Open label, multicenter, prospective phase II study to investigate the efficacy and safety of Trastuzumab biosimilar (Herzuma®) plus treatment of physician's choice (TPC) in Patients with HER-2 Positive Metastatic Breast Cancer Who Progressed after 2 or more HER-2 directed Chemotherapy

Compound name: Trastuzumab biosimilar

Phase: II

Protocol version: 3.0 (2018-07-31)

Principal investigator: In Hae Park MD, PhD

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

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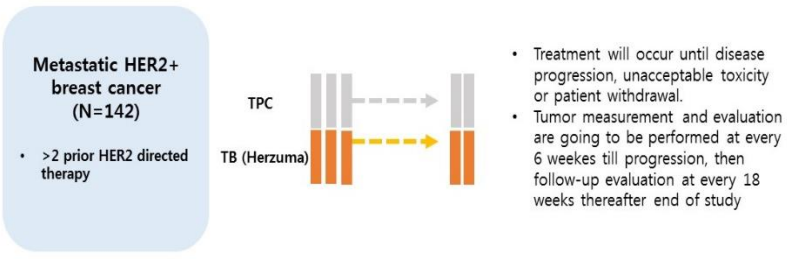
Protocol summary

PROTOCOL SYNOPSIS	
Title	Open label, multicenter, prospective phase II study to investigate the efficacy and safety of Trastuzumab biosimilar plus treatment of physician's choice (TPC) in Patients with HER-2 Positive Metastatic Breast Cancer Who Progressed after 2 or more HER-2 directed Chemotherapy
Study duration	Sep 2018 – Sep 2021 (24 month enroll and additional 1-year follow-up)
Study chair/ Institution	In Hae Park, M.D., Ph.D National cancer center, Goyang, Korea
Study Sub-investigators	Breast subcommittee, KCSG
Study method	Multicenter, Prospective, Single-arm, Phase II study
Study hypothesis	The combination of trastuzumab biosimilar plus TPC will provide a benefit in terms of progression free survival in patients with HER2-positive metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy.
Study Objectives	**1. Primary Objective** ● Progression free survival (PFS): defined as the time from study entry until the first observation of disease progression according to the above schedule or death due to any cause. **2. Secondary Objectives** ● Objective response rate (ORR) defined as the percentage of patients experiencing confirmed complete response (CR) and partial response (PR) assessed by RECIST criteria v.1.1 ● Overall survival (OS): defined as the time from study entry until death ● Safety ● Biomarker: Genetic aberrancies in tissue and plasma, Immune cell profile in tissue and PBMC, Ag-specific T cell frequencies before and after treatment, Th1 vs Th2 cytokine profile, HER2 CNV in cell free tumor DNA, antibody dependent cellular cytotoxicity (ADCC) ● QoL: measured by the European Organization for Research and Treatment Care Quality of Life Questionnaire
Study Rationale	Trastuzumab combined with chemotherapy has been approved as the first line therapy in HER2+ metastatic breast cancer. When patients experienced progression beyond trastuzumab containing therapy, T-DM1 is considered as the second line therapy followed by trastuzumab plus any other chemotherapeutic agents or lapatinib plus capecitabine. A biosimilar drug is a biological product that is highly similar to a licensed biological product, with no clinically meaningful differences in terms of safety, purity, or potency. Several

	trastuzumab biosimilar products have been approved after efficacy and safety studies which were usually as the first line setting with taxane combined. Even though trastuzumab biosimilar drugs demonstrated similarity of equivalence with trastuzumab in these studies, the efficacy of their second use beyond progression with other chemotherapeutic agents has not been tested yet. In addition, we don't have any data regarding possible cross reactivity between trastuzumab and trastuzumab biosimilar drugs. In this study, we plan multicenter phase II clinical trial to test the efficacy, safety and immunogenicity of trastuzumab biosimilar in combination with TPC in patients with HER2+ metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy.
Subject Selection	**1. Eligibility criteria** 1) Patient is an adult, female ≥ 19 years old at the time of informed consent. 2) Patient has histologically and/or cytologically confirmed diagnosis of HER2-positive breast cancer (HER-2/neu 3+ as defined by immunohistochemistry and/or HER-2/neu gene amplification as defined by fluorescence in situ hybridization). 3) Metastatic or unresectable disease documented on diagnostic imaging studies. 4) Prior 2 or more HER-2 directed therapy for metastatic disease is mandatory. 5) Patient must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1) 6) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 7) Adequate bone marrow and organ function including: a) WBC ≥ 3500/ml; b) Platelets ≥ 100,000/ul; c) Hemoglobin >9.0 g/dl; d) Total bilirubin ≤ 1.5x ULN; e) AST and ALT < 2.5 x ULN; f) Alkaline phosphatase <2.5x ULN; g) Creatinine ≤ 1.5x ULN or CCr >60 ml/min for patients with abnormal serum Cr level function. 8) Life expectance longer than 3 months 9) Patient has an adequate left ventricular ejection function of at least 50 % at baseline, as measured by echocardiography. 10) Written informed consent **2. Exclusion criteria** 1) Patient is pregnant or lactating, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. 2) Patient has symptomatic and unstable CNS metastases, except for treated brain metastases. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants (stable dose) are allowed. 3) Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus syndrome (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. Baseline viral assessment is not required in patients with no known infection. 4) Major surgery within 4 weeks of first dose of investigational product or not fully recovered from any side effects of previous procedures. 5) Any other malignancy within 3 years prior to first dose of investigational product except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of

