evaluation to be completed within 30 days of last study dose.

4.5.1 Assessments during Treatment

The following are recommended evaluations:

- Complete metabolic panel day 1 of each cycle, complete blood count with differential prior to each gemcitabine administration
- Regular assessment of cardiac function by either MUGA or echocardiography q3months +/- 1 week while on treatment. If trastuzumab is discontinued for a

decline in LVEF, a repeat measure of LVEF will be obtained in 1 month to assess whether the decline has resolved.

- Radiologic imaging for response assessment should be obtained at baseline and after every 6 weeks (+/- 3 days) of study therapy. This includes diagnostic CT of thorax/abdomen/pelvis with contrast, and bone scans in patients with known or suspected bone metastases.

4.5.2 Follow-Up Assessments

Patients would be followed up 30 days after last study therapy, or in the event of a study treatment related adverse event until resolution, stabilization, or death. Follow up intervals for these adverse events will be as clinically indicated by their treating oncologist.

4.6 DISCONTINUATION OF PROTOCOL-SPECIFIED THERAPY

Protocol-specified therapy may be discontinued for any of the following reasons:

- Progressive disease
- Unacceptable toxicity
- Pregnancy on study
- Patient non-compliance or election to discontinue therapy (for any reason)
- Physician's judgment
- Adverse event causing a dosing delay of greater than 28 days

4.7 SUBJECT DISCONTINUATION

Subjects may be discontinued for any of the reasons outlined in section 4.6. Patients experiencing study treatment related adverse events requiring discontinuation should be treated as medically indicated by their treating oncologist. The patient should be followed until the adverse event has stabilized/resolved or death. Patients discontinuing prematurely for non-adverse event related issues should be followed up 30 days from the last study treatment. Patients who are non-evaluable for the primary endpoint due to premature discontinuation can be replaced with approval from the study sponsor and IRB (if applicable).

4.8 STUDY DISCONTINUATION

Genentech Study Center and the Principal Investigator have the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects (see early stopping rule 4.8.1)
- Subject enrollment is unsatisfactory

- Data recording are inaccurate or incomplete
- Study protocol not followed

4.8.1 Early stopping rule for toxicity: There will be an interim analysis for toxicity after the first stage of the phase II trial (20 patients) has completed accrual. The study will terminate early for excessive toxicity if >50% of the patients experience a study treatment related (probably or definitely) grade 3/4 toxicity requiring permanent discontinuation of treatment despite appropriate supportive care/dose reductions.

4.9 STATISTICAL METHODS

4.9.1 Analysis of the Conduct of the Study

All data regarding subject enrollment, patient flow, patient demographics, performance status, prior therapy, screening success/failures, number of study treatments administered, disposition, and follow up will be captured via eCRFs into the Oncore study system. Descriptive statistics will be used to characterize the study patients. Patients who receive at least one treatment on study are eligible for safety analyses. Patients who receive at least two cycles of therapy followed by response scans will be evaluable for the efficacy analyses.

4.9.2 Analysis of Treatment Group Comparability

Selected exploratory retrospective subset analyses will be undertaken only when possible to evaluate impact of demographics, lines of prior treatment (1 or >1), prior pertuzumab exposure, or performance status (0-1 or 2).

4.9.3 Efficacy Analysis

Primary Endpoints:

Phase I: Establishing the RP2D of gemcitabine/pertuzumab/trastuzumab based on safety/feasibility. Toxicity events will be tabulated and summarized for all patients at each dose level using CTCAE 4.0 criteria. The dose level at which 0-1 DLTs occur in six patients (as defined in section 3.1) will be selected as the RP2D.

Phase II: Overall response rate (CR+PR) (ORR) using RECIST 1.1 criteria: The 95% confidence interval for the response rate will be calculated based on the exact binomial distribution. Those patients in the phase I and phase II portions who have undergone at least two cycles of therapy at the RP2D followed by a response scan will be evaluable for this primary endpoint.

Secondary Endpoints:

Median progression free survival (in months): The time-to-event data will be summarized using Kaplan-Meir curve method for all patients who are evaluable for the ORR endpoint.

Clinical benefit rate (CR+PR+SD) using RECIST 1.1 criteria: Defined as proportion of patients evaluable for response who attain a complete response,

partial response, or stable disease for > 6 months. This will be calculated using the same method as the ORR endpoint.

Safety/toxicity: CTCAE 4.0 descriptive/frequency data for all patients who receive any study treatment will be tabulated. See safety analysis section below.

