CITY OF HOPE NATIONAL MEDICAL CENTER
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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: TOLERABILITY OF THE COMBINATION OF LAPATINIB AND TRASTUZUMAB IN ADULTS AGED 60 OR OLDER WITH HER2 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER

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COH Amendment 27	Title Page dated 04/19/19	Version: 27

SITE: Breast
HISTOLOGY: HER2/Neu+ Breast Cancer
STAGE: IV
MODALITY: Chemotherapy
TYPE: Phase II

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Roswell Park Cancer Institute

Experimental Design Schema

	Pre-Study (up to 14 days prior to enrolling)[j]	Cycl 1 Day 1 (21 day cycle)	Cycl 1 Day 8	Cycl 1 Day 15	Cycl 2 Day 1	Cycl 2 Day 8	Cycl 3 Day 1	Cycl 4 Day 1	Cycl 5 Day 1	Every cycle There-after	Every 4 cycles	Off Study[i]
Lapatinib (day 1-7 of each wk)[a]		X	X	X	X	X	X	X	X	X		
Trastuzumab (±1 day if qwk, ±3 days if q3wk)[a,b]		X			X		X	X	X	X		
Demographics	X											
Medical history	X											
Concurrent meds (± 1 wk)	X	X			X		X	X	X	X		
Physical exam (± 1 wk)	X	X			X		X	X	X	X		X
Vital signs (± 1 wk)	X	X			X		X	X	X	X		X
Height	X											
Weight (± 1 wk)	X				X		X	X	X	X		X
Performance Status (± 1 wk)	X	X			X		X	X	X	X		X
CBC w/diff, plts (± 1 wk)	X	X[c]			X		X	X	X	X		X
Complete Metabolic Panel[d] (± 1 wk)	X	X[c]	X		X		X	X	X	X		X
Nurse brief toxicity evaluation			X	X		X						
EKG	X											
Pharmacokinetic samples (± 1 days)[k]				X	X	X						
Adherence evaluation (pill count, diaries) (± 1 wk)					X		X	X	X		X	
Adverse event evaluation (± 1 wk)					X		X	X	X		X	X
Tumor measurements using CT or PET-CT (± 1 wk)	X[e]								X		X[f]	X[g]
LVEF Assessment	X[e]								X		X[f]	X[g]
Geriatric Assessment Survey (±1 wk)	X								X		X	X[h]

a: Dose as assigned; lapatinib 1000mg orally daily; trastuzumab 4mg/kg IV cycle one day 1, 2mg/kg IV every week thereafter; OR trastuzumab 8mg/kg cycle 1, day 1, 6mg/kg each cycle (3 wks) thereafter. Doses held due to toxicity will not be made up.

b: X in schema for trastuzumab applies to q3 week schedule.

c: If baseline laboratory tests are done within 14 days of start of treatment, these labs do not need to be repeated prior to day 1.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

e: Baseline radiologic imaging may be done up to 30 days prior to start of treatment

f: Tumor measurements and LVEF assessment are repeated every 4 cycles ± 1 wk until patient comes off study. Documentation (radiologic or clinical) must be provided for patients removed from study for progressive disease.

g: Off-study radiologic evaluation will only be done if clinically indicated

h: Geriatric assessment should be repeated off study ONLY if it had not been administered within the previous month

i: Patients will be followed for 30 days following discontinuation of therapy in order to capture toxicity attributable to therapy

j. Chart review data must be within 14 days to determine if patient meets study criteria. Once patient is deemed to meet study criteria, then

all criteria must be within window specified in protocol from Day1 as indicated in column one in the schema above.
k: Phamacokinetic samples will be drawn after the patient has been taking lapatinib at the same dose level for a period of at least 7 days.

Protocol Synopsis

Protocol Title:
TOLERABILITY OF THE COMBINATION OF LAPATINIB AND TRASTUZUMAB IN ADULTS AGED 60 OR OLDER WITH HER2 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER
Brief Protocol Title for the Lay Public (if applicable):
Lapatinib/Trastuzumab in Older Adults
Study Phase:
Phase II
Participating Sites:
City of Hope Comprehensive Cancer Center , Duke University, Jefferson University, and Roswell Park Cancer Institute
Rationale for this Study:
Limited evidence exists to guide therapy with targeted agents in the older adult because older adults have been under-represented in clinical trials. Adults age 70 and older make up only 20% of subjects enrolled in FDA registration trials but 46% of all patients with cancer. Dose-finding studies specifically in older adults are not routinely performed. This is despite changes in drug metabolism, absorption, and distribution with increasing age. Lapatinib is an oral targeted agent in the treatment of HER2+ breast cancer. Lapatinib is a tyrosine kinase inhibitor that binds to the intracellular domain of both the HER2 receptor and the EGFR receptor (HER1), thus inactivating downstream signaling essential to tumor proliferation. Though currently approved only in combination with capecitabine or letrozole, recent data suggest benefit of lapatinib in combination with trastuzumab, a monoclonal antibody directed to the extracellular domain of the HER2 transmembrane receptor. It is thought that lapatinib and trastuzumab, both HER2 targeted agents, may act synergistically against HER2 overexpressing tumors. Additionally, it is believed that lapatinib combined with trastuzumab may potentiate the anti-tumor effects of trastuzumab, even after a patient has already progressed on trastuzumab, possibly by blocking a mechanism of drug resistance. The mean age of subjects to date on lapatinib trials is 58. The pivotal trial of lapatinib with capecitabine included patients up to age 83 but age distribution was not reported and no subset analysis of lapatinib safety or efficacy in older adults was performed. In the study by Blackwell et al which combined trastuzumab and lapatinib, the median age of patients was only 52, with few patients over age 60. The most common toxicities of lapatinib are diarrhea and rash. Though usually grade 2 or lower, even grade 2 diarrhea (4-6 stools per day over baseline) is often poorly tolerated in older adults secondary to limited fluid reserves and predisposition to dehydration. Trastuzumab has a known association with cardiomyopathy, thought to be directly related to HER2 blockade. Lapatinib also carries this theoretical risk. While in younger adults, the combination did not appear to be related to unacceptable numbers of cardiac events, the cardiac toxicity profile in older adults could be different. It is important to elucidate the toxicity profile in older adults as the combination of trastuzumab and lapatinib would likely be very attractive to older adults and their oncologists as the combination is efficacious and as these agents do not tend to carry the traditional debilitating risks of cytotoxic chemotherapy.

This is an open label, single arm, phase II study of the combination of lapatinib and trastuzumab in 40 patients age 60 or over with HER2 positive locally advanced or metastatic breast cancer. The goal of this study is to estimate the tolerability of the combination of trastuzumab and lapatinib in older adults with locally advanced or metastatic HER2 overexpressing breast cancer as evidenced by rates of grade 3 or higher toxicities and rates of symptomatic serious cardiac adverse events. Secondary aims are to evaluate disease response in this population and to explore factors other than chronologic age that predict toxicity using a cancer-specific geriatric assessment.

Primary Objective:

To estimate the safety and tolerability of the combination of trastuzumab and lapatinib in adults age 60 or older with locally advanced or metastatic breast cancer

Secondary Objective(s):

1. To describe the full toxicity profile including all grades, including

   - To estimate the rate of all grades of diarrhea, nausea, and vomiting

   - To estimate the rate of all grades of cardiac toxicity

2.To describe the pharmacokinetic parameters of lapatinib in older adults

3.To estimate objective response rate and clinical benefit rate as defined by modified RECIST criteria

4.To estimate median progression-free and overall survival

5.To explore factors other than chronologic age that can affect toxicity rates as identified using a cancer-specific geriatric assessment

6.To estimate adherence rates to lapatinib in older adults

Study Design:

The study will be an open label, single arm, phase II safety and tolerability study of the combination of lapatinib and trastuzumab in patients age 60 or over with HER2 positive locally advanced or metastatic breast cancer with a sample size of 40 patients. After 20 patients have completed one full cycle of therapy there will be an interim analysis, at which time the study team will review the data and access the toxicity profile and rates of dose reduction, delays, interruptions, and hospitalization related to the combination of ages. Within this interim analysis a specific review will be made of the data for the patients over 75 years of age. In response to the DSMB review of the planned interim analysis results, we are adding a second interim analysis after 30 patients have completed one full cycle of therapy.

Primary Endpoint and Secondary Endpoints:

Primary:

Grade 3 or higher non-hematologic toxicities in patients taking the combination of lapatinib and trastuzumab, or symptomatic congestive heart failure

Secondary:

1. All toxicities associated with the combinations as measured by NCI CTCAE v.4.0
2. Dose reductions, delays, and discontinuations
3. Pharmacokinetic parameters
4. Response as determined by RECIST criteria
5. Progression free survival
6. Overall survival

7. Percentage of doses of lapatinib taken

Sample Size:

40

Estimated Duration of the Study

48 months

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

1 Locally advanced or metastatic Her2/Neu positive breast cancer (defined as IHC 3+ or FISH amplified) Locally advanced breast cancer (LABC) includes breast cancers with advanced primary tumors, ie, large diameter (at least 5 cm) or those with skin and/or chest wall involvement, and advanced regional lymph node involvement. It also includes a rare subgroup, inflammatory breast cancer.

In the 2010 American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) TNM breast cancer staging system, locally advanced breast cancer (LABC) includes patients with stage III disease. This comprises:

- Advanced primary tumors [Tumors > 5 cm in greatest dimension (T3). direct extension to the chest wall and/or to the skin (T4): ulceration, skin nodules, and/or
- edema (including peau d'orange) confined to the same breast, Inflammatory breast cancer (IBC, T4d)]
- Advanced regional lymph nodes [Ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases (N2), Ipsilateral infraclavicular (level III axillary) lymph nodes, ipsilateral internal mammary lymph node(s) with axillary lymph nodes, or ipsilateral supraclavicular lymph nodes (N3)]

2 Age 60 or older

3 Life expectancy of greater than 12 weeks

4 ECOG performance status $\leq$2 (Karnofsky performance status $\geq$60%)

5 Normal organ and marrow function as defined below:

- hemoglobin $\geq$10g/dL (after transfusion, if necessary)
- absolute neutrophil count $\geq$1,500/mcL
- platelets $\geq$100,000/mcL
- total bilirubin within normal institutional limits

- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
- creatinine clearance ≥30 mL/min

6 Cardiac ejection fraction ≥50% as measured by echocardiogram or MUGA scan. Note that baseline and on treatment scans should be performed using the same modality and preferably at the same institution

7 The ability to provide informed consent

8 The ability to swallow and retain oral medication

9 Resolution of grade ≥2 toxicity from prior therapy (other than alopecia)

10 Both measurable as well as unmeasurable disease will be allowed

11 Patients may have received any number of prior chemotherapies or prior treatments for their cancer

12 Prior treatment with lapatinib or trastuzumab are allowed, provided that the agents have never been given in combination

Exclusion Criteria:

1 Concurrent investigational treatment, chemotherapy, or targeted therapy.

2 All toxicities grade ≤2 must have resolved by the time of study commencement (except alopecia). However, prior chemotherapy, hormonal therapy, targeted therapy, and investigational agents are allowed. Prior trastuzumab and/or lapatinib therapy is allowed.

3 Unstable or symptomatic brain metastases (Patients with stable or treated brain metastases who do not require steroids at doses greater than 10mg prednisone daily or its equivalent may be enrolled)

4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to lapatinib or trastuzumab. However, patients with a history of infusion reaction to trastuzumab which was controlled with premedication on subsequent infusions without a recurring infusion reaction are eligible.

5 Concomitant medications that are inhibitors or inducers of CYP3A4. (see Appendix C)

6 Ongoing or active infection (including HIV) or psychiatric illness/social situations that would limit compliance with study requirements

7 Inability to take oral medication

8 Malabsorption syndrome, (prior surgical procedures affecting absorption), or uncontrolled inflammatory GI disease (e.g., Crohn's, ulcerative colitis)

9 Current active hepatic or biliary disease (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per investigator assessment)

10 Active cardiac disease, defined as (but not limited to):

- History of documented congestive heart failure (CHF) or systolic dysfunction (LVEF < 50%)
- High-risk uncontrolled arrhythmias (ventricular tachycardia, high-grade AV-block, supraventricular tachycardias which are not adequately rate-controlled)
- Angina pectoris requiring antianginal medications

- Evidence of transmural infarction on EKG
- Clinically significant valvular heart disease
- Poorly controlled hypertension (e.g. systolic >180mmHG or diastolic >100mm Hg)

Investigational Product Dosage and Administration:

Lapatinib will be given as 1000mg orally daily throughout the study period. Subjects will be instructed to take lapatinib ≥1 hour before or after a meal.