	the cervix. 6) QTc interval >480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes. 7) Any of the following within 6 months of first dose of investigational product myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE v. 4.03 Grade ≤2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism. 8) History of symptomatic interstitial pneumonitis. 9) Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
Study Design & Treatment plan	● This study is a multicenter, prospective, single-arm, phase II study to evaluate the efficacy, safety and immunogenicity of trastuzumab biosimilar in combination with TPC in patients with HER2+ metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy. ● Study drug information, dosage, and mode of administration - Trastuzumab biosimilar, Herzuma®, Celltrion, Inc. (Incheon, Republic of Korea): Intravenously administered on cycle 1 day 1 at a dose of 8mg/kg, then at a dose of 6mg/kg every 3 weeks - Treatment of physician's choice (TPC): gemcitabine, vinorelbine, eribulin, capecitabine, nab-paclitaxel ; treatment cycles will be 3 weeks and dosages will be determined by each investigator's discretion. ● Treatment will occur until disease progression, unacceptable toxicity or patient withdrawal. ● Tumor measurement and evaluation are going to be performed at every 6 weekes till progression, then follow-up evaluation at every 18 weeks thereafter end of study. 
Statistical Consideration	**1. Sample size**

	The primary object of this study is to assess PFS in patients with HER-2 positive metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy. One sided type I error rate 0.1, power 80%; 24 months of accrual period and 12 months of follow-up. H0 = 2.8 months, H1=3.8 months. Then, a total of 108 patients will be needed in this trial. Considered 10% drop-out rate, we will enroll 119 patients. (ref. TH3RESA trial, Lancet Oncol 2014;15:689-99) **2. Efficacy analyses** ● Primary endpoint : PFS - The PFS curve for single arm will be estimated using the Kaplan-Meier method. ● Secondary endpoint of ORR and OS : - ORR will be presented as a proportion and its corresponding 95% exact CI. - The OS curve for single arm will be estimated using the Kaplan-Meier method. **3. Biomarker analyses** ● Immune cell profiling and cytokine analysis using peripheral blood ● ADCC analysis ● CfDNA analysis : NGS, ddPCR ● Not all exploratory analyses will be included in the Clinical Study Report (CSR) unless they present meaningful findings or rare relevant to subject management. **4. QoL analyses** ● Baseline – after 3 Cycles – at the end of treatment date ● Measured by the European Organization for Research and Treatment Care Quality of Life Questionnaire (Korean version, EORTC QLQ-C30)
Site of study	This protocol is performed as an : □Inpatient □Outpatient ■Both
	Where will study be conducted : ■Multi-Center Arrangements: KCSG breast subcommittee member sites

Study flow chart

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Visit Identifier	**Baseline**	**Cycle 1-2**		**Cycle 3 and Beyond**		**Follow up**
Protocol Activity	**Screen/ Baseline[1]**	**Day 1**	**Day 8**	**Day 1**	**(Day 8)**	**Follow Up[22]**
Informed Consent[2]	X					
Tumor History[3]	X					
Medical History[4]	X					
Signs and Symptoms[5]	X	X	X	X	X	
Physical Examination[6]		X	X	X	X	
Weight/height		X	X	X	X	
Vital Signs[7]		X	X	X	X	
ECOG Performance Status[8]	X	X	X	X	X	
Laboratory[9] Assessments						
Hematology[10]	X	(X)	X	X		
Blood Chemistry[11]	X	(X)		X		
Urinalysis[12]	X					
Coagulation[13]	X					
Pregnancy Test[14]	X					
Triplicate ECG (12-lead)[15]	X					
Echocardiography or MUGA scan[16]	X			X		
Adverse Events (AE)[17]	X	→	→	→	→	→
Concomitant Treatments[18]	X	→	→	→	→	
Tumor Assessment[19]	X			X		
Whole Blood Biospecimen for PD analysis[20]		X		X		
Serum for Biomarker (BM) analysis[21]		X		X		
Plasma Biospecimen for Exploratory BM Assessments[21]		X		X		
QoL[23]		X		X		
FFPE tumor samples for K-master panel analysis[24]	X					

Abbreviations: ECG = electrocardiogram; → = ongoing/continuous event; AEs = adverse events; CT = computed tomography; MRI = magnetic resonance imaging; FFPE= Formalin-Fixed, Paraffin-Embedded; ( ) = Optional activity to be executed only if applicable. Please refer to the footnotes below for more details.

Tests and procedures should be done on schedule, but occasional changes by ± 3 days (unless otherwise stated differently) are allowed for holidays, vacations and other administrative reasons.

Footnotes

1. Screening/Baseline Assessments: completed within 28 days of beginning investigational product unless otherwise specified as shown in the schedule of activities above.

2. Informed Consent: obtained prior to undergoing any study specific procedures.

3. Tumor History: collected within 28 days prior to first dose of study medication. Includes history of oncology disease including details of primary diagnosis and treatment history (systemic treatment, prior surgery and radiotherapy). When available primary diagnosis history should include known molecular characteristics of the patient's tumor include mutations, amplifications, etc.