4.9.4 Safety Analysis

Toxicity events will be tabulated and summarized for all patients at each dose level (Phase I) and each stage (Phase II) using CTCAE 4.0 criteria. Descriptive analysis including frequency of each AE (all grades and grade 3/4/5) will be provided. Demographics, baseline characteristics, and compliance for the study patients will be summarized. An interim analysis after the first stage of the phase II trial as previously described in 4.8.1 will evaluate for excessive toxicity.

The incidence of clinically significant CHF will be estimated. Symptomatic CHF is defined as the occurrence of objective findings on clinical examination (e.g., rales, S3, elevated jugular venous pressure) and confirmed by chest X-ray and either MUGA or ECHO.

4.9.5 Missing Data

Whenever possible the source data (patient records, scans, labs) will be reviewed to correct any missing data elements in the CRFs entered into Oncore. In the event that the missing data cannot be obtained then the data will be counted as such for all efficacy and safety analyses.

4.9.6 Determination of Sample Size

The phase I trial will use the standard 3+3 design. The RP2D will be the dose level where 0-1 dose limiting toxicities (DLTs) in six patients occur. Six patients should be treated at the RP2D to acquire sufficient safety data to proceed with the phase II portion of the study. No PK analysis is planned as there is no expected meaningful drug interaction. Between 6 -18 patients will be enrolled in

the phase I portion of the study, depending on DLTs. Patients treated in the phase I at the RP2D will count towards the efficacy analysis as well.

Phase II will be a single arm, open label, multi-center study. The primary endpoint will be objective response rate (ORR), with PFS and safety as secondary endpoints. Simon's two-stage minimax design will be used. The null hypothesis that the true ORR is 40% (based on ORR of 32-47% in prior gemcitabine/trastuzumab trials) will be tested against the alternative that the ORR is greater or equal to 55% with a probability of early termination of 0.60. If there are 8 or fewer responses in the first 20 patients, the study will be stopped. Otherwise, 17 additional evaluable patients will be accrued for a total of 37 (including 6 patients from Phase I). The null hypothesis will be rejected if 19 or more responses are observed in 37 patients. This design yields a type I error rate of .0996 and power of .703 when the true response rate of the experimental therapy is 55%.

4.10 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

[redacted]

[redacted]

5. REPORTING OF ADVERSE EVENTS

5.1 ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to study treatment, all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with metastatic breast cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study treatment (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship

to study treatment administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

5.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A

preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study treatment should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior study treatment exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

[redacted]

5.4 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

[redacted]

5.5 Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of trastuzumab and pertuzumab. An unexpected adverse event is one that is not already described in the trastuzumab and pertuzumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use trastuzumab and pertuzumab. An unexpected adverse event is one that is not already described in the trastuzumab and pertuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

[redacted]

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current *curriculum vitae* of the Principal Investigator
- Written documentation of IRB approval of protocol
- A signed Clinical Research Agreement

6.2 STUDY COMPLETION

The following materials are requested by Genentech when a study is considered complete or terminated:

- Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

[redacted]

[redacted]

6.3 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file.

6.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific adverse event requirements that investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 STUDY MONITORING REQUIREMENTS

The study will be internally monitored according to institutional requirements and as stipulated by the study sponsor.

6.6 DATA COLLECTION

All patient, safety, treatment, response and disposition data will be entered on electronic CRF forms within the Oncore trial management system by clinical trial coordinators/data specialists trained in its use. Data security will be maintained using both software (authorized user accounts with access restrictions) and physical measures (systems will be in locked rooms). All efforts should be made to enter routine study data within two weeks from the date of the patient encounter or study procedure.

6.7 STUDY MEDICATION ACCOUNTABILITY (IF APPLICABLE)

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the NCI drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

6.8 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB for each study site, if appropriate.

6.9 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Genentech will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with the record retention policies of the relevant national and local health authorities.