Trastuzumab will be given in one of two schedules at the discretion of the treating physician. Dosing will be either:

1) Weekly, first as a loading dose of 4mg/kg intravenously during week one, and then at a maintenance dose of 2mg/kg intravenously weekly thereafter, or
2) Every three weeks, first as a loading dose of 8mg/kg intravenously during week one, and then at a maintenance dose of 6mg/kg intravenously every three weeks thereafter

Patients initially started on weekly trastuzumab can be changed to a every 3 week regimen at the discretion of the treating physician. Likewise, patients initially started on trastuzumab every 3 weeks can be changed to weekly trastuzumab at the discretion of the treating physician.

These medications will be continued until disease progression, death, drug intolerance or other limiting factor, removal from protocol due to patient or physician preference, or loss to follow-up.

Clinical Observations and Tests to be Performed:

Patients who fulfill the eligibility criteria described above will undergo the full informed consent process. Prior to starting treatment, all subjects will undergo history and physical exam, and laboratories (CBC, CMP). Baseline disease will be documented with CT scan of chest, abdomen, and pelvis, or PET-CT as long as there is a diagnostic CT component (within 30 days prior to starting treatment). All subjects will have cardiac function evaluation (within 30 days prior to starting treatment) using either echocardiogram or MUGA scan, and an EKG.

Each cycle will be three weeks with lapatinib continued daily and trastuzumab continued either weekly or every three weeks as described above. During each cycle, history and physical, CBC and CMP (Chem-7, calcium, LFTs) will be performed once every three weeks (+/- 1 wk). Toxicity will be evaluated at these appointments as well as during the interim if the subject contacts the participating clinician with concerns. Evaluations will continue once per cycle until disease progression, death, discontinuation of the drug, or loss to follow-up.

Due to the risk of early toxicity in this population, during the first cycle and part of the second cycle, the patient will be seen weekly at a brief nurse visit during those weeks in which no full physician assessment is required. During these visits, full case report forms will not be filled out, but limited history and physical exams will be done to ensure that any severe side effects that could benefit from intervention are identified.

While on study, CT of the chest, abdomen, and pelvis (or PET-CT as above); and LVEF evaluation will be performed at the end of every four cycles (every 12 weeks). The modality of cardiac evaluation must be consistent throughout the study for each individual patient.

A cancer specific geriatric assessment will be given at baseline and at the end of every four cycles (12 weeks). The cancer-specific geriatric assessment includes an evaluation of functional status, co-morbidity, cognition, psychological status, social functioning and support, and nutritional status.[1] This assessment has been piloted in the CALGB.

Adherence to trastuzumab will be measured by proportion of doses given in the infusion center. Adherence to lapatinib will be measured by pill count as well as by patient self-report in dedicated patient diaries. Pill counts and review of diaries will be performed once per cycle until cycle 5, after which point they will be performed once every 4 cycles (12 weeks). In the event of discrepancy in these two measures of adherence, we will follow whichever indicates the lower measure of adherence (i.e. If patient states they took 13 of 14 doses, but only 10 doses are missing, we will count the patient as having taken only 10 days. Alternatively, if 14 doses are missing, but the patient states she only took 11 doses, we will count the patient as having taken only 11 doses.) All toxicity related dose interruptions or reductions, hospitalizations, and adverse events will be noted. Subjects will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade $\geq$2 toxicities.

Lapatinib troughs to assess drug pharmacokinetics will be drawn prior to daily lapatinib use at the beginnings of week 3, 4, and 5only, provided that the patient has taken lapatinib at the same dose level for each of the seven days prior to this study. In the event that the lapatinib dose is held or the dose level is changed, pharmacokinetic sample will be rescheduled accordingly.

Statistical Considerations:

Tables will be created to summarize the toxicities and side effects for each dose schedule by dose, course, organ and severity for all patients. We will describe all serious adverse events and other serious toxicities on a patient by patient basis. Numbers of cycles received and dose reductions will be tabulated by dose. Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 3 or higher toxicities, 2) all grade nausea, diarrhea and vomiting, 3) all grade cardiac events, 4) dose reductions, delays, interruptions and hospitalizations, and 5) the objective response rate (CR+PR) and clinical benefit rate (CR+PR+SD). Descriptive statistics will be provided for study patient demographics and pharmacokinetic measures. We will use general linear models of these data to determine if any of these factors independently predict toxicity, efficacy, and/or pharmacokinetic parameters of interest.

Sponsor/Licensee:

City of Hope Comprehensive Cancer Center

Case Report Forms

Paper or via Medidata Electronic Data Collection (EDC))

Table of Contents

Abbreviation	Meaning
AE	Adverse Event
AI	Aromatase Inhibitor
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CALGB	Cancer and Leukemia Group B
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CMP	Complete Metabolic Panel
CNS	Central Nervous System
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCIS	Ductal Carcinoma *in situ*
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ECHO	Echocardiogram
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EKG	Electrocardiogram

ER	Estrogen Receptor
ErbB	Epidermal Growth Factor
FDA	Food and Drug Administration
FISH	Florescence *In Situ* Hybridization
GAS	Geriatric Assessment Survey
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GSK	GlaxoSmithKline
HCG	Human Chorionic Gonadotropin
HER2	Human Epidermal Growth Factor Receptor 2 (also HER-2/neu or ErbB2)
HIPAA	Health Insurance Portability and Accountability Act
HR	Hormone Receptor
IB	Investigator Brochure
ICF	Informed Consent Form
IDS	Investigational Drug Services
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate Dehydrogenase
LFTs	Liver Function Tests
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute

NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PI	Principal Investigator
PK	Pharmacokinetics
PMT	Protocol Monitoring Team
PO	*Per Os* (orally)
PR	Partial Response
q	Every (as in q3 weeks, meaning “every three weeks”)
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SWOG	Southwest Oncology Group
TKI	Tyrosine Kinase Inhibitor
TOX	Toxicity
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
Wk	Week(s)

1.0 Goals and Objectives (Scientific Aims)

1.1 Primary Objective

To estimate the safety and tolerability of the combination of trastuzumab and lapatinib in adults age 60 or older with locally advanced or metastatic breast cancer

1.2 Secondary Objectives

1. To describe the full toxicity profile including all grades
   - To estimate the rate of all grades of cardiac toxicity
   - To estimate the rate of all grades of diarrhea, nausea, and vomiting
2. To describe the pharmacokinetic parameters of lapatinib in older adults
3. To estimate objective response rate and clinical benefit rate as defined by modified RECIST criteria
4. To estimate median progression-free and overall survival
5. To explore factors other than chronologic age that can affect toxicity rates as identified using a cancer-specific geriatric assessment
6. To estimate rates of adherence to lapatinib among older adults

2.0 Background

2.1 Introduction/Rationale for Development

This proposal addresses a key research priority of the Cancer and Aging Research Group: the assessment of the pharmacology of cancer therapy in older adults.[2] While several studies have demonstrated that older adults are more likely to experience chemotherapy toxicity,[3-5] the comparative risk of targeted therapies has not been studied. Though chronological age does not entirely correlate with physiologic age, older adults do have changes in physiology that can predispose to drug toxicity.[6] A progressive reduction in the functional reserve of various organ systems may alter the pharmacokinetics of anti-cancer therapies[7-8] and increase the susceptibility of older individuals to complications of treatment.[9-12] Normal tissues may be less able to repair the molecular damage caused by antineoplastic agents due to cellular senescence, resulting in greater potential cardiotoxicity, neurotoxicity, mucositis, and hematologic toxicities.[6] And finally, there may be age-related changes in the biology of cancer which may impact the therapeutic efficacy and approach.[13-14] Older adults are an important population to study because 60% of all cancer cases and 70% of cancer mortality occur in patients over the age of 65.[15] Furthermore, the number of older adults with cancer is expected to rise significantly with the aging of the US population. Older adults with cancer are an understudied population. Cancer patients age 70 or greater made up only 20% of subjects enrolled in FDA registration trials from 1995 to 1999, though they made up fully 46% of the US cancer population.[16]

The goal of this study is to utilize a phase II design to examine the tolerability of anti-HER2 directed therapies among older adults with HER2 overexpressing breast tumors. Specifically, we aim to study the effect of the combination of lapatinib, an oral small molecule tyrosine kinase inhibitor targeted at both the intracellular domains of HER2 and EGFR[17] and trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of HER2. There is significant interest in studying this drug among the elderly as it is an oral targeted therapy. However, there is concern that without definitive studies in the older adult population, oncologists may have reservations in giving lapatinib or in dose reducing the agent without guidance.

2.2 **HER Signaling in Cancer**

The human HER (ErbB) receptor family consists of four closely related transmembrane receptor tyrosine kinases. Upon binding of ligands, HER receptors become activated and undergo hetero- or homodimerization. Dimerization in turn, results in phosphorylation of specific receptor cytoplasmic tyrosines with subsequent recruitment of downstream signaling proteins. Ligands have been identified for the HER1 (also known as EGFR), HER3 and HER4 receptors. No ligand has yet been identified for HER2 (also known as Her-2/neu) which is the preferred dimerization partner for HER1, HER3, and HER4.[18] HER3 possesses a defective tyrosine kinase and therefore, requires heterodimerization with another HER member to be activated. HER4 has an active tyrosine kinase, but its role in breast cancer is currently unknown.

HER1 (aka EGFR) and HER2 receptors are often upregulated in many human cancers.[19-20] Elevated levels of the HER2 extracellular domain in sera of patients with breast cancer correlate with a poorer response to both chemotherapy and endocrine therapy.[21-23] Additionally, increased expression of the EGF or TGF-α ligands indicates a poor prognosis in some cancer patients.[24-25] Expression of these ligands appears to be responsible for maintaining HER receptors in an activated state even in the absence of receptor over-expression.[24, 26-27] Many therapeutic strategies have therefore been employed to block the HER signaling pathways as a means to improve the therapeutic efficacy of hormonal and chemotherapy regimens.

2.3 **Trastuzumab**

Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody that binds with high affinity to the extracellular domain of the HER2 protein, is currently approved as a first-line agent in combination with taxanes or as a single agent in advanced Her2/neu overexpressing breast cancer.[28-29] In adjuvant trials, trastuzumab has been shown to decrease the risk of recurrence of breast cancer by 39-52%[30-32] and decreases the risk of death by 33%.[30] Trastuzumab has also been found effective in the neoadjuvant setting.[33]

Though generally well tolerated, trastuzumab can produce cardiotoxicity in the form of either asymptomatic decreased ejection fraction or overt heart failure, particularly when given together with anthracycline containing chemotherapy regimens.[28, 34-38]

Although trastuzumab based regimens have improved recurrence rates and overall survival in patients with HER2 positive breast cancer only 26% of patients treated with trastuzumab as a first-line single agent have an overall response.[39] Additionally, most women who have response develop acquired resistance within months to years.[40] The mechanisms behind HER2 refractoriness or resistance are varied. Recent data have shown that dysregulation of the HER2/HER2/PI3 kinase/PTEN pathway, PI3 kinase mutations, or PTEN depletion have are associated with resistance to HER2 targeted therapies.[41-44] The full length HER2 (p185ErbB2) undergoes proteolytic cleavage shedding its extracellular domain which is detectable in cell culture media or patient sera.[45] Cleavage of HER2 appears to be mediated by a member of the matrix metalloprotease (MMP) family.[46] Truncated HER2 receptor (p95ErbB2) exhibits increased autokinase activity and transforming efficiency compared with p185ErbB2, implicating the extracellular domain as a negative regulator of HER2 kinase and oncogenic activity.[47-48] One study found that p95ErbB2 is expressed more frequently in lymph node metastatic tissue than in primary breast tumors.[49] It is unlikely that an antibody such as trastuzumab directed against the extracellular domain of HER2 can bind to and/or inhibit the truncated, activated p95ErbB2 receptor. Small molecule tyrosine kinase inhibitors may however, prove to be effective against p95ErbB2 positive breast cancer.[49]

Small molecule HER tyrosine kinase inhibitors (TKI's) compete for the ATP binding site and inhibit the receptor's activity. In principle, small molecule TKI's should inhibit the activity of HER1 (EGFR) in the

presence of elevated levels of ligand and should also inhibit the activity of ErbB receptors with truncated extracellular domains. Single agent small molecule TKI's have been reported to exhibit clinical activity.[50]