4. Medical History: collected within 28 days prior to first dose of study medication. Includes history of disease process other than oncology (active or resolved), and concomitant illnesses. Includes prior treatment including dosing and duration of administration as well as verification of concurrent medication.

5. Signs & Symptoms: patients will be asked about any signs and symptoms experienced within the 14days of C1D1. During trial treatment any new or worsened conditions since baseline should be reported on the Adverse Event CRF.

6. Physical examination: is a symptom directed exam conducted by a physician, trained physician's assistant or nurse practitioner, as acceptable according to local regulation.

7. Vital signs: blood pressure and heart rate and should be recorded in the sitting position after approximately 5 minutes of rest.

8. Performance status: ECOG scale to be assessed within 14 days prior to the first dose of investigational product, and as described in the table above.

9. Laboratory Tests:

- Screening labs to be performed within 28 days of Cycle 1, Day 1 (C1D1). For subsequent cycles, pre-dose labs may also be drawn up to 24 hours in advance of scheduled dosing in order to obtain results prior to infusion.

10. Hematology: No need to repeat on C1D1 if screening assessment performed within 28 days prior to C1D1.

11. Blood Chemistry: No need to repeat on C1D1 if screening assessment performed within 28 days prior to C1D1

12. Urinalysis: No need to repeat on C1D1 if screening assessment performed within 28 days prior to C1D1

13. Coagulation Tests: No need to repeat on C1D1 if screening assessment performed within 28 days prior to C1D1. To be performed every per the schedule in the table above (± 3 day time window).

14. Pregnancy Test: For female patients of childbearing potential, a pregnancy test, with sensitivity of at least 25mIU/mL, will be performed during screening period. Pregnancy test will also be repeated whenever potential pregnancy is suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.

15. ECG: Triplicate 12-lead ECG (per institutional practice) will be performed. Additional ECGs may be performed as clinically indicated.

16. Echocardiography: an echocardiography or MUGA scan is required within 28 days of C1D1. Only subjects with LVEF of 50% or higher should be enrolled in the study. During study treatment period, echocardiography or MUGA scan is performed at Cycle 5 Day 1 (± 7 days) and then every 24 weeks during active treatment period.

17. Adverse Event (AE) Assessments: AEs should be documented and recorded at each visit using NCI CTCAE version 4.0.

18. Concomitant Treatments: All concomitant medications and treatments should be recorded in the CRF including supportive care drugs, and the drugs used to treat adverse events or chronic diseases.

19. Tumor Assessments:

- Baseline tumor assessments must be within 28 days of first dose.
- After C1D1, tumor assessments will be performed every 6 weeks ± 5 days while patient are receiving treatment. Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on-study as appropriate to follow disease. Baseline CNS imaging is not required with the exception of symptomatic patients to rule out CNS metastases.
- Confirmation of response (CR/PR) is not required.
- Tumor assessment should be repeated at the end of study visit if more than 9 weeks have passed since the last evaluation.
- For those patients who discontinue for reasons other than disease progression, tumor assessments should be continued until progression of disease is documented.

20. Whole blood biospecimens: will be collected pre dose on C1D1 and C3D1 to conduct pharmacodynamics assessments

21. Serum/plasma biospecimens: Serum/plasma biospecimens will be collected on C1D1, on C3D1 and at end of treatment (EOT) visit for potential circulating nucleic acid analysis.

22. Follow up: approximately 30 days (+/-10 days) after discontinuation of treatment patients will return to undergo review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the

clinical judgment of the investigator, that no further improvement is expected. In addition, patients will be followed up every 18 weeks until death, loss to follow-up, withdrawal of consent, or study termination for collecting survival data.

23. Quality of life: Quarlity of life (QoL) will be checked at baseline, after C3, and on PD. This QoL will be measured by the European Organization for Research and Treatment Care Quality of Life Questionnaire (Korean version, EORTC QLQ-C30).

24. During screening period, tumor tissue (FFPE) should be obtained to perform CancerScan (K-master cancer panel). Tumor specimen from metastatic sites is preferred, though it is not limited to.

1. INTRODUCTION

1.1 HER2 amplified metastatic breast cancer

Breast cancer is the most common cancer worldwide in women. Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of breast cancers and several anti-HER2 targeted therapy based treatments are considered as standard in this patient population. In addition to the first approved anti-HER2 therapy, trastuzumab, pertuzumab and T-DM1 are used as therapeutic options in HER2 positive metastatic breast cancer (MBC). The current consensus includes dual blockade (trastuzumab plus pertuzumab) with taxanes in the first line, followed by trastuzumab-emtanxine (T-DM1) in the second line. Tyrosin kinase inhibitors, such as lapatinib or neratinib are also considered in case there is resistance to trastuzumab based therapy. Despite the remarkable progress in treatment of HER2 positive breast cancer, metastatic disease is still incurable in the majority of patients. Especially, those who progressed on anti-HER2 therapy at the first and second lines, their prognosis are dismal. Even after patients experienced disease progression on trastuzumab containing chemotherapy, sufficient data including guidelines such as NCCN and ABC3 recommended continuing trastuzumab with any other chemotherapy agents including but not limited to vinorelbine, taxanes, capecitabine, eribuline, platinum, or gemcitabine. However, in our country anti-Her2 therapy, trastuzumab can only be used once in the metastatic setting since its use beyond progression is not approved and not reimbursed. In those cases, patients should be treated using just cytotoxic chemotherapy only.