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APPENDIX A SAMPLE ORDER SET FOR STUDY THERAPY

GEMCITabine-standard

DIAGNOSIS: Breast	HT: IN CM	WT: LB KG	BSA: M^2	9/2012 Last Reviewed
DOSAGE WEIGHT: (CIRCLE ONE) ACTUAL / IDEAL / ADJUSTED WT		IDEAL WT: KG	ADJUSTED WEIGHT: KG	
STUDY: (CIRCLE ONE) Y N	PROT #	DRUG REGIMEN: GEMCITabine standard	COURSE#:	START DATE:
LABS DRAWN ON: DATE		Lit. Reference: JCO 1995;13:2731-2736		
INITIATE TREATMENT IF:	WBC:	PLT: ≥100,000	ANC: ≥1000	CR: BILI:

PRE-CHEMO LAB ORDERS: CBC/diff weekly, CMP day 1 only

ANTINEOPLASTIC AND RELATED DRUGS (Antiemetics and Hydration)						ADMINISTRATION RECORD						
SEQ	Drug	Dose Mg/m^2, Mg/Kg	Dose MG	Route PO, IV	Solution And Volume	Duration Rate Frequency	T Date i m e Week 1	T Date i m e Week 2	T Date i m e Week 3	T Date i m e	T Date i m e	T Date i m e	T Date i m e
	Prochlorperazine 10mg PO 30 min prior to chemotherapy												
	Check box if indicated: ☐ Dexamethasone 8mg PO 30 min prior to chemotherapy												
	GEMCITabine _____mg ($1000mg/m^2$) in 250ml 0.9% NaCl IVPB over 30 min weekly for _____week(s),followed by _____week(s) off												

Date/Time	Signature	Date	Signature	Date	Signature
	MD		RPh		RPh
Print Dr Name + Pager#			RN		RN
	RPh		RN		RN
	RN		RN		RN
	RN		RN		RN
	RN		RN		RN

Infusion Chair time: 75 min

MOFFITT CANCER CENTER

Created 05/11

Inpatient/Outpatient Chemotherapy Orders and Administration Record

WHITE-NURSING WORKSHEET /PERMANENT CHART MAR

PERTUzumab/TRASTuzumab/DOCetaxel Q 21

DIAGNOSIS: Metastatic HER2 Breast Cancer	HT: IN CM	WT: LB KG	BSA: M^2	07/2012
DOSAGE WEIGHT: (CIRCLE ONE) N/A		IDEAL WT: KG	ADJUSTED WEIGHT: KG	
STUDY: (CIRCLE ONE) Y (N)	PROT # N/A	DRUG REGIMEN: PERTUzumab Q 21	COURSE#:	START DATE:
LABS DRAWN ON: DATE		Lit. Reference: N Engl J Med 2012 Jan 12;366(2):109-19		
INITIATE TREATMENT IF:	WBC :	PLT:	ANC:	CR: BILI:

PRE-CHEMO LAB ORDERS:

ANTINEOPLASTIC AND RELATED DRUGS (Antiemetics and Hydration)						ADMINISTRATION RECORD						
SEQ	Drug	Dose Mg/m2, Mg/Kg	Dose MG	Route PO, IV	Solution And Volume	Duration Rate Frequency	Date Time	Date Time	Date Time	Date Time	Date Time	Date Time	Date Time
	First Infusion Loading Dose: PERTUzumab **840mg** (total dose) IVPB in 250mL 0.9% NaCl IVPB over 60 minutes. Observe for 60 min post infusion							[redacted]					
	Second Infusion PERTUzumab **420mg** (total dose) IVPB in 250mL 0.9% NaCl IVPB over 30 minutes if no prior reaction or 60 min if prior reaction. Observe for 30 min if no prior reaction, or 60 min if prior reaction.						[redacted]		[redacted]		[redacted]		[redacted]
	If previous dose not tolerated, continue at previous infusion rate. May give advanced rate with next dose if tolerated												
	Monitor patient for adverse reactions: **Vital signs Q 15 minutes during 1st infusion and 1 hr after.**												
	If fever, chills, rigors, hypotension, pain dyspnea, or nausea occur, stop infusion and call MD. **Acetaminophen 325mg #2 tablets Q 6 hours for fever, chills, rigors** **Diphenhydramine 25 mg IV push Q 4 hours for fever, chills, rigors** **Restart infusion to run at previous infusion rate if symptoms resolve. Call MD if no relief of symptoms. Do not discharge patient without complete resolution of adverse reactions.**												
	Patient has had one of the following to rule out cardiac dysfunction prior to PERTUZumab treatment: Date Result _____ _____ Cardiac Echo _____ _____ MUGA												

Date/Time	Signature	Date	Signature	Date	Signature
	MD		RPh		RPh
Print Dr Name + Pager#			RN		RN
	RPh		RN		RN
	RN		RN		RN
	RN		RN		RN
	RN		RN		RN