Additionally, members of the HER class of transmembrane proteins often heterodimerize. HER2-containing heterodimers elicit potent mitogenic signals and as such, targeting HER1 and HER2 simultaneously may provide therapeutic synergy.[51]

2.4 **Lapatinib**

Lapatinib is an oral small molecule tyrosine kinase inhibitor directed at the intracellular domain of both HER2 and EGFR (HER1).[17] A randomized phase III clinical trial including women with HER2-overexpressing advanced breast cancer who had progressed on a regimen containing trastuzumab, showed that lapatinib in combination with capecitabine was superior to capecitabine alone.[52] This study ultimately resulted in FDA approval for lapatinib in 2007 in combination with capecitabine. Additionally, a Phase III trial showing that lapatinib in combination with letrozole, an aromatase inhibitor, was effective in the first-line metastatic setting in a subset of 219 patients whose breast cancer was HER-2 positive and hormone receptor positive. Median progression-free survival was 8.2 months for those receiving letrozole and lapatinib versus 3.0 months for those getting letrozole alone (HR 0.71 [0.53-0.96], p=0.019).[53]

The pivotal trial that led to FDA approval of lapatinib involved the combination of lapatinib with capecitabine. More recently, lapatinib has been given FDA approval in combination with the aromatase inhibitor letrozole for those patients who are both HER2 as well as hormone receptor overexpressing. Lapatinib is not currently approved as a single agent. However, Phase III clinical trials are currently ongoing or completed that suggest that lapatinib is effective when given in combination with other agents, including trastuzumab, in both the first and second line treatment of metastatic breast cancer.[53-55] An ongoing trial is testing lapatinib in the adjuvant treatment of breast cancer together with chemotherapy and/or trastuzumab.[56]

As a member of the 4-anilinoquinazoline class of kinase inhibitors, lapatinib is thought to react with the ATP binding site of EGFR/ErbB2, resulting in inhibition of autophosphorylation and subsequent proliferative signaling.[57]

The pharmacokinetics of lapatinib are similar in healthy volunteers and patients, demonstrating oral absorption that is incomplete, highly variable, and sometimes delayed. After dosing, plasma concentrations rise to a peak at approximately 4 h and thereafter decline with measured half-lives averaging up to 14 h. However, accumulation with daily dosing achieves steady state in 6-7 days, which suggests a true elimination half-life on the order of 24 h. Administration of the same daily dose in a twice daily schedule results in 2-fold greater systemic exposure than a once daily schedule. Despite this inconsistency, systemic exposure generally increases with increasing dose. Absorption is increased by ingestion with food. Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with negligible renal excretion. Significant changes in systemic exposure to lapatinib result from co-administration of drugs that are potent inhibitors or inducers of CYP3A.[58]

2.5 **Rationale for Combining Trastuzumab and Lapatinib**

Data from multiple lapatinib studies support the preclinical data that have shown a relative lack of cross-resistance between trastuzumab and lapatinib.[59] Despite both trastuzumab and lapatinib inhibiting the same HER2 receptor, the combination of the two drugs is potentially attractive because each agent targets a different part of the receptor: trastuzumab the extracellular domain,[60] and lapatinib, the intracellular domain.[61] In addition, the two drugs have different mechanisms of action. Trastuzumab efficiently recycles with the HER-2 receptor following endocytosis and internalization and degradation of HER2, and its down-regulation seems to be less important to its mode of action.[62] Trastuzumab leads to an initial stimulatory effect of HER-2 phosphorylation[63] and lapatinib inhibits the HER2 tyrosine kinase activity

and that of its co-receptor EGFR.[61, 64] EGFR may play an important role as a co-receptor for HER2 and the cooperation between EGFR and HER2 provides a rationale to target EGFR when HER2 is overexpressed.[65] This may lead to sustained inhibition of activation of the HER2 receptors, and may constitute a superior way of inhibiting a dysregulated signaling network.

Preclinical data indicate that lapatinib has a synergistic effect with trastuzumab in HER2 positive breast cancer cells.[66] In addition, lapatinib shows activity against cells selected for long-term growth in trastuzumab-containing media, suggesting non-cross-resistance between the two agents.[66]

A phase I study of lapatinib administered with trastuzumab in 54 heavily pretreated patients who had progressive disease during previous trastuzumab treatment and whose tumors overexpressed HER2 or had HER2 gene amplification (by IHC or FISH, respectively), demonstrated an overall response rate of 22%. The recommended phase 2 dose of lapatinib was 1000 mg daily with weekly trastuzumab (4mg/kg IV load followed by 2mg/kg IV once weekly), with fatigue being dose-limiting at higher doses and with no occurrence of symptomatic or asymptomatic decline in left ventricular ejection fraction.[67-68]

Diarrhea, nausea, fatigue, and anorexia appear to be increased in both frequency and intensity with this combination. All 54 subjects enrolled experienced at least one adverse event (AE) with a total of 864 AEs reported; the majority of these were of Grade 1 or 2 intensities (797/864 or 92%). The most frequently reported events were diarrhea (83%), nausea (61%), fatigue (57%), rash (57%), and anorexia (41%). A total of 553 drug-related AEs were reported; thirty-four Grade 3 events in 20 subjects were drug related. No drug-related Grade 4 events were reported. Thirteen of 54 subjects experienced 29 serious AEs; four events were considered drug-related: fatigue and diarrhea in one patient and nausea and vomiting in another. No deaths were reported.

One patient experienced asymptomatic changes in LVEF values that included a decrease from a baseline value of 58% to 45% approximately 8 months after initiating treatment. During continued treatment, subsequent LVEF values have been 50% (9 months), 60% (11 months), and 55% (13 months).

A phase III randomized, multicenter, open label trial was recently performed to compare the safety and efficacy of lapatinib alone versus lapatinib in combination with trastuzumab in patients with HER2 positive metastatic breast cancer who had experienced progression on prior trastuzumab therapies. The intent-to-treat population was 296 patients, and patients had received a median of three prior trastuzumab containing regimens. Trastuzumab, when given, was given on a weekly schedule and lapatinib was given at 1000mg daily when together with trastuzumab, and at 1500mg daily as a single agent. Median age was 52, and 73% of patients had documented visceral disease. Six month progression free survival was 28% in the combination arm compared to only 13% in the lapatinib alone arm.[59] Recently, overall survival data has been reported, and median overall survival was 20 weeks longer in the combination arm than in the lapatinib alone arm (61 weeks versus 41 weeks).[69] The combination was well tolerated with the most frequent events being diarrhea, rash, nausea, and fatigue. The rate of diarrhea in the combination arm was 60% compared to 48% in the lapatinib alone arm. However, grade 3 and 4 diarrhea only occurred in 7% of patients in each arm. Symptomatic cardiac events occurred in 2% of patients on the combination arm and 0.7% of patients on the lapatinib-alone arm.[59]

2.6 **Aging and Decreased Tolerance of Cancer Treatment**

Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace.[70-71] The age-related physiological decline in organ systems typically begins in the 3rd decade of life and is not evident at times of rest but becomes most apparent when the body is stressed.[72] Either cancer or cancer treatment can be considered a physiological stressor, and the age-related decrease in physiologic reserve may affect tolerance to cancer treatment.

Several studies have demonstrated that older adults are more likely to experience chemotherapy toxicity,[3-5] and older adults are at greater risk for myelosuppression, cardiotoxicity, neurotoxicity, and mucositis.[6]

Older adults can in most cases tolerate chemotherapy in doses and schedules similar to those in younger adults, but side effects need to monitored closely and occasionally more aggressive prophylactic measures need to be employed.[73] However, most studies to date have determined tolerability of cancer therapies in older adults retrospectively rather than using prospective interventional trials. With some therapies it has been suggested that a lower starting dose in older adults, while causing less toxicity, does not impact efficacy.[74]

A number of age-related changes in drug absorption, distribution, metabolism, and excretion with aging may contribute to differences in treatment tolerance between older and younger patients. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.[8, 75] With the increased use of oral therapy, medication compliance is an important issue as well.[76] As a person ages, body composition changes, with an increase in body fat and decrease in lean body mass and total body water. The increase in body fat leads to a rise in the volume of distribution for hydrophilic drugs. In the population of older adults with cancer, malnutrition and hypoalbuminemia may result in an increased concentration of drugs that are albumin-bound.[12]

Hepatic mass and blood flow also decrease with age.[70] The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is controversial.[77] In a study of 226 patients, the cytochrome P-450 content in liver biopsy samples decreased by approximately 30% in patients over the age of 70.[78] Renal function also declines with age, and renal insufficiency is common in older adults.[79-80]

A progressive reduction in the functional reserve of various organ systems may alter the pharmacokinetics of anti-cancer therapies[7-8] and increase the susceptibility of older individuals to complications of treatment.[9-12] Normal tissues may be less able to repair the molecular damage caused by antineoplastic agents due to cellular senescence, resulting in greater potential cardiotoxicity, neurotoxicity, mucositis, and hematologic toxicities.[6] And finally, older adults may develop tumors that are more resistant to treatment.[13-14]

In fact, pharmacokinetics and pharmacodynamics of antineoplastic agents have been shown in some cases to be affected by increasing age. In a study of patients across different age groups receiving paclitaxel chemotherapy, the mean area under the curve significantly increased and the mean clearance significantly decreased with age. Additionally, older patients experienced an increased incidence of grade 3 neutropenia and lower absolute neutrophil count nadir than younger patients, though there was no increase in neutropenic fevers or hospitalizations.[81] In a study of 73 women with advanced breast cancer between the ages of 65 and 89 (median age 73), 30% of participants taking standard doses of capecitabine, but only 5% of patients starting at a lower dose required dose reductions from the starting dose due to severe toxicity. The two groups had similar rates of response and time to disease progression.[74]

Older adults are an important population to study because 60% of all cancer cases and 70% of cancer mortality occur in patients over the age of 65.[15] Furthermore, the number of older adults with cancer is expected to rise significantly with the aging of the US population. Older adults with cancer are also an understudied population. Accrual of older adults to clinical trials has been shown to be significantly lower than their proportion in the general population in both an analysis of SWOG trials[82] as well as in studies of drugs approved by the FDA over a seven year period.[16] Cancer patients age 70 or greater made up only 20% of subjects enrolled in FDA registration trials from 1995 to 1999, though they made up fully 46% of the US cancer population.[16]

2.7 **Factors Other than Chronological Age that Impact Drug Tolerance**

Aging is a heterogeneous process. While certain declines in organ function are universal as the human body ages, the rate of this decline and the consequences of this decline on everyday function proceeds at a

unique pace in each individual. Therefore, chronologic age tells us relatively little about the specific individual. A more detailed evaluation of an older adult patient is needed in order to capture factors other than chronological age that predict for morbidity and mortality. A comprehensive geriatric assessment may serve this purpose. The comprehensive geriatric assessment includes an evaluation of functional status, comorbid medical conditions, cognitive function, nutritional status, social support and psychological state, and a review of medications. Conclusions from several studies are emerging regarding the benefits of performing a comprehensive geriatric assessment for older patients with cancer.