1.2 Trastuzumab biosimilar- Celltrion

CT-P6 (CELLTRION, Incheon, Republic of Korea) is a biosimilar of reference trastuzumab, already approved in South Korea for the same indications as the reference product. CT-P6 has been found to be similar to reference trastuzumab in in vitro studies, including with respect to HER2 binding affinity, ADCC and anti-proliferation activity. CT-P6 also exhibited a similar profile to reference trastuzumab in in vivo toxicology studies.

The PK similarity of CT-P6, and trastuzumab-US has been evaluated in a Phase 1, randomised, double-blind, parallel-group study following a single intravenous (IV) administration of the study drugs to 70 healthy male subjects. Pharmacokinetics, safety and immunogenicity were evaluated up to 10 weeks post-dose. Primary endpoints were area under the serum concentration–time curve (AUC) from time 0 to infinity (AUC inf); AUC from time 0 to last quantifiable concentration (AUC last); and observed maximum serum concentration (Cmax). The pre-determined equivalence criterion was a 90% confidence interval of 80–125% for ratios of geometric least squares (LS) means.

Equivalence of CT-P6 and reference trastuzumab was demonstrated. Ratios (CT-P6/reference trastuzumab) of geometric LS means (90% confidence interval) were: AUC inf 99.05 (93.00, 105.51); AUC last 99.30 (92.85, 106.20); Cmax 96.58 (90.93, 102.59). Safety profiles were similar; treatment-emergent adverse events occurred in ten subjects (28.6%) in the CT-P6 group and 11 (31.4%) in the

reference trastuzumab group. No serious adverse events or deaths occurred. No subjects tested positive for anti-drug antibodies.

These data add to the totality of evidence required to demonstrate biosimilarity. A phase III study of CT-P6 showed equivalent efficacy (pathologic complete remission rate) to reference trastuzumab and adverse events were similar in the neoadjuvant setting with HER2 positive early stage breast cancer patients. Even though many trastuzumab biosimilar including CT-P6 (trastuzumab-celltrion) demonstrated biological equivalence and comparable clinical efficacy to the reference drug, there was no further data regarding combination with other diverse cytotoxic chemotherapeutic drugs. More data of trastuzumab biosimilar with various combination partners would give an alternative and more cost-effective treatment option in the clinical practice.

2. STUDY DESIGN

2.1 Overall design

This is a phase II multicenter, open-label one arm trial in patients with HER2-positive metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy.

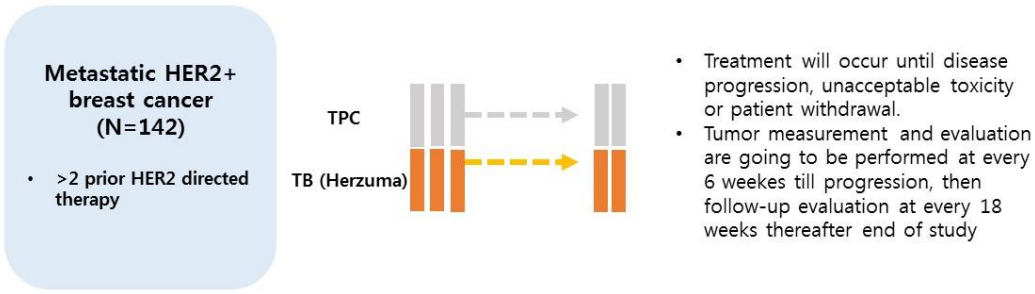


Figure 1. Study scheme

2.2 Patient enrollment

After written informed consent has been obtained and all screening procedures have been completed, eligibility has been established. For those patients who are eligible for enrollment, investigator should choose the chemotherapeutic regimen for TPC and record it on eCRF. The study site will obtain the patient identification number and treatment assignment from the system.

2.3 Study objectives

2.3.1 Primary objectives

- to determine PFS of trastuzumab biosimilar based therapy in patients with HER2 positive MBC who are resistant to two and more than two lines of anti-HER2 based treatment.

2.3.2 Secondary objectives

- to determine objective response rate (ORR) assessed by RECIST criteria v.1.1

- to evaluate overall survival (OS)

- to evaluate the safety profiles

- to evaluate the QoL

2.3.3 Exploratory objectives

- to evaluate potential biomarkers of outcomes such as clinical efficacy and safety

2.4 Endpoints

2.4.1 Primary endpoint

- PFS defined as the time from study entry until the first observation of disease progression or death due to any cause.