Infusion Chair Time: Loading Dose 135 minutes, Subsequent Doses 75 to 135 minutes

MOFFITT CANCER CENTER

Created 07/12

Inpatient/Outpatient Chemotherapy Orders and Administration Record

WHITE-NURSING WORKSHEET /PERMANENT CHART MAR

TRASTUZumab q 21 days

DIAGNOSIS: Breast Cancer	**HT:** IN N/A CM	**WT:** LB KG	**BSA:N/A** M^2 9/2012 Last Reviewed
DOSAGE WEIGHT: (CIRCLE ONE) ACTUAL / IDEAL / ADJUSTED WT		**IDEAL WT:** KG	**ADJUSTED WEIGHT:** KG
STUDY: (CIRCLE ONE) Y N	**PROT #** N/A	**DRUG REGIMEN:** TRASTUZumab q 21 days	**COURSE#:** **START DATE:**
LABS DRAWN ON: DATE		Lit. Reference: N Eng J Med 2005; 353:1659	
INITIATE TREATMENT IF:	**WBC:** N/A	**PLT:** N/A	**ANC:** N/A **CR:** N/A **BILI:** N/A

PRE-CHEMO LAB ORDERS: N/A

SEQ	ANTINEOPLASTIC AND RELATED DRUGS (Antiemetics and Hydration) Drug	Dose Mg/m^2, Mg/Kg	Dose MG	Route PO, IV	Solution And Volume	Duration Rate Frequency	ADMINISTRATION RECORD T Date / Time
	Loading Dose: TRASTUZumab _____ mg **(8 mg/kg)** in 250 ml 0.9% NaCl IVPB over **90 minutes** followed 21 days later by:						
	Subsequent Infusions: TRASTUZumab _____mg (**6 mg/kg**) in 250ml 0.9% NaCl IVPB over **30 minutes** Every 21 days						
	MUGA/ECHO Date LVEF _____ _____ _____ _____						
	Hypersensitivity Reactions: Methylprednisolone 125 mg IV Push x 1 PRN anaphylaxis Diphenhydramine 25 mg IV Push x 1 PRN anaphylaxis HYDROmorPHONE 0.5 mg IV Push x 1 PRN rigors/chills. (May repeat in 15 minutes x 1 if symptoms persist) EpINEPHrine 0.5 mg (1:1000) SQ x 1 PRN anaphylaxis						

Date/Time	Signature	Date	Signature	Date	Signature
	MD		RPh		RPh
Print Dr. Name + Pager#			RN		RN
	RPh		RN		RN
	RN		RN		RN
	RN		RN		RN
	RN		RN		RN

Infusion Chair time: Loading Dose: 105 minutes
Subsequent Doses: 45 minutes

MOFFITT CANCER CENTER

Created 3/11

Inpatient/Outpatient Chemotherapy Orders and Administration Record

WHITE-NURSING WORKSHEET /PERMANENT CHART MAR

APPENDIX B Response Evaluation Criteria in Solid Tumors (RECIST 1.1 Criteria)

The RECIST 1.1 criteria should be used to assess response to treatment. Only subjects with measurable disease should be entered in the study. Measurable disease is defined as the presence of one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques (or as ≥1.0 cm by spiral CT). Evaluable lesions should be followed for the assessment of response. Non-measurable lesions include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitic carcinomatosis, abdominal masses that are not confirmed by CT, and cystic lesions.

All measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

- Complete response (CR)

Disappearance of all evidence of tumor for at least two cycles of therapy. Tumor markers must be normal.

- Partial response

At least a 30% decrease in the sum of the longest diameter of target lesions, taking a reference the baseline sum longest diameter.