1. Factors evaluated in a comprehensive geriatric assessment predicts survival;[83]
2. Factors evaluated in a comprehensive geriatric assessment predicts toxicity to chemotherapy;[84]
3. A comprehensive geriatric assessment uncovers problems not detected by routine history and physical in initial consultation and follow-up care;[85]
4. Patients undergoing a comprehensive geriatric assessment and intervention based on the results had improved pain control;[86]
5. A comprehensive geriatric assessment and intervention improves an older patient's mental health and well-being.[86]

Consensus guidelines recognize the benefits and recommend the inclusion of a geriatric assessment as part of the evaluation of an older patient.[87]

2.8 **Aging and Targeted Therapy**

Limited evidence exists to guide therapy with lapatinib in the older adult. The pivotal trial of lapatinib included patients up to 83 years of age, however only 17% of adults in this study were 65 years or older and only 1% were 75 or older (Table 1).[88] No subset analysis of lapatinib safety and efficacy in older adults was reported.[52] Mean age of subjects on lapatinib trials to date has been 58 years.[56] The effect of age on lapatinib pharmacokinetics has also not been formally evaluated. Review of the data obtained from 326 subjects in Phase I trials, which included individuals ranging in age from 18 to 82 showed no apparent differences in systemic exposure related to age. However, pharmacokinetic parameters were only evaluated in a total of 11 patients over the age of 70 across all trials. Clinically significant changes in pharmacokinetics associated with age generally emerge above the age of 70-75 years. Therefore, the available data cannot be interpreted as indicating that patients older than 70-75 years will display similar pharmacokinetics to younger individuals.[56]

Table 1: Lapatinib Exposure in Older Adults[89]

Patient age (years)	≥65	≥75
Lapatinib + capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
Lapatinib + letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent lapatinib (N=599) (EGF20002, EGF20008, EGF20009, EGF103009)	101 (17%)	24 (4%)

There are rationales to indicate that lapatinib could reasonably have different pharmacokinetics and pharmacodynamics in older adults as well. Lapatinib is highly protein bound in serum.[90] In elderly patients with cancer, malnutrition and hypoalbuminemia might result in increased free concentrations of drugs, like lapatinib, that are heavily protein bound.[12] Lapatinib is also extensively metabolized in the liver, and hepatic mass and blood flow decrease with age.[70] Additionally, the most frequently reported

serious adverse event in trials with lapatinib is diarrhea.[56] Diarrhea can be more serious in the older adult with little social support or impaired sensory or cognitive function, and could lead to dehydration, hospitalization, or even death at a rate greater than in younger adults.

Trastuzumab has also not been well studied in older adults due to poor enrollment of older adults in the relevant clinical trials. While not associated with an increased risk of diarrhea as a single agent, it has been documented that age greater than 60 is a risk factor for developing trastuzumab-related cardiotoxicity.[34-35] The HER2 protein is widely believed to play a role in cardiac contractility and myocyte survival, and as such, cardiomyopathy is likely a class effect of all HER2 directed agents.[91] A recently reported study randomized 297 women previously treated with trastuzumab to either lapatinib monotherapy or lapatinib combined with trastuzumab.[59] The results showed a clinically and statistically significant difference in overall survival.[69] However, the median age in this study was only 52.[59] Few patients were over the age of 60. However, this is a combination that would be potentially attractive to older adults and their physicians who may want to avoid cytotoxic chemotherapy treatment. Given the growing population of older adults with cancer additional study of the benefits and risks of targeted therapies remains an unmet need.

2.9 **Cardiac Toxicity of Lapatinib and Trastuzumab**

2.9.1 Cardiac Effects of Trastuzumab

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab can also cause a symptomatic decline in left ventricular ejection fraction (LVEF). There is a 4−6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab as a single agent or in combination therapy compared with those not receiving trastuzumab.[28, 35-38] The highest absolute incidence occurs when trastuzumab is administered with an anthracycline.[28]

As a single agent, the cardiotoxicity of trastuzumab is variable. In Study H0650g, Vogel et al reported the results of one hundred fourteen women with HER2-overexpressing metastatic breast cancer who were randomized to receive first-line treatment with trastuzumab 4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4 mg/kg weekly. Cardiac dysfunction occurred in only two patients (2%), and both had histories of cardiac disease and did not require additional intervention after discontinuation of trastuzumab.[39] However, in the early study of trastuzumab given in the second or third line setting, the rates were different. Cobleigh et al, in Study H0649g, treated 213 women with HER2-overexpressing metastatic breast cancer that had progressed after one or two chemotherapy regimens. Patients received a loading dose of 4 mg/kg intravenously, followed by a 2-mg/kg maintenance dose at weekly intervals. In this group severe symptomatic cardiac dysfunction occurred in 4.7% of patients, including one death that may have been due to trastuzumab related cardiac failure,[38] and symptomatic heart failure was seen in 8.5% of subjects in a retrospective analysis.[37] It is thought that the difference in rates is likely due to previous treatment with an anthracyclines. In study H0649g, trastuzumab was given in the second or third line. Nine of ten patients with reported severe cardiac dysfunction had previously received an anthracyclines. In study H0650g trastuzumab was given front line, and therefore the risk of having received an anthracyclines in the past was limited.[37]

The risk of trastuzumab in combination with an anthracycline was elucidated in the pivotal trial of trastuzumab given in combination with chemotherapy in the metastatic setting. In study H0648g, Slamon et al. assigned 234 patients to receive standard chemotherapy and 235 to receive standard chemotherapy plus trastuzumab. One hundred thirty eight of the 234 women receiving chemotherapy alone received an anthracycline and cyclophosphamide, while 96 received paclitaxel alone. Of the 235 women who received chemotherapy with trastuzumab, 143 received trastuzumab with an anthracycline and cyclophosphamide, while 92 received trastuzumab with paclitaxel. In addition to showing a statistically

significant benefit in overall survival, the study identified "cardiac dysfunction" as the most important adverse event. It was not clearly specified what constituted cardiac dysfunction. A total of 27 percent of the group given an anthracycline and trastuzumab, but only 8 percent of the group given an anthracycline and cyclophosphamide alone, had cardiac dysfunction. In those who received paclitaxel and trastuzumab, 13 percent of the group given paclitaxel and trastuzumab experienced cardiac dysfunction, compared to only 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.[28, 92]

The presentation of the above data prompted retrospective analyses to evaluate cardiac safety in the above trastuzumab trials. On re-analysis of symptomatic heart failure alone in the study by Slamon et al., the rate of cardiac dysfunction was 8.8% in those who received paclitaxel together with trastuzumab (*N*=8). For the paclitaxel group alone, later analysis showed that 4.2% (*N*=4) of patients had received treatment for symptomatic heart failure events, as against 1% (*N*=1) in the earlier analysis. As had been reported in the initial analysis, the incidence of symptomatic cardiac dysfunction was significantly higher in patients receiving trastuzumab in combination with anthracyclines (28.0%; *N*=40) than in those receiving anthracyclines alone (9.6%; *N*=13).[37] See Table 1 below for a summary of the findings of cardiac toxicity of trastuzumab in the early metastatic studies.

Table 2. Retrospective analysis of data from pivotal trials: incidence of symptomatic heart failure in the pivotal trastuzumab trials, including follow-up to March 1999 (Roche data on file—Cardiac Task Force final report).[37]

	Study					
	H0649g	H0650g	H0648g			
	T alone	T alone	T+P	P	T+AC	AC
Classification	(N = 213)	(N = 114)	(N = 91)	(N = 95)	(N = 143)	(N = 135)
Symptomatic heart failure*	8.5%	2.6%	8.8%	4.2%	28.0%	9.6%
NYHA III-IV	5%	<1%	4%	1%	19%	3%

T=trastuzumab; P=paclitaxel; AC=anthracycline/cyclophosphamide.
*** Defined as congestive heart failure, cardiomyopathy, heart failure, left ventricular failure, lung edema or information from case report forms indicating cardiac failure (e.g. a combination of shortness of breath, dyspnea, increased coughing, or pulmonary congestion on X-ray, echo or MUGA scan).[37]**

In the adjuvant setting, trastuzumab related cardiotoxicity has been well studied. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31, doxorubicin and cyclophosphamide (AC) followed by paclitaxel was compared with AC followed by paclitaxel plus 52 weeks of trastuzumab beginning concurrently with paclitaxel in patients with node-positive, HER2-positive breast cancer. All patients required normal left ventricular ejection fractions between completion of AC and commencement of trastuzumab. If symptoms suggestive of congestive heart failure developed, source documents were

blindly reviewed by an independent panel of cardiologists to determine whether criteria were met for a cardiac event, which was defined as New York Heart Association class III or IV CHF or possible/probable cardiac death. Among patients with normal post-AC LVEF who began post-AC treatment, five of 814 control patients subsequently had confirmed cardiac events compared with 31 of 850 trastuzumab-treated patients. The difference in cumulative incidence at 3 years was 3.3% (4.1% for trastuzumab-treated patients minus 0.8% for control patients; 95% CI, 1.7% to 4.9%). Cardiac events were more frequent in older patients and patients with lower post-AC LVEF (50-55%). Fourteen percent of patients discontinued trastuzumab because of asymptomatic decreases in LVEF; 4% discontinued trastuzumab because of symptomatic cardiotoxicity.[34]

In the Intergroup adjuvant trial (NCCTG N9831), patients with Her2-positive early breast cancer were assigned to AC followed by either paclitaxel, paclitaxel followed by trastuzumab, or paclitaxel together with trastuzumab followed by trastuzumab alone. Left ventricular ejection fraction (LVEF) was evaluated at registration and 3, 6, 9, and 18 to 21 months. Of 1944 patients with satisfactory LVEF following AC, CHF developed in 2.8%, and 3.3%, in the two trastuzumab containing arms, compared with only 0.3% in the paclitaxel alone arm. Cardiac function improved in most CHF cases following trastuzumab discontinuation and cardiac medication. Older age, lower registration LVEF, and antihypertensive medications were associated with increased risk of cardiac dysfunction in patients receiving trastuzumab following AC.[36]

In the Herceptin Adjuvant (HERA) trial, an open-label randomized trial which compared 1 or 2 years of trastuzumab given once every 3 weeks with observation in patients with HER-2-positive breast cancer, cardiac toxicity was also well elucidated. Data were available for 1,693 patients randomly assigned to 1 year trastuzumab and 1,693 patients randomly assigned to observation. The incidence of trastuzumab discontinuation due to cardiac disorders was low (4.3%). The incidence of cardiac end points was higher in the trastuzumab group compared with observation (severe congestive heart failure [CHF], 0.60% v 0.00%; symptomatic CHF, 2.15% v 0.12%; confirmed significant LVEF drops, 3.04% v 0.53%). Most patients with cardiac dysfunction recovered in fewer than 6 months. Patients with trastuzumab-associated cardiac dysfunction were treated with higher cumulative doses of doxorubicin (287 mg/m^2 v 257 mg/m^2) or epirubicin (480 mg/m^2 v 422 mg/m^2) and had a lower screening LVEF and a higher body mass index.[93]

In summary, the above data demonstrate the risk of symptomatic congestive heart failure with trastuzumab. This risk is amplified by concurrent administration of anthracyclines, increased age, lower baseline LVEF, and higher cumulative doses of prior anthracyclines. As a result of this experience, it is recommended that thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan, be conducted prior to the first dose of trastuzumab. The following schedule was used to monitor cardiac function in clinical studies:

- Baseline LVEF measurement immediately prior to initiation of trastuzumab
- LVEF measurements every 3 months during and upon completion of trastuzumab
- LVEF measurements every 6 months for at least 2 years following completion of trastuzumab
- Repeat LVEF measurement at 4 week intervals if trastuzumab is withheld for significant left ventricular cardiac dysfunction

It is recommended in the Herceptin© package insert to withhold trastuzumab for a ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.[94]

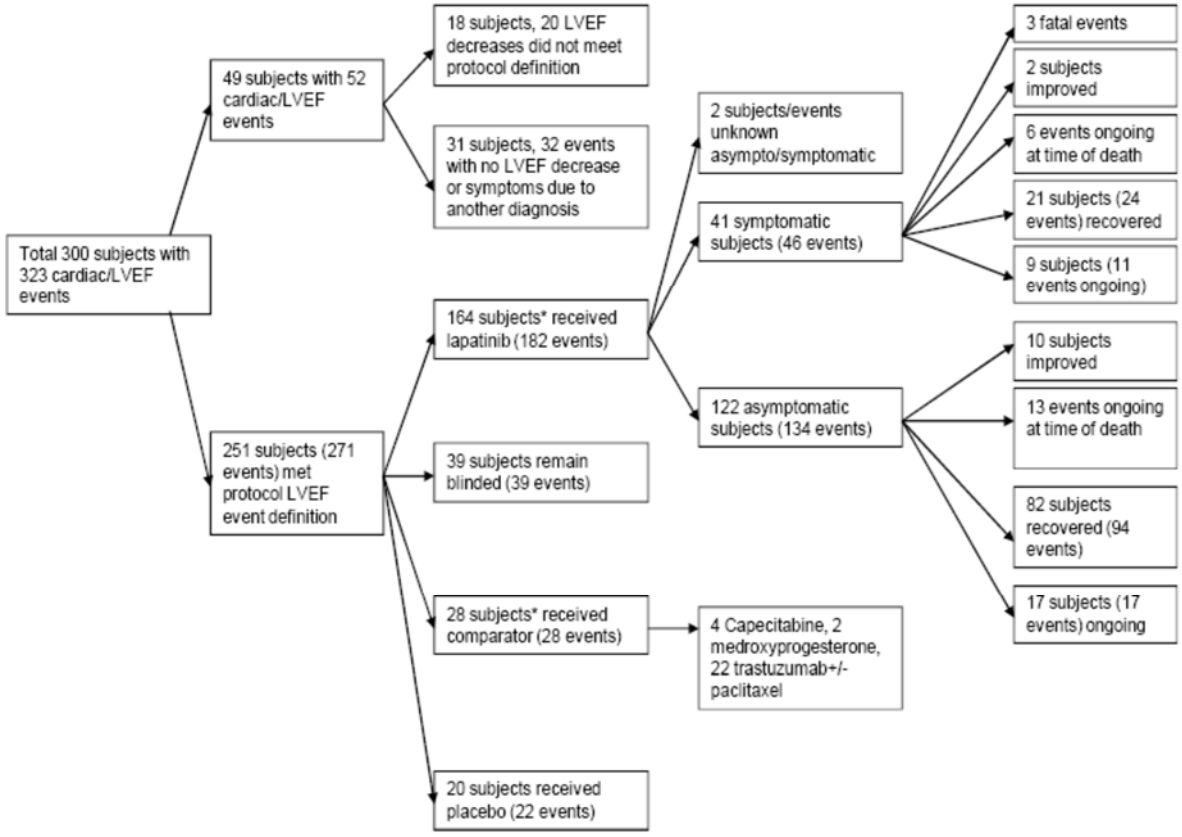
2.9.2 Cardiac Effects of Lapatinib

Left Ventricular Ejection Fraction (LVEF) has been evaluated using MUGA scans or echocardiogram during lapatinib phase I, II and III trials. A total of 300 subjects on lapatinib clinical trials sponsored by