2.4.2 Secondary endpoints

- ORR defined as the percentage of patients experiencing confirmed complete response (CR) and partial response (PR) assessed by RECIST criteria v.1.1
- OS defined as the time from study entry until death or last follow-up date
- Safety including adverse events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [NCI CTCAE v. 4.0]), timing, seriousness and relationship to study therapy and laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.0) and timing.
- Quality of life (QoL) measured by the European Organization for Research and Treatment Care Quality of Life Questionnaire

2.4.3 Exploratory endpoints

- Immune cell profile in PBMB, Th1 vs Th2 cytokine profile, NGS analysis using cfDNA, ADCC

3. STUDY POPULATION

Patients must meet all of the following inclusion/exclusion criteria to be eligible for enrollment into the study. Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

3.1 Inclusion criteria

1) Patient is an adult, female ≥ 19 years old at the time of informed consent.
2) Patient has histologically and/or cytologically confirmed diagnosis of HER2-positive breast cancer (HER2/neu3+ as defined by immunohistochemistry and/or HER-2/neu gene amplification as defined by fluorescence in situ hybridization).
3) Metastatic or unresectable disease documented on diagnostic imaging studies.
4) Prior 2 or more HER-2 directed therapy for metastatic disease is mandatory.
5) Patient must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1)
6) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1
7) Adequate bone marrow and organ function including: a) WBC ≥ 3500/ml; b) Platelets ≥ 100,000/ul; c) Hemoglobin >9.0 g/dL; d) Total bilirubin ≤ 1.5x ULN; e) AST and ALT < 2.5 x ULN; f) Alkaline phosphatase <2.5x ULN; g) Creatinine ≤ 1.5x ULN or CCr >60 ml/min for patients with abnormal serum Cr level function.
8) Patient has an adequate left ventricular ejection function of at least 50 % at baseline, as measured by echocardiography.
9) Written informed consent

3.2 Exclusion criteria

1) Patient is pregnant or lactating, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
2) Patient has symptomatic and unstable CNS metastases, except for treated brain metastases. Treated brain metastases are defined as having no evidence of progression or hemorrhage after treatment and no ongoing requirement for dexamethasone, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Anticonvulsants (stable dose) are allowed.
3) Active and clinically significant bacterial, fungal or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus syndrome (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. Baseline viral assessment is not required in patients with no known infection.
4) Major surgery within 4 weeks of first dose of investigational product or not fully recovered from any side effects of previous procedures.
5) Any other malignancy within 3 years prior to first dose of investigational product except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
6) QTc interval >480 msec (based on the mean value of the triplicate ECGs), family or personal

history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes.

7) Any of the following within 6 months of first dose of investigational product myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE v. 4.03 Grade ≤2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.
8) History of symptomatic interstitial pneumonitis.
9) Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

4. TREARMENT

4.1 Allocation to treatment

For those patients who are eligible for enrollment, investigator should choose the chemotherapeutic regimen for TPC and record it on eCRF. The study site will obtain the patient identification number and treatment assignment from the system.

4.2 Treatment administration

Trastuzumab biosimilar (CT-P6), Herzuma® will be supplied by KCSG. Study centers will receive trastuzumab prior to enrollment of the first patient. The clinical site pharmacy will prepare the study medication supply that is appropriate for the patient. The drug of TPC will not be supplied nor reimbursed by this trial. Instead, it will be selected and used as current national standard treatment guideline and be covered by National Insurance program.

4.2.1 Trastuzumab biosimlar, CT-P6

CT-P6, Herzuma® is available in its commercial package. It is supplied as a powder for IV infusion containing 150mg/dose vial and/or 420mg/dose vial trastuzumab.

4.2.1.1 Dosage, administration, and storage

Drug preparation and administration will be performed at the site by a physician, registered nurse or other qualified health care provider. Refer to the package insert for trastuzumab for instructions and steps necessary for preparation and administration.

Trastuzumab requires a loading dose during the first cycle of treatment, if patient did not received

trastuzumab treatment within 8 weeks from the time of 1st study treatment. Doses of trastuzumab (8mg/kg at a loading dose, and then 6mg/kg at a maintenance dose) are given once every 3 weeks of the cycle. Trastuzumab loading dose should be administered as a 90-minute IV infusion. Do not administer as an IV push or bolus. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

4.2.1.2 Dosage modification

Dose adjustment for trastuzumab will be determined by the investigator's discretion. Per the trastuzumab SPC, no reductions in the dose of trastumab were made during clinical trials. Patients may continue trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. In the event that trastuzumab is discontinued, the patient may continue to receive TPC based on the investigator's discretion. For monitoring of LVEF, please refer to the algorithm in Figure.

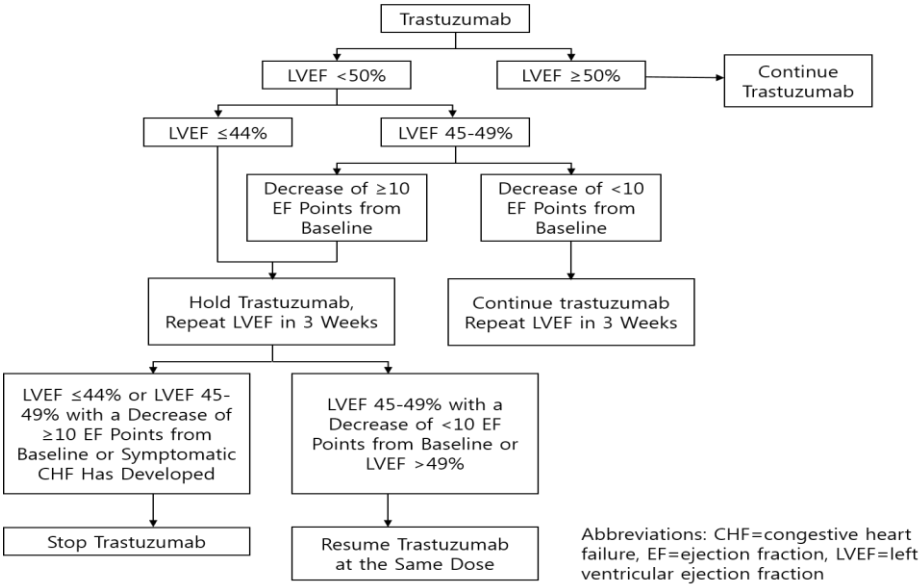


Figure 2. Algorithm for monitoring LVEF in study

4.2.2 Treatment of physician's choice (TPC)

In this trial, gemcitabine, vinorelbine, eribulin, nab-paclitaxel or capecitabine are allowed as combinational drugs with trastuzumab biosimilar. The proposed treatmend of physician's choice will be documented prior to patient allocation.