- Stable disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

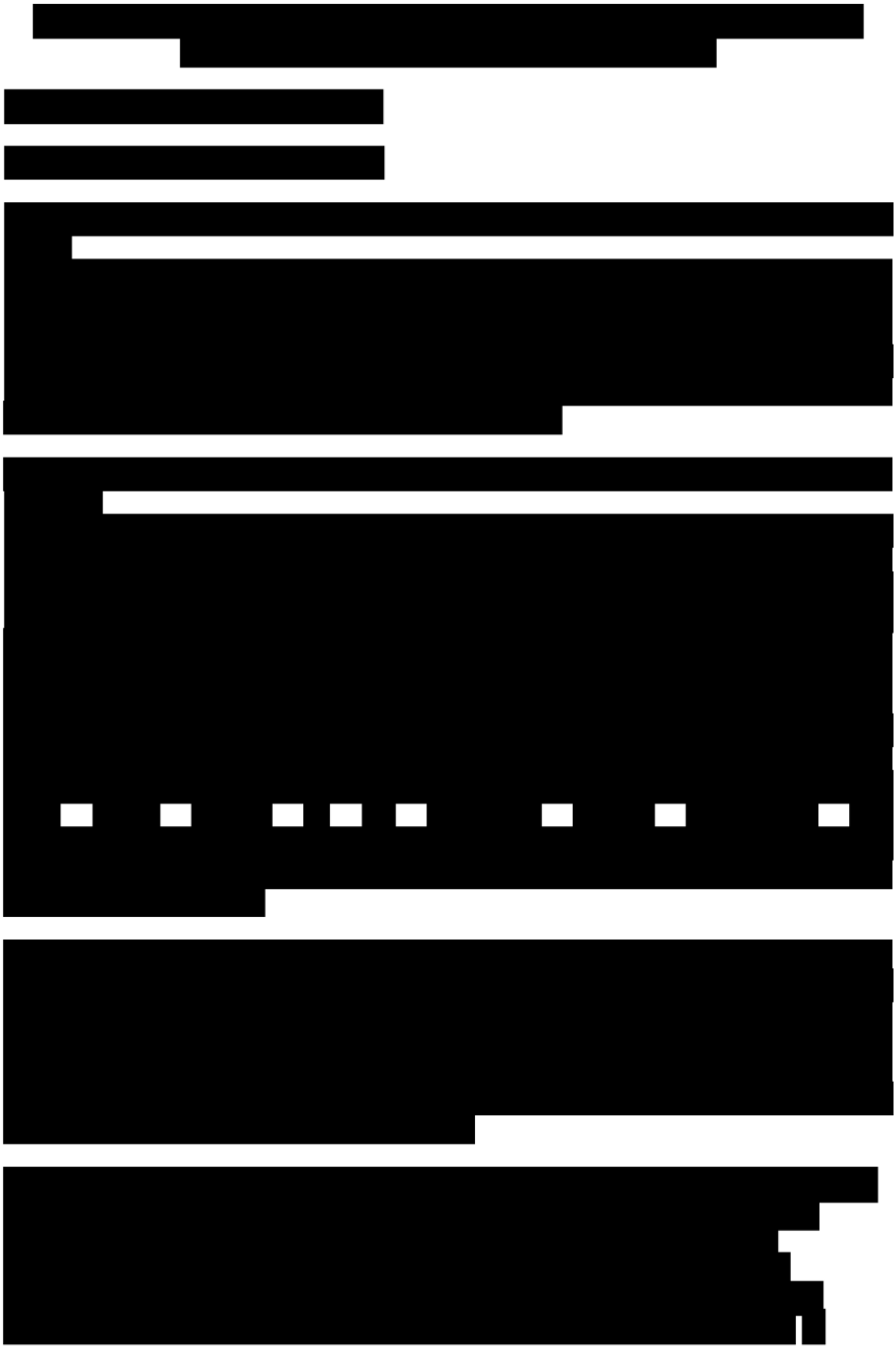
- Progressive disease (PD)

At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the beginning of treatment or the appearance of one or more new lesions.

- Clinical progressive disease

Subjects, who in the opinion of the treating physician investigator have had a substantial decline in their performance status and have clinical evidence of progressive disease may be classified as having progressive disease.

APPENDIX CNational Cancer Institute Common Toxicity Criteria
obtained from http://evs.nci.nih.gov/ftp1/CTCAE/About.html