GSK experienced 323 events of decreased LVEF, regardless of investigational product received, as of December 2009. These 300 subjects/323 events are summarized below in Figure 1. Eighty eight percent of the reports were for female subjects, which may be attributed to the fact that the majority of large studies in the lapatinib program are for breast cancer.[89] The protocol-specific definition of a serious cardiac event is defined as follows:

- NCI CTC Grade 3 or 4 left ventricular systolic dysfunction *or*
- LVEF decrease ≥20% relative to baseline value *and* below the institutions lower limit of normal

Figure 1: Summary of decreased LVEF reports which met the protocol specific definition as of December 4, 2009[89]



* One subject experienced an LVEF decrease while receiving capecitabine monotherapy and a second LVEF decrease after crossing-over to lapatinib/capecitabine combination

Of the 251 patients whose LVEF decrease met the protocol specific serious definition, 164 (with 182 events) received lapatinib, giving an incidence of 0.9% (164/17,687) or 1.1% if all 39 subjects who remain blinded as of the latest safety evaluation received lapatinib.[89] Of note, one subject received capecitabine monotherapy then crossed to lapatinib-capecitabine combination therapy, and experienced an LVEF decrease event in each treatment group.[58]

Among the 164 lapatinib subjects, 41 were participating in monotherapy studies and 123 received lapatinib in combination (capecitabine, cisplatin, letrozole, paclitaxel, paclitaxel+trastuzumab, trastuzumab or trastuzumab/docetaxel).

The majority (74%) of decreased LVEF events which occurred on lapatinib treatment were asymptomatic. The mean time to onset of decreased LVEF in the 122 asymptomatic lapatinib-treated subjects was 17.4 weeks (range: 14 days to 2.6 years). The mean LVEF decrease relative to baseline value was 29.5% (range: 20% to 69%). This corresponded to a mean absolute LVEF decrease of 18.4% from baseline (range: 10% to 45%).[89] Among the 122 subjects who experienced asymptomatic LVEF decreases, the majority (85%, 104/122) had pre-existing conditions and/or previous concurrent medications which may have contributed to their LVEF disease. Examples included: previous episodes of decreased LVEF, myocardial infarction, arrhythmia, left-chest radiation, and exposure to anthracyclines, trastuzumab, or paclitaxel, all of which have been associated with cardiac adverse events.[89]

Overall, 92 of 122 asymptomatic subjects (75%) recovered or improved, 69 of these subjects after interruption/discontinuation of lapatinib (positive dechallenge). Forty one of the subjects who recovered or improved continued to receive lapatinib. Lapatinib had already been discontinued in twelve patients prior to detection of an LVEF decrease. Seventeen asymptomatic events were ongoing, and thirteen LVEF decrease events were ongoing at the time of the subject's death due to disease progression.[89]

Forty-one lapatinib subjects experienced 46 symptomatic LVEF decreases while receiving lapatinib (8 during monotherapy and 31 during combination therapy). This gives an approximate incidence of 0.3% for symptomatic events (46/17,687). The symptoms observed were dyspnea, chest pain, cardiac failure, and palpitations. The majority (90%) pf these subjects had pre-existing conditions (e.g. pericardial effusion, pleural effusion, hypertension, diabetes) and/or previous/concurrent medications (e.g. exposure to anthracyclines, trastuzumab, or radiotherapy) which could have contributed to the event.

Many of the subjects in the lapatinib trials had previously received treatment with either anthracyclines and/or trastuzumab, both of which have been associated with cardiotoxicity. In addition some ongoing studies combine lapatinib with trastuzumab, paclitaxel, or capecitabine, which are associated with cardiotoxicity. This therefore increases the risk of cardiotoxicity in the lapatinib patients irrespective of any cardiac toxicity attributed to lapatinib. Decreased ejection fraction is included in the core safety information (CSI) for lapatinib.[58]

These results are similar to results analyzed by Perez et al. in 3689 patients who had been in studies conducted between January 5, 2001, and September 30, 2006. Cardiac events (symptomatic or asymptomatic) were reported in 60 patients. Those patients who had prior treatment with anthracyclines had a 2.2% rate of cardiac events, prior treatment with trastuzumab was associated with a 1.7% rate of events, and those who had not had either previously had a 1.5% incidence of cardiac events. In most patients (53 patients, 83%), events were not preceded by symptoms. The decrease in LVEF was rarely severe; the mean nadir was 43%. In 40 patients for whom outcome was determined, 35 (88%) had a partial or full recovery regardless of continuation or discontinuation of lapatinib. No cardiac deaths occurred among patients treated with lapatinib.[95]

2.10 **Other Important Safety Issues with Lapatinib**

The most extensive study of lapatinib toxicities was in combination with capecitabine. Of note, many of these toxicities may be synergistic when given in combination, and the following two tables cannot serve as reliable predictors of toxicity with lapatinib monotherapy.

Table 3: Common Adverse Events in the Combination of Lapatinib with Capecitabine versus with Capecitabine Alone[52]

	Lapatinib 1,250 mg/day + Capecitabine 2,000 mg/m2/day (N = 198)			Capecitabine 2,500 mg/m2/day (N = 191)		
Reactions	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythro-dysesthesia	53	12	0	51	14	0
Rash†	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.
† Grade 3 dermatitis acneiform was reported in <1% of patients in lapatinib plus capecitabine group.

Table 4: Other Selected Laboratory Abnormalities in the Combination of Lapatinib with Capecitabine versus with Capecitabine Alone[52]

Lapatinib 1,250 mg/day + Capecitabine 2,000 mg/m2/day				Capecitabine 2,500 mg/m2/day		
Parameters	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	22	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	1	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

2.10.1 Interstitial Pneumonitis

Manufacturer-sponsored lapatinib protocols include specific requirements for reporting of signs or symptoms of pneumonitis. As of December 4, 2009, 55 pulmonary events have been reported suggestive of pneumonitis: 42 of these subjects received lapatinib, one subject remained blinded, 11 subjects received a comparator agent (trastuzumab, paclitaxel, cyclophosphamide, or radiotherapy), and one subject received placebo. This gives an approximate incidence of 0.2% (42/17,687) for pulmonary events in lapatinib clinical trials.[89]

Among the 42 lapatinib subjects, 11 were participating in monotherapy studies. Of these 11 subjects, four recovered, and two events were ongoing (one these subjects died due to disease progression while the event was ongoing.) In four monotherapy subjects, the pulmonary event was associated with a fatal outcome: three subjects had evidence of disease progression (including lung metastases and esophageal carcinoma); the fourth subject developed interstitial lung disease and died approximately seven months after the last dose of lapatinib. This subject had recently completed radiotherapy and the investigator felt that lapatinib may have affected the subject's tolerance to radiotherapy. In on subject the outcome of the event was unknown.[89]

Thirty-one subjects experienced pulmonary events while receiving lapatinib in combination (irinotecan, paclitaxel, pazopanib, docetaxel, letrozole, trastuzumab, and radiation). Eighteen of these combination therapy subjects recovered or improved. Five events were associated with a fatal outcome, however all five subjects had evidence of disease progression. Five subjects had not recovered by the time of GSK's last safety evaluation. Outcome remained unknown for three events.[89]

Post-marketing reports have revealed 16 pulmonary events suggestive of pneumonitis as of December 2009. This is based on patient exposure of 7,823 patient years, giving an estimated reporting rate of approximately 0.2% per patient year for pulmonary events. Seven events resolved, three events were ongoing at the time of reporting, four events reported outcome as unknown at the time of reporting, and

two events were reported as fatal as the patients died due either due to progression of disease or of other unknown causes.[89]

2.10.2 Liver Chemistry

As part of ongoing pharmacovigilance by GlaxoSmithKline, a review of all hepatobiliary events reported across the entire lapatinib clinical development program has been performed. Two hundred sixteen reports of hepatic events were retrieved from the GSK safety database as of December 31, 2007 regardless of source (clinical trials, spontaneous/marketed use data). In 39 of the 216 cases, a causal association to lapatinib could not be ruled out: 38.5% (15/39) of these subjects received lapatinib monotherapy, 53.8% (21/39) of subjects received lapatinib in combination with other chemotherapies, such as capecitabine, and 3 cases were still blinded.

The 216 cases noted were the overall number of events associated with hepatobiliary system organ class in the global safety database. After further analysis, a total 177 reports were found to be confounded by factors such as underlying or concomitant diseases or the use of concomitant medications leading to hepatobiliary events. There were 39 cases where a causal association to lapatinib was possible. Therefore, the number 39/8704= 0.4% accurately reflects the crude incidence for hepatobiliary events on the lapatinib program. An incidence of 0.4% falls into the category of 'uncommon' (>/= 0.1% and <1%) per ICH guidelines.

A total of 13 deaths were identified which contained hepatobiliary events. In 3 of these cases, an association with lapatinib could not be excluded. The remaining 10 cases were confounded by the patients underlying condition (progressive disease and/or progression of pre-existing liver metastases).

Based on an additional sub-analysis, of 18 clinical studies of lapatinib in breast cancer, using Hy's Law (defined as AST or ALT >3 x ULN, and total bilirubin >2 x ULN, with no initial findings of cholestasis i.e.: ALP <2 x ULN) as a predictor for potential drug induced liver injury, the liver injury associated with lapatinib seems to be the result of a prolonged exposure to the drug. All the subjects whose events potentially met Hy's Law received study medication for three months or longer. The majority of these cases appeared reversible. Most patients experienced a decline in liver enzymes with drug cessation.