4.2.2.1 Dosage, administration, and storage

Dose administration should be performed according to the drugs national prescribing duidelines. Refer to the appropriate package insert or national prescribing information as needed for details.

4.2.2.2 Dosage modification

Dose modification should be performed according to the investigator's discretion.

4.2.3 Dose interruptions and delay

Patients experiencing grade 3 or 4 treatment related toxicity or intolerable grade 2 toxicity despite supportive care should have their treatment interrupted and may not be restarted until the toxicity has recovered to grade ≤1 or tolerable grade 2. Appropriate follow up assessments should be done until adequate recovery as assessed by the investigator. If a treatment interruption continues beyond Day 21 of the current cycle, then the day treatment is restarted will be counted as Day 1 of the next cycle, and the previous cycle is extended accordingly.

Treatment resumption for patients recovering from treatment related toxicity after >2 weeks of treatment interruption or cycle delay can be considered only if the patient is deemed to be deriving clinical benefit per the investigator's medical judgment and needs to be agreed between the investigators. In the event of a treatment interruption for reasons other than treatment related toxicity (e.g., elective surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the PI of this trial.

Tumor assessments should be performed every 6 weeks (±5 days), regardless of cycle delays.

If a dose of trastuzumab is missed/omitted by 1 cycle (3 weeks), then the usual maintenance dose should be administered as soon as possible. Then, subsequent maintenance doses should be administered every 21 days. If the patient requires omission of 2 and more than 2 trastuzumab maintenance doses for toxicity, the patient should be considered to be withdrawn from trastuzumab. In exceptional circumstances, a longer delay or omission of TPC may be permitted upon agreement between the investigators. In those cases, trastuzumab maintenance will be permitted if investigator believe clinical benefit of it to patients until study termination, disease progression or patient withdrawal.

4.3. Concomitant and excluded therapies

4.3.1 Concomitant therapy

Concomitant therapy and premedication are defined as non-investigational medicinal products. Concomitant therapy includes any prescription medication, over –the – counter preparation, or herbal therapy bewteen the 14 days preceding enrollment and the study treatment discontinuation visit. Afterward, only anti-cancer therapies will be collected as part of the survival follow-up period.

Premedication is allowed according to standard practice guidelines. Concomitant use of erythropoiesis-stimulating agents, G-CSF, or GM-CSF is allowed if clinically indicated in accordance with local prescribing guidelines. Palliative radiotherapy may be permitted to treat pre-existing painful bone metastases unless there is evidence of disease progression. Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. Use of biophosphonates is permitted for the control of bone pain and treatment of osteoporosis. If

bisphosphonates are required for the treatment of symptomatic malignancy associated hypercalcemia, tumor assessments should be performed to assess for potential disease progression.

4.3.2 Excluded therapy

Use of the therapies described below is prohibited during the study prior to discontinuation of study treatment. Any therapies intended for the treatment of breast cancer other than trastuzumab and TPC including cytotoxic chemotherapy, immunotherapy, biologic or targeted agents are not allowed. Refer to the local prescribing guidelines for durg-drug interactions and excluded concomitant medications and precautions for the selected TPC.

Radiotherapy for unequivocal disease progression is not permitted while on study treatment.

4.4 Study assessments

All patients will be closely monitored for safety and tolerability during all cycles of therapy and at the study treatment discontinuation visit. Patients should be assessed for toxicity prior to each dose. Each cycle will be 21 days (3 weeks) in length. Study assessments are outlined in this section and the study flowchart.

4.4.1 Screening and pretreatment assessments

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria. Written informed consent for participation in the study must be obtained before performing any study specific screening tests or evaluations. Screening tests will be performed within 28 days preceding the 1st treatment Day 1 of cycle 1.

4.4.1.1 Medical history, concomitant medication, and demographic data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, will be recorded at baseline.

All medications used by the patient within 7 days prior to initiation of study treatment will be recorded.

4.4.1.2 Physical examination & vital sign

A complete physical examination will be performed at screening. Any abnormality identified at baseline should recorded on the eCRF.

Limited, symptom-directed physical examination should be performed at post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded.

Vital signs will include measurements of blood pressure, pulse rate, respiratory rate, and body temperature. At every clinic visit to receive study treatment, vital sign should be measured and if clinically indicated, during or after the infusion. Vital signs are not required to be entered into the eCRF unless abnormal and clinically significant.

4.4.1.3 Electrocardiogram, echocardiograms or multiple-gated acquisition scans (MUGA)

A 12-lead ECG is required at screening and when clinically indicated. Any ECG abnormalities must be reviewed by the investigator and documented on the eCRF.