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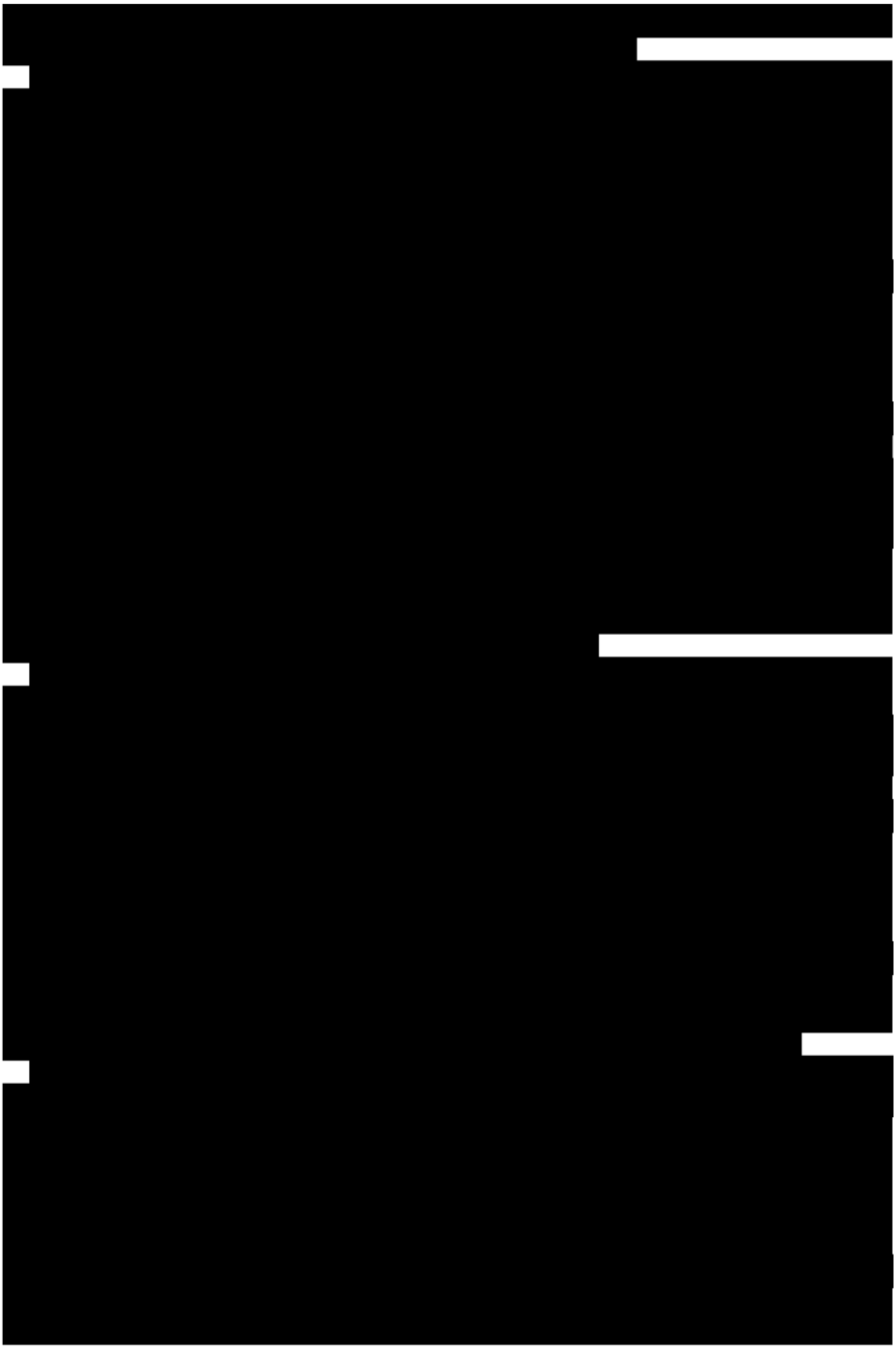

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HFSA Guidelines
Criteria for NYHA functional classification for chronic heart failure patients, functional capacity (130)

CLASS 1	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
CLASS 2	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
CLASS 3	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnea.
CLASS 4	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

HFSA Guidelines
Glossary of Clinical Trials

AVID	Antiarrhythmics Versus Implantable Defibrillators
BEST	Beta-blocker Evaluation of Survival Trial
CAMIAT	Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
CAPRIE	Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events
CASH	Cardiac Arrest Study Hamburg
CHF-STAT	Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy
CHARM	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity
CIBIS	Cardiac Insufficiency BIsoprolol Study
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CIDS	Canadian Implantable Defibrillator Study
COMET	Carvedilol or Metoprolol European Trial
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Trial
DEFINITE	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation
DIAMOND	Danish Investigation of Arrhythmia and Mortality on Dofetilide
DIG	Digitalis Investigation Group
ELITE	Evaluation of Losartan In The Elderly
ELITE II	Losartan Heart Failure Survival Study - ELITE II
EMIAT	Infarction Amiodarone Trial
GESICA	Grupo de Estudio de Sobrevida en Insuficiencia Cardiaca en Argentina
GUSTO 1	Global Utilization of Streptokinase and TPA for Occluded coronary arteries
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MADITII	Multicenter Automatic Defibrillator Implantation Trial II
	Metoprolol in Dilated Cardiomyopathy trial
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Heart Failure
MOCHA	Multicenter Oral Carvedilol in Heart-failure Assessment
MTT	Myocarditis Treatment Trial
OPTIMALL	Optimal Therapy in Myocardial Infarction with the
Angiotensin II	Antagonist Losartan
PRECISE	Prospective Randomized Evaluation of Carvedilol In Symptoms and Exercise
PROVED	Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin
RADIANCE	Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme

RALES	Randomized Aldactone Evaluation Study
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
SAVE	Survival And Ventricular Enlargement
SCD-HeFT	Sudden Cardiac Death in Heart Failure: Trial of prophylactic amiodarone versus implantable defibrillator therapy
SOLVD	Studies Of Left Ventricular Dysfunction
SWORD	Survival With Oral D-sotalol
ValHeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction

Genentech
A Member of the Roche Group

[redacted]

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

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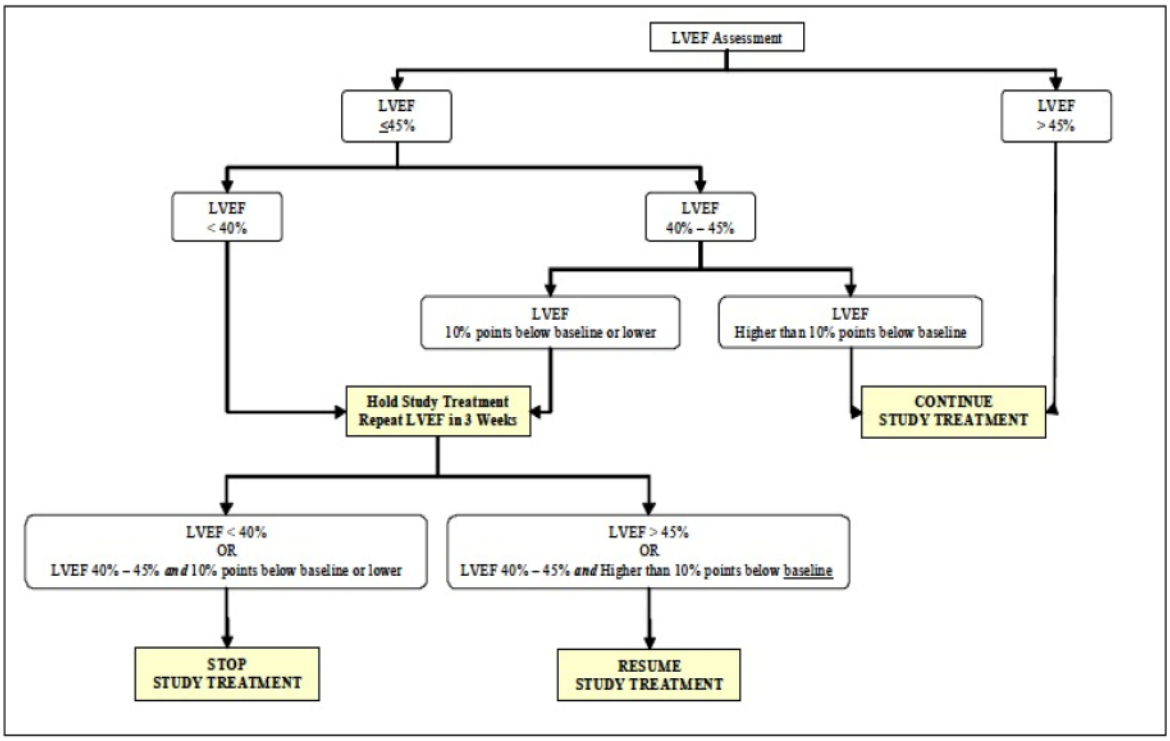
APPENDIX F (MBC ISTs) Algorithm for Continuation and Discontinuation of Pertuzumab and Trastuzumab Based on LVEF Assessments in MBC ISTs



LVEF=left ventricular ejection fraction.
Patients for whom study treatment was permanently discontinued due to a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 3 months, until the LVEF values return to ≥ 50%, or 1 year after the Treatment Discontinuation Visit, whichever comes first. Thereafter, LVEF assessments will be performed annually for up to 3 years after the Treatment Discontinuation Visit.