Based on the results of this review, GSK concluded a causal relationship between hepatobiliary disorders (specifically transaminase elevations) and lapatinib cannot be excluded. As a consequence, hepatotoxicity was added to the core safety information (CSI) for lapatinib. In addition, for ongoing clinical trials, the monitoring interval for hepatic function has been increased to every 4-6 weeks during treatment, and stopping rules have been added for severe hepatic events. Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated.[58]

2.10.3 Diarrhea

While cardiac, pulmonary, and hepatic toxicity may be the most concerning potential toxicities of lapatinib, diarrhea is by far the most common. Most cases of diarrhea are Grade 1-2, however the rates of Grade 3 or higher diarrhea (using the definition in the NCI CTCAE v.3.0) have been shown to be relatively high (5-10%) on the lapatinib arm of all pivotal trials to date. In the pivotal trial of capecitabine with or without lapatinib (given 1250mg daily), Geyer et al described diarrhea occurring in 60% of subjects in the combination arm (98/164) compared to only 39% in the capecitabine alone arm (60/152), and this difference was highly statistically significant. The difference in Grade 3-4 diarrhea was not as pronounced. Thirteen percent of those on the combination arm had grade 3 or higher diarrhea (Grade 3=19, Grade 4=2) compared to eleven percent receiving capecitabine alone (Grade 3=17, Grade 4=0).[52]

Johnston et al described a study in which 654 patients treated with letrozole combined with 1500mg daily of lapatinib were compared to 624 patients treated with letrozole plus placebo. In this study diarrhea was also the most prevalent side effect in the lapatinib arm with rates of all grades of diarrhea similar to those reported in the paper by Geyer et al. However, in this study, while less than 1% of those who received

letrozole alone had Grade 3 or higher diarrhea, 11% of those who received lapatinib plus letrozole had Grade 3 or higher diarrhea (Grade 3=58, Grade 4=2).[53] This high rate of grade 3 or higher diarrhea may have been due to the higher dose of lapatinib given, or it may have been due to different demographics between the two studies. The population described by Johnston et al had a much higher median age (62) than the population in the study by Geyer et al (median age 54).[52-53]

More recently, Blackwell et al described the results of the combination of trastuzumab and lapatinib (given at 1000mg daily) with lapatinib alone (given at 1500mg daily). In this study, both arms had a rate of grade 3 or higher diarrhea of 7%. Median age in the study, though, was only 52 years.[59]

Looking at this data in aggregate, it appears that higher doses of lapatinib as a single agent, or lapatinib in combination with other agents, whether chemotherapy, hormonal therapy, or targeted therapy, is associated with relatively high rates of grade 3 or higher diarrhea (7-13%). It is possible that increased age may be associated with an increased risk of diarrhea as well as decompensation from the results of diarrhea (dehydration, electrolyte imbalances), and thus could lead to more severe clinical effects. The rate of high-grade diarrhea in older adults versus younger adults receiving lapatinib has not yet been studied.

2.11 **Overview of Proposed Study**

We propose to study the tolerability of the combination of lapatinib and trastuzumab in older adults with advanced breast cancer who have previously received trastuzumab. This will entail the administration of daily doses of 1000mg of oral lapatinib and either weekly doses of 2mg/kg of IV trastuzumab after an initial load of 4mg/kg, or 6mg/kg of IV trastuzumab every three weeks following an initial load of 8mg/kg until disease progression, death, unacceptable side effects, or study withdrawal.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

2.11.1 Trastuzumab Dosing

Two acceptable ways of dosing trastuzumab have been described in the literature. While most major studies in the metastatic setting have used weekly dosing, many experts believe that every three week dosing of 6mg/kg (following an initial load of 8mg/kg) is adequate due to the drug's low systemic clearance, low volume of distribution, and very long half-life.[96] Post marketing studies of trastuzumab given in the every-three-week setting in metastatic cancer have been studied and found to be a good alternative to weekly dosing and tolerability seemed unaffected.[97-100] Conventional wisdom thus concludes that every three week trastuzumab is substitutable for trastuzumab administered weekly. We will thus allow either form of dosing, as per the discretion of the treating physician.

2.11.2 Strict Rules for Cardiac Toxicity

As cardiac toxicity is a serious adverse event reported with the combination of these agents[59], we will have strict rules for holding lapatinib and trastuzumab in the event of asymptomatic drop in the left ventricular ejection fraction. In some previous trials of lapatinib, dose reductions of lapatinib were recommended in asymptomatic decreases of LVEF only when the LVEF both fell by an absolute amount more than 20%, AND to a level below 50% (the lower limit of normal for most institutions). These were the criteria that were used in the most recently reported lapatinib-trastuzumab combination study[59] as well as the criteria that are being used in the ALLTO adjuvant trial which includes the combination of lapatinib and trastuzumab in one of the study arms.[101] However, as detailed above, the trastuzumab

package insert recommends holding trastuzumab for a ≥16% absolute decrease in LVEF from pre-treatment values OR an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.[88] These criteria are clearly more conservative. Because we are attempting use in a population who has a higher risk of trastuzumab cardiotoxicity than the average population[35], we will use a stricter hold criteria defined as a drop of 10% OR a drop to below the lower limits of normal.

We additionally plan to have study stopping rules in place (described in section 12 below), that will ensure that we do not continue to enroll patients on the study if the symptomatic cardiac toxicity (defined as NYHA Class III or IV heart failure) is higher than is seen in previous studies of trastuzumab (>4%).

Finally, there will be safety assessments ongoing through the institutional oversight board. There will be two formal interim analyses; one following enrollment of 20 patients who have completed one cycle of treatment and a second following enrollment of 30 patients who have completed one cycle of treatment, to allow us to modify starting dose or close the protocol if the starting dose of lapatinib appears overly toxic. We will especially be looking at gastrointestinal toxicity, as diarrhea is an oft-reported side effect of lapatinib, and the severity of diarrhea may be higher in older adults than in younger for a number of reasons described above.

2.11.3 Secondary Objectives

We plan to assess for efficacy of the combination. CT or PET-CT (which contains a diagnostic CT component) will be performed every 4 cycles (12 weeks) to assess for response or progression. Progression-free and overall survival will also be evaluated.

A Geriatric Assessment Survey (Appendix E) will be administered at baseline and every 4 cycles (12 weeks) while on study. The Geriatric Assessment Survey measures various domains including functional status, comorbidity, cognition, psychological status, social functioning and support, and nutritional status. This information may allow us to form hypotheses regarding factors that influence toxicity or response in older adults on dual biologic therapy.

Adherence to lapatinib therapy will be assessed utilizing drug diaries and pill counts. Documentation of non-adherence both may serve as a descriptor of any dose-related toxicity determinations as well as a surrogate for unreported drug toxicities.

As reported above, the pharmacokinetics of lapatinib are widely variable, with variable absorption that is influenced by food, concomitant medications, and potentially other unknown variables. While multiple pharmacokinetic studies of lapatinib have been performed during drug development, only a very small number of these were done in older adults. Steady-state lapatinib pharmacokinetic measures will be gathered. Patients will have a single blood draw during each of week 3, 4, and 5 after starting treatments, immediately prior to their lapatinib dose. However, if the patient undergoes a dose reduction or a hold in treatment the pharmacokinetic samples will be rescheduled accordingly. .

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Disease Status

1. Locally advanced or metastatic Her2/Neu positive breast cancer (defined as IHC 3+ or a FISH ratio of ≥ 2.0). This may be on either a primary tumor or a metastatic site, and there is no time limit from the time the specimen was obtained. Locally advanced breast cancer (LABC) includes breast cancers with advanced primary tumors, ie, large diameter (at least 5 cm) or those with skin and/or chest wall involvement, and advanced regional lymph node involvement. It also includes a rare subgroup, inflammatory breast cancer.

In the 2010 American Joint Committee on Cancer and the International Union for Cancer Control (AJCC-UICC) TNM breast cancer staging system, locally advanced breast cancer (LABC) includes patients with stage III disease. This comprises:

- Advanced primary tumors [Tumors > 5 cm in greatest dimension (T3). direct extension to the chest wall and/or to the skin (T4): ulceration, skin nodules, and/or edema (including peau d'orange) confined to the same breast, Inflammatory breast cancer (IBC, T4d)]
- Advanced regional lymph nodes [Ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases (N2), Ipsilateral infraclavicular (level III axillary) lymph nodes, ipsilateral internal mammary lymph node(s) with axillary lymph nodes, or ipsilateral supraclavicular lymph nodes (N3)]

2. Both measurable and non-measurable disease are allowed

3.1.2 Age Criteria and Life Expectancy

1. Age 60 or older
2. Life expectancy of greater than 12 weeks

3.1.3 Child Bearing Potential

The effects of lapatinib and trastuzumab on the developing fetus are unknown. For this reason, women of child-bearing potential and sexually active men must agree to use adequate contraception prior to study entry and for six months following duration of study participation.

3.1.4 Protocol-Specific Criteria

ECOG performance status ≤2 (Karnofsky performance status ≥60%)

1. (See Appendix A)
2. Normal organ and marrow function as defined below:

-	hemoglobin	≥10 g/dL (after transfusion if necessary)
-	absolute neutrophil count	≥1,500/mcL
-	platelets	≥100,000/mcL
-	total bilirubin	within normal institutional limits
-	AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
-	creatinine clearance	≥30 mL/min as measured using either the Cockroft-Gault method or 24-hour creatinine clearance

- The above tests must be obtained within 14 days of study treatment

3. Cardiac ejection fraction ≥50% as measured by echocardiogram or MUGA scan.
4. The ability to swallow and retain oral medication
5. Prior treatment with lapatinib or trastuzumab are allowed, provided that the agents have never been given in combination

6. Any number of prior cancer treatments, including investigational agents, chemotherapy, hormone therapy, or targeted therapy are allowed.

3.1.5 Informed Consent

All patients must have the ability to understand and the willingness to sign a written informed consent.

3.2 **Exclusion Criteria**

3.2.1 Study-Specific Exclusions

1 Concurrent investigational treatment, chemotherapy, or targeted therapy. Prior chemotherapy, hormonal therapy, targeted therapy, and investigational agents are allowed but all toxicities grade ≥2 must have resolved by the time of study commencement (except alopecia).

2 Unstable or symptomatic brain metastases (However, patients with stable or treated brain metastases who do not require steroids at doses above those permitted in Appendix C for control of symptoms may be enrolled)

3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to lapatinib or trastuzumab. However, patients with a history of infusion reaction to trastuzumab which was controlled with premedication on subsequent infusions without a recurring infusion reaction are eligible.

4 Concomitant medications listed in Appendix C are prohibited. Inhibitors or inducers of CYP3A4 not listed in Appendix C can be used with caution.

5 Ongoing or active infection (including HIV) or psychiatric illness/social situations that would limit compliance with study requirements

6 Inability to take oral medication

7 Malabsorption syndrome, (prior surgical procedures affecting absorption), or inflammatory GI disease (e.g., Crohn's, ulcerative colitis) which in the opinion of the study coordinator is likely to limit normal absorption of the drug

8 Current active hepatic or biliary disease (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per investigator assessment)

9 Active cardiac disease, defined as (but not limited to):

- History of documented congestive heart failure (CHF) or systolic dysfunction (LVEF < 50%)
- High-risk uncontrolled arrhythmias (ventricular tachycardia, high-grade AV-block, supraventricular tachycardias which are not adequately rate-controlled)
- Angina pectoris requiring antianginal medications
- Evidence of transmural infarction on ECG
- Clinically significant valvular heart disease
- Poorly controlled hypertension (e.g. systolic >180mmHG or diastolic >100mm Hg)
- Any other cardiac condition, which in the opinion of the treating physician would make this protocol unreasonably hazardous for the patient

3.2.2 Non-Compliance

Subjects who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study are not eligible.

3.3 Inclusion of Women and Minorities

This is a study of patients with locally advanced or metastatic breast cancer. Therefore, we anticipate the majority of participants will be female; however, accrual is open to both genders. The study is open to anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population.

4.0 Screening and Registration Procedures

4.1 Screening Procedures

4.1.1 General Guidelines

Eligible patients will be entered on study at the participating site and centrally at the City of Hope Comprehensive Cancer Center by the Study Coordinator. An Eligibility Screening Worksheet is attached as Appendix D.

Following registration, patients should begin protocol treatment after receiving the oral medication and after being told to do so by the study team. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were performed within 2 weeks for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained.

4.1.2 Procedure for On-study and Treatment Deviations

Any amendments to the study protocol need to be approved by the IRBs at both the study sponsor site as well as at all participating centers. All deviations or single subject exceptions to the study protocol must be reported to the primary IRB of the participating site, and to Dr. Arti Hurria, the study coordinator at the sponsoring institution.

4.2 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

4.3 Registration Requirements/Process

The participating clinicians who are approved at City of Hope may obtain informed consent: Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section "Patient Eligibility" (3.0), and using the checklist in Appendix D.

Obtain written informed consent by following procedures defined in the section entitled "Informed Consent Processes" (see section 14.7).

To register a **City of Hope patient**, the treating physician should contact the responsible Clinical Research Associate (CRA) in the Clinical Trials Office or the protocol nurse to determine whether the patient meets all of the eligibility criteria, and to assist with the informed consent process. After verifying the eligibility and receiving the signed informed consent, the CRA will register the patient onto the study.