LVEF will be assessed by echocardiography or MUGA scan at screening and before cycle 5 day 1. After then, echo (or MUGA) should be performed at every 24weeks. If circumstances allow, patients should be reassessed with the same technique used for baseline evaluation throughout the study.

4.4.1.4 Baseline tumor status

Disease status at baseline should be done with CT scan (chest CT, abdomen CT) and bone and recorded in the eCRF. If patients performed bone scan within 3 months, have no evidence of bone metastasis, or no symptom associated with progression of bone metastasis, bone scan could be skipped at the discretion of each investigator. If clinically indicated, other modalities such as MRI, or PET are allowed and any abnormal findings should be recorded into the eCRF.

4.4.2 Assessments during treatment

Visits are based on a 21-days cycle. All visits must occur within +/- 3 business days from the scheduled date, unless otherwise noted. All tumor assessments will be performed after every 6 weeks (+/- 5 days) of treatment. Assessments scheduled on the day of treatment administration should be performed prior to study treatment administration unless otherwise noted. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend, it should be performed on the nearest following date. In case that the treatment cycle exceeds more than 8, tumor assessments can be performed every 9 weeks depending on physician's discretion.

Local laboratory assessments scheduled for day 1 of all cycles must be performed within 72 hours prior to study treatment administration unless otherwise specified.

4.4.3 Study treatment discontinuation visit.

Patients who discontinue study treatment will be aksed to return to the clinic approximately 30 days (+/-10 days) after the last study treatment administration for the study treatment discontinuation visit. Please, refer the study flow chart for assessment to be performed at this visit.

4.4.4 Follow-up assessment.

After the study treatment discontinuation visit, all participants will be followed for survival every 3 months until death, loss to follow-up, withdrawal of consent, or study termination for collecting survival data.

4.5 Patient discontinuation.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for discontinuation of may include:

- Objective disease progression according to RECISTv1.1;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Lost to follow-up;
- Medication error without associated adverse event;
- Significant protocol violation;
- Patient refused further treatment;
- Significant patient noncompliance;
- Study terminated by Sponsor;
- Death.

4.6 Statistical method

4.6.1 Rationale for sample size

This study is aiming to assess PFS of TPC plus trastuzumab biosimilar, CT-P6 in patients with HER-2 positive metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy.

One sided type I error rate 0.1, power 80%; 24 months of accrual period and 12 months of follow-up. H0 = 2.8 months, H1=3.8 months. Then, a total of 108 patients will be needed in this trial. Considered 10% drop-out rate, we will enroll 119 patients. (ref. TH3RESA trial, Lancet Oncol 2014;15:689-99)4.6.2 Efficacy analysis

4.6.2.1 Progression free survival (PFS)

PFS is defined as the time from randomization to docutmented disease progression or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the time of the last tumor assessment date or, if no tumor assessment was performed after the baseline visit, at the time of allocation plus 1 day. Data from patients who are lost to follow-up will be censored at the last tumor assessment date that the patient was known to be progression free.

Kaplan-Meier approach will be used to estimate median PFS and the corresponding confidential interval (CI).

4.6.2.2 Overall survival (OS)

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who are alive at data cutoff date will be censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of allocation plus 1 day.

Methods for OS analyses are similar to those described for the PFS endpoint.

4.6.2.3 Objective response rate (ORR)

Objective response is defined as a complete or partial response based on RECIST v 1.1. The ORR is the percentage of patients who are determined to have an objective response. For the ORR analysis, patients who do not have any record of post-baseline tumor assessment will be counted as non-responders.

4.6.3 Safety analysis

Safety analyses will be performed on the treatment population who received any amount of study treatment.

4.6.3.1 Study treatment exposure

Treatment duration, number of cycles, dose intensity, and dose modification will be summarized with descriptive statistics.

4.6.3.2 Adverse events

All adverse events (AE), seriouse adverse events (SAE) occuring on and after the first dose of study treatment will be summarized by NCI-CTCAE grade. For events of varing severity, the highest grade will be used in the summaries.

4.6.4 Quality of life (QoL) analysis

The EORTC-QLQ-C30 data will be scored according to the EORTC- QLQ- C30 scording manual. Percentages of missing data will also be summarized at each timepoint. Assessment will be done at 3 time points (baseline, after 3 cycles of treatment, and at the end of treatment date). Summary statistics of absolute scores of the QLQ-C30 scales and the changes from baseline will be summarized. Only patients with baseline assessment and at least one post-baseline assessment will be included in this analysis.

4.7 Assessment of safety

4.7.1 Adverse event (AE)

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

This includes the following :

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with breast cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions

- AEs that occur prior to assignment of study treatment that are related to a protocol mandated intervention
- Preexisting medical conditions other than breast cancer judged by the investigator to have worsened in severity or frequency or change in character during the protocol specified AE reporting period.

4.7.2 Serious adverse event (SAE)

An SAE is any AE that is any of the following

- Fatal (i.e. the AE actually causes or leads to death)
- Life threatening (i.e. the AE, in the view of the investigator, places the patient at immedicate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e. the AE results in substantial disruption of the patient ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infacnt born to a mother exposed to the investigational products
- Considered a significant medical event by the investigator (e.g. may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Hospitalization is defined as any initial admission (even less than 24hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for workup of persistent pretreatment laboratory abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

4.7.3 Causality assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

4.7.4 AE reporting period

After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol mandated intervention will be collected. After initiation of study treatment, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation, whichever is later.