4.3.1 Registration Process (City of Hope patients)

4.3.1.1 Registrations for protocols must be made through the CTO office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m. PST, Monday through Friday (except holidays).
4.3.1.2 Patients must be registered within 2 weeks prior to initiation of protocol therapy.
4.3.1.3 A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact (626) 256-4673 ext. 62468 and ask for the CRA in charge of this study.
4.3.1.4 Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to the study calendar.
4.3.1.5 Patients must sign an informed consent prior to registration.
4.3.1.6 Confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol.
4.3.1.7 Complete the Eligibility Checklist.
4.3.1.8 Verify that all required prestudy tests were performed.
4.3.1.9 Fax the completed Eligibility Checklist and the signed, dated informed consent to CTO. The FAX number is (626) 301-8393.
4.3.1.10 Call CRA at (626) 256-4673 x 62468 to confirm the FAX arrival. If the Coordinator is not in the office, have her paged.
4.3.1.11 If the patient qualifies, the City of Hope Coordinator will assign the patient's study ID number.
4.3.1.12 Once a patient has been registered, CRA will confirm registration of the patient.

The outside institution patient registration process will be handled by the Department of Clinical Research Information Support (CRIS) Data Coordinating Center (DCC) at City of Hope. Documentation of current IRB approval must be on file with the DCC prior to registration of patients on this study for participating institutions.

The steps below are to be taken when registering a **patient at a participating institution**:

4.3.2 Registration Process (Participating Institutions)

4.3.2.1 The participating institution's research staff must assure they have the most current and updated version of the protocol and informed consent prior to enrolling a patient. If a question arises, please contact the Data Coordinating Center at 626-256-4673 extension 63968 or via pager at 626-423-6486.
4.3.2.2 The participating institution must assure that all prestudy laboratory tests, scans and x-rays have been completed prior to registration according to the study calendar.

4.3.2.3 The participating institution must assure that the patient has signed an approved informed consent prior to registration, including Experimental Subject Bill of Rights (if applicable) and appropriate HIPAA authorization.

4.3.2.4 The participating institution must confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol. The eligibility checklist must be completed in its entirety.

4.3.2.5 A patient failing to meet all protocol requirements may not be registered. Patients must be registered within 2 weeks prior to initiation of protocol therapy.

4.3.2.6 Once a patient is eligible, all the pre-study requirements have been fulfilled, and the informed consent obtained, the research nurse or the data manager (study coordinator) at the participating center will inform the Data Coordinating Center (626-256-4673, ext 63968; pager 626-423-6486) and **FAX** (fax number 626-301-8422) a copy of the signed informed consent, patients' Bill of Rights, signed HIPPA consent, completed eligibility checklist and corresponding source documentation confirming eligibility (including pathology reports, lab reports, x-ray reports, etc.).

4.3.2.7 The Data Coordinating Center will:

4.3.2.7.1 Review all materials received to ensure the patient is eligible.

4.3.2.7.2 Ensure the consent form is valid and is signed correctly by all parties. If additional information is needed or should there be any questions, the Data Coordinating Center will immediately contact the participating institution and registration will not occur until all issues are resolved. No exceptions will be granted.

4.3.2.7.3 The patient will be registered centrally at City of Hope.

4.3.2.7.4 Confirmation of Registration will be emailed/faxed to the participating institution noting study number as well as assigning the dose (if applicable) within 24 hours via fax or email.

4.3.2.7.5 The Data Coordinating Center will call the research nurse or data manager (study coordinator) at the participating site and verbally confirm registration.

4.3.2.8 If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Data Coordinating Center should be notified of cancellations as soon as possible.

4.4 **Dose Assignment**

All study patients will receive the same initial dose of study agents (see section 5.0). Dose reductions can occur as medically necessary as will be described below (see section 6.0).

5.0 Treatment Program

5.1 **Treatment Overview**

Treatment will be administered in an outpatient setting.

Lapatinib will be administered at 1000mg (Four 250mg tablets) orally daily.

Trastuzumab will be administered in one of the two following schedules (per preference of the treating physician):

1. Trastuzumab loading dose of 4mg/kg IV during week 1, and 2mg/kg IV weekly thereafter (± 1 day)

2. Trastuzumab loading dose of 8mg/kg IV during week 1, and 6mg/kg IV every 3 weeks thereafter (± 3 days)

Patients already receiving trastuzumab treatment do not need to receive the loading dose.

Patients initially started on weekly trastuzumab can be changed to an every 3 week regimen at the discretion of the treating physician. Likewise, patients initially started on trastuzumab every 3 weeks can be changed to weekly trastuzumab at the discretion of the treating physician.

Doses missed for toxicity will not be made up.

Management and dose modification associated with adverse events are outlined in **Section 6**.

5.2 Planned Duration of Therapy

Treatment may continue until one of the following occurs:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) as defined in Section 6 below
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.3 Criteria for Removal from Treatment

Any subject who is removed from treatment prior to obtaining the first doses of both lapatinib and trastuzumab may be replaced. Reason for removal should be documented and noted in the patient's case report form.

5.3.1 Criteria for Removal

- *Adverse Events*
- *Intercurrent illness that prevents further administration of treatment*
- *General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator*
- *Clinical disease progression confirmed by imaging*
- *Withdrawal of Consent*

5.3.2 Subject Follow-Up

Subjects will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade ≥2 toxicities. Patients removed from study for unacceptable

adverse events will be followed until resolution or stabilization of the adverse event even if after disease progression is noted. All patients will be passively followed until death, though active follow-up will cease upon removal from study.

5.4 Supportive Care and Other Concomitant Therapy

All concomitant medications taken during the study treatment will be recorded in the Case Report Form. The minimum requirements are that drug name and the dates of administration are to be recorded. All prescription and over-the-counter medications that have been taken within 1 month prior to the first dose of investigational treatment should also be reported in the Case Report Form.

Patients should receive full supportive care during the study, including treatment with antibiotics, antiemetics, blood transfusions, antidiarrheals, and analgesics as appropriate, with the exception of drugs listed in Appendix C.

5.4.1 Medications Prohibited in Combination with Lapatinib

Lapatinib is predominantly metabolized by CYP3A4. Medications listed in Appendix C that are either inducers or inhibitors of CYP3A4 are prohibited throughout the study period until two weeks after the last dose of lapatinib. The following are additional points of interest.

- Washout period: The period of time between the last dose of a prohibited medication and the first allowed dose of lapatinib is dependent on the prohibited medication and is listed in column 3 of Appendix C.
- Medications that are inducers or inhibitors of CYP3A4 and are not listed in Appendix C may be used with caution
- Though use of intravenous and oral steroids is prohibited in Appendix C at doses above 10mg of prednisone daily or its equivalent, short term oral or intravenous steroid use of up to two weeks is allowed as treatment for any acute reaction or for prevention of an anticipated reaction for which in the opinion of the treating physician steroids are warranted.
- Lapatinib must be taken on an empty stomach. Patients must avoid use of grapefruit or grapefruit juice while on lapatinib. Other prohibited food items are listed in Appendix C.
- Warfarin may be used together with lapatinib with caution. Lapatinib potentially interacts with warfarin and quinazoline derivatives to increase INR and bleeding. While these medications are permitted to be taken during the study, it is recommended that INR and PT determinations should be collected at least weekly for the first month after starting lapatinib, and weekly for the first month after discontinuing lapatinib.

NOTE: Lapatinib should NOT be taken with grapefruit or grapefruit juice.

5.4.2 Medications Prohibited in Combination with Trastuzumab

There have been no formal drug interaction studies performed with trastuzumab in humans. Administration of paclitaxel in combination with trastuzumab resulted in a two-fold decrease in trastuzumab clearance in a non-human primate study and a 1.5-fold increase in trastuzumab clearance in clinical studies. There are no formal recommendations prohibiting any medication in combination with trastuzumab. However, clinical studies have shown that the administration of trastuzumab in combination with anthracyclines likely increase the risk of both clinical and subclinical risk of decreased cardiac ejection fraction, and therefore concurrent use is discouraged. This is of minimal concern in this study as patients will not receive concurrent chemotherapy.

5.5 **Laboratory/Monitoring Studies**

5.5.1 Required Clinical, Laboratory and Disease Evaluation at Baseline

Complete blood count and differential, comprehensive metabolic panel (including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, and albumin), must be performed within 14 days of enrolling on trial. Laboratory tests within this time period may be accepted from third-party sites as long as an official laboratory report (or photocopy thereof) is provided.

A full history and physical exam including demographics, medical history, concurrent medications, vital signs, height measurement, weight measurement, and performance status analysis must be done within one week of enrolling on trial.

Radiologic evaluation including computed tomography (CT) of the chest, abdomen, and pelvis; or combined PET-CT with a diagnostic CT component, must have been performed within 30 days of the start of treatment. If measurable disease is present, tumor measurements must be performed and reported from this scan. Central review is not required for treatment decisions in individual subjects.

The patient must complete a Geriatric Assessment prior to starting therapy (see Appendix E).

Cardiac imaging (either by echocardiogram or MUGA scan) with a reported left ventricular ejection fraction must have been obtained within 30 days of the start of treatment, or since the most recent dose of prior trastuzumab, whichever is later. Regardless of where the baseline evaluation is performed, future cardiac evaluation must be performed using only the same modality as the baseline evaluation. A baseline EKG before starting treatment is also required.

5.5.2 Studies Obtained During the Trial

5.5.2.1 Disease evaluation

CT scan of the chest, abdomen, and pelvis; or PET-CT with a diagnostic CT component must be performed every 12 weeks (±1 week) in the absence of symptoms to document disease response or progression. In the presence of symptoms, these tests may be performed at the discretion of the treating physician.

5.5.2.2 Cardiac evaluation

Echocardiogram or MUGA scan must also be performed every 12 weeks (±1 week) in the absence of symptoms. The modality must be the same as the modality used in the baseline cardiac evaluation. In the presence of symptoms, or in the setting in which a prior study showed an abnormality requiring confirmation, echocardiogram or MUGA will be done either at the discretion of the treating physician, or according to the algorithm described below in section 6.1.

5.5.2.3 Blood evaluation

Complete blood count with differential and complete metabolic panel must be performed every three weeks (+/- 1 wk). If screening laboratories are performed within 14 days of the first study treatment, repeat laboratory tests will not be required before week 1, day 1.

5.5.2.4 Pharmacokinetics

One blood sample for lapatinib trough pharmacokinetics will be drawn on each of the following dates: cycle 1 day 15; cycle 2, day 1; and cycle 2, day 8 (±1 day for each) immediately prior to taking the lapatinib dose for that day. Patients must not have taken anything by mouth other than water for 8 hours prior to the drawing of the pharmacokinetic sample. The sample will be drawn at week 3, 4, and 5, only,

provided that the patient has taken lapatinib at the same dose level for each of the seven days prior to this study. **If lapatinib has not been taken at the same dose level according to schedule for seven days prior to the pharmacokinetic lab draw, the draw will be rescheduled accordingly for the pharmacokinetic analysis.**

At each of the required timepoints, 2 mL venous blood will be collected into a tube containing EDTA (to be provided by GSK). Samples will be inverted several times and kept on ice until processing can begin. Plasma will be separated from whole blood by centrifugation at 1,500 x g for 10 minutes at 4° C and transferred to appropriately-labeled polypropylene tubes (to be provided by GSK) and frozen at < -20°C until shipping. Specimens will be batched at each participating site and stored in freezers at each site. At City of Hope, the specimens will be stored in a freezer accessible only to members of the City of Hope pharmacokinetic staff working under the auspices of Tim Synold, PharmD.

Each tube will be labeled with the study number, patient registration number, time point, and the date and time the sample was drawn.

Frozen serum samples at each site will be packed in the shipping container (provided by GSK) in sufficient dry ice to last at least 3 days (typically 6-8 kg), this shipment will occur yearly. The container will be sealed and shipped along with the packing worksheet via courier to:

PharmaNet Canada, Inc

Sample Controller

2500 rue Einstein

Quebec (Quebec), Canada G1P 0A2

Phone: 1-418-527-40000
Fax: 1-418-688-5242
E-mail : vcholette@anapharm.com

5.5.3 Monitoring Studies

5.5.3.1 Toxicity Evaluation

Monitoring will take place every three weeks (± 1 week) consisting of a physician visit and assessment

As early toxicity may be common with lapatinib, during cycles 1 and 2, during each week that the patient is not seeing an MD, patients will have a focused visit with a registered nurse to evaluate for new toxicities. (Week 2, Week 3, Week 5). A complete case report form does not need to be filled out for these short visits, which are rather designed to ensure that interventions may occur should toxicity be apparent.

5.5.3.2 Adherence evaluation

Adherence to trastuzumab will be measured by proportion of doses given in the infusion center as compared to number of doses scheduled. Adherence to lapatinib will be measured by pill count every three weeks during the first five cycles during the investigator assessment, and every twelve weeks thereafter, as well as by patient self-report in dedicated patient diaries evaluated at the same time as pill count. In the event of discrepancy in these two measures of adherence, we will follow whichever indicates the lower measure of adherence (i.e. If patient states they took 26 of 28 doses, but only 20 doses are missing, we will count the patient as having taken only 20 days. Alternatively, if 26 doses are missing, but the patient stated she only took 20 doses, we will count the patient as having taken only 20 doses.) All toxicity related dose interruptions or reductions, hospitalizations, and adverse events will be noted. Subjects will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade $\geq$3 toxicities.

5.5.3.3 Geriatric Assessment

Geriatric assessment surveys will be administered at baseline, after every four cycles, and at the end of the study if it had not been performed in the previous 1 month (see Appendix E for Geriatric Assessment Survey).

5.5.3.4 Survival Status

Patients will be followed indefinitely to establish overall survival. All participants enrolled on the study will be informed that their medical condition will be followed indefinitely. In order to obtain survival status on the enrolled patients we will need the patient's first and last name, middle initial, social security number, date of birth, and gender. This information will be securely transferred to the primary coordinating institution (City of Hope) and will be kept in a separate password protected file, which will only be linked for the purpose of establishing survivor status. The investigators will utilize the Social Security Death Index and the National Death Index to establish survival status. Survival analysis will be conducted once a year.

6.0 Dose Delays/Modifications for Adverse Events

Patients will be treated per protocol or until disease progression or withdrawal from treatment due to unacceptable adverse events or treatment consent withdrawal. At each study assessment, subjects are to be evaluated for evidence of drug-related adverse events.

In all cases where the subject is withdrawn due to unusual or unusually severe adverse event considered related to lapatinib or trastuzumab, the investigator must report the withdrawal as a Serious Adverse Event.

Treatment may be delayed for up to 4 weeks, to allow for resolution of toxicity except in the event of those toxicities described below in which cases treatment must be discontinued permanently (see Table 6).

If one full cycle or more of trastuzumab is missed due to toxicity, on resumption of trastuzumab, an additional loading dose should be given (8mg/kg if q3wk schedule, 4mg/kg if q1wk schedule).

Table 5: Dose reduction schema

Dose Level	Dose of lapatinib	Dose of trastuzumab
Level 0	1000mg orally daily	2mg/kg IV weekly or 6mg/kg q3wks
Level -1	750mg orally daily	2mg/kg IV weekly or 6mg/kg q3wks
Level -2	500mg orally daily	2mg/kg IV weekly or 6mg/kg q3wks

Lapatinib may not be used at doses below 500mg in combination with trastuzumab.

6.1 **Non-hematological adverse events**

The below discussion outlines situations in which lapatinib and trastuzumab must be either permanently discontinued, interrupted, or dose-reduced. In general, when dose interruption is indicated, administration of lapatinib may be interrupted for up to 4 weeks to allow the adverse event to resolve or decrease in severity

At a minimum, reassessment of adverse events will be done every three weeks and more frequently if clinically indicated.

If toxicities are ≥ grade 3, except for anemia, or related to a pre-existing comorbidity, or any toxicity deemed unrelated to cancer or cancer treatment (such as hypertension, hyperglycemia, decreased lymphocyte count, non-cancer related pain, fracture or orthopedic surgery) using NCI CTCAE v.4.0, treatment should be withheld until resolution to ≤ grade 1 or to baseline levels, then reinstituted, if medically appropriate, at the next lower dose level (see Table 5). Patients who present with grade 1 or 2 toxicities may have their treatment held, continued with dose-reduction, or continued at current dose with increased supportive care measures at the discretion of the treating physician unless meeting other stopping criteria below (see specifically section 6.2, 6.3, and 6.5.2). Treatments skipped due to toxicity will be omitted and total cycle length remains the same. If toxicity is attributable to lapatinib (ie, rash, diarrhea, nausea) then dose modification should be initiated as detailed in section 6. Treatment with trastuzumab may continue

For a summary of dose modifications required for adverse events, see Table 6 in section 6.7 below.

6.2 **Cardiac toxicity**

Cardiac toxicity with trastuzumab or lapatinib is most often manifested as Congestive Heart Failure. The grading of CHF will follow the system developed by the New York Heart Association. The following is a summary of the grading system:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

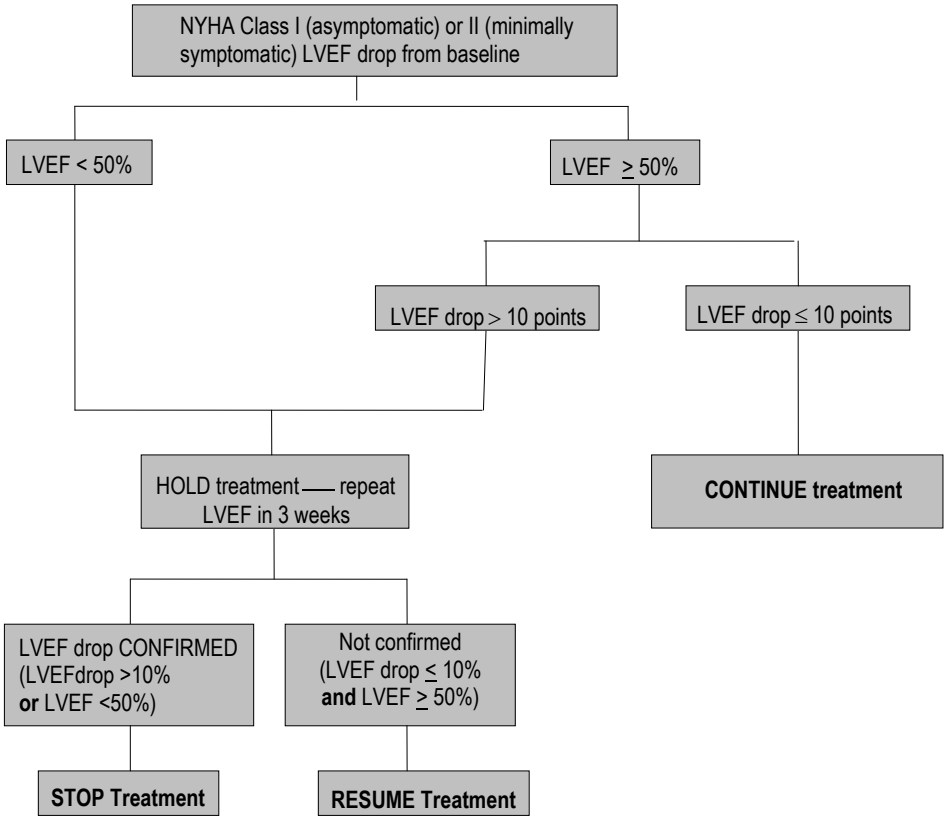
Source: Heart failure society of America. http://www.abouthf.org/questions_stages.htm. Accessed on November 22, 2010.

Treatment with lapatinib and trastuzumab must be **permanently stopped** for each of the following events:

- Cardiac arrest defined as either

    - Cardiac death due to heart failure, myocardial infarction or arrhythmia
    - Probable cardiac death defined as sudden unexpected cardiac arrest within 24 hours of a definite or probable cardiac event.
- Severe symptomatic congestive heart failure defined as NYHA Class III or IV (Class III defined as being not capable of climbing one flight of stairs and Class IV defined as having symptoms at rest)
- A significant drop in LVEF, (confirmed by a second LVEF assessment after 21 days of holding the study drug also showing a significant drop). A significant LVEF drop is defined as an absolute decrease of more than 10 points below the baseline LVEF or to below 50%. See Figure 2 for an algorithm for dose interruptions and discontinuations for lapatinib and trastuzumab related cardiac toxicity manifesting as Class I or II Heart Failure.

Figure 2: Algorithm for continuation and discontinuation of lapatinib and trastuzumab based on interval LVEF assessments, for patients with NYHA Class I or II congestive heart failure



6.3 **Hepatic toxicity**

For grade 1 ALT or bilirubin increases (ALT>ULN - 3x ULN; bilirubin >ULN - 1.5x ULN), no dose modification is necessary.

For grade 2 increases in ALT or bilirubin (ALT > 3x ULN - 5x ULN; bilirubin >1.5x ULN - 3x ULN, see Figure 3 below.

For grade 3 or higher increases of ALT or bilirubin (ALT >5x ULN; bilirubin >3x ULN), lapatinib must be permanently discontinued.

In any instance of hepatic toxicity in which lapatinib requires permanent discontinuation, the following actions should be taken as soon as possible for the purposes of patient safety and attribution of adverse events:

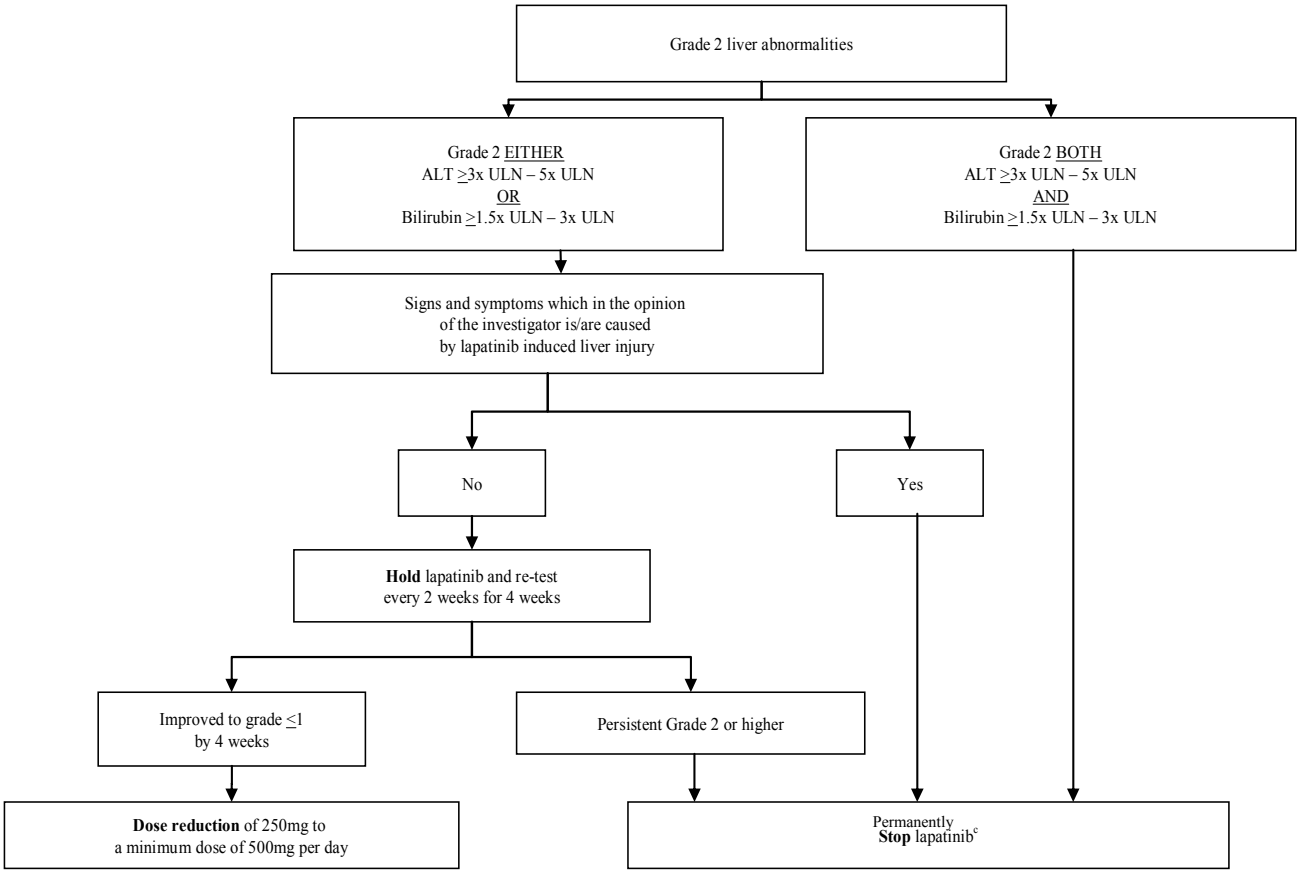
- Liver imaging should be performed to rule out the potential of disease progression.
- Other blood tests should be performed including direct (fractionated) bilirubin