The AE severity scale found in the NCI-CTCAE v 4.0 will be used for assessing AE severity

5. QUALITY CONTROL AND QUALITY ASSURANCE

Investigators will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow KCSG monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by KCSG and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify KCSG immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with KCSG to prepare the study site for the inspection and will allow KCSG, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to KCSG. Before response submission to the regulatory authorities, the investigator will provide KCSG with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

6. DATA HANDLING AND RECORD KEEPING

6.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of KCSG and should not be made available in any form to third parties, except for authorized representatives of KCSG or appropriate regulatory authorities, without written permission from KCSG.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely

(contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at KCSG and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

6.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or KCSG, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), KCSG should be prospectively notified. The study records must be transferred to a designee acceptable to KCSG, such as another investigator, another institution, or an independent third party arranged by KCSG. Investigator records must be kept for a minimum of 15years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain KCSG's written permission before disposing of any records, even if retention requirements have been met.

7. ETHICS

7.1 Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to KCSG.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and KCSG in writing immediately after the implementation.

7.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH1996), and the Declaration of Helsinki (World Medical Association1996 & 2008.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

7.3 Subject Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to KCSG and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by KCSG in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, KCSG will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisional impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g.,

parent, spouse), and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent/assent document.

7.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

7.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, KCSG should be informed immediately.

In addition, the investigator will inform KCSG immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

8. DEFINITION OF END OF TRIAL

The end of the study will be at the 12 months after the last patient enrollment for purposes of closing out sites and informing the institutional review board/independent ethics committee (IRB/IEC).

8.1. KCSG discontinuation criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the end of K-master program. If a study is prematurely terminated or discontinued, KCSG will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) promptly. As directed by KCSG, all study materials must be collected and all CRFs completed to the greatest extent possible.

9. PUBLICATION OF STUDY RESULTS

9.1 Communication of Results by K-MASTER

K-MASTER fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), CRIS (cris.nih.go.kr/cris/index.jsp), and/or www.KCSG.org, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by KCSG in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study.

KCSG posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on CRIS (cris.nih.go.kr/cris/index.jsp) and www.clinicaltrials.gov.

9.2 Publication by Investigators

Drug supplier (Celltrion) support the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the study product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide drug suppliers an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “Publication”) before it is submitted or otherwise disclosed.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication.

For all publications relating to the study, the K-MASTER will comply with KCSG ethical standards concerning publications and authorship. Publication of study results is also provided for K-MASTER and the investigators.

10. REFERENCES

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Appendix 1. Abbreviations

Abbreviation	Term
ADCC	Antibody-dependent cellular cytotoxicity
AE	adverse event
BC	breast cancer
CI	confidence interval
CR	complete response
CRF	Case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECHO	echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
eCRF	electronic Case Report Form
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen B
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	human epidermal growth factor 2
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IRB	Institutional Review Board
ITT	intention-to-treat
IV	intravenous
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MRI	Magnetic resonance imaging
MUGA	multi-gated acquisition scan
NCI	National cancer institute
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PD	progressive disease
PI3K	Phosphoinositide 3 kinase
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse events
SD	Stable disease
ULN	Upper limit of normal

Appendix 2. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guideline

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10mm or greater when assessed by CT or MRI (slice thickness 5-8mm).
- Lesions with longest diameter at least 20mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28days prior to randomization and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be non-evaluable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5mm should be recorded.

NOTE: When nodal lesions decrease to <10mm (normal), the actual measurement should still be recorded.

Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as CR, Non-CR/Non-PD, PD, Non-evaluable (NE). Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses might be non-evaluable.

Target Disease

1. Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10mm). All target lesions must be assessed.

2. Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

3. Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

4. Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5mm.

5. Non-evaluable (NE): Progression has not been documented, and

- One or more target measurable lesions have not been assessed; or

- One or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure); or
- One or more target lesions were excised or irradiated.

Non-target disease

1. CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10mm short axis).

2. Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

3. PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

4. NE: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation

Table 1. Objective Response Status at each Evaluation			
Target Lesions	**Non-target Disease**	**New Lesions**	**Objective status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE or Missing	No	PR
PR	Non-CR/Non-PD, NE or Missing	No	PR
SD	Non-CR/Non-PD, NE or	No	Stable

	Missing		
NE or Missing	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only		
Non-target Disease	**New Lesions**	**Objective status**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
NE	No	NE
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Best Overall Response

The best overall response (BOR) is the best response recorded from the randomization until disease progression or death due to any cause. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories.

- Complete response (CR): At least one objective status of CR documented before progression.
- Partial response (PR): At least one objective status of PR documented before progression.
- Stable disease (SD): At least one objective status of stable documented at least 8weeks after randomization date and before progression but not qualifying as CR, PR.
- Progressive Disease (PD): Objective status of progression within 16weeks of randomization, not qualifying as CR, PR or SD.
- Non-evaluable (NE): Progression not documented within 16weeks after randomization and no other response category applies.

Appendix 3. Quality of Life

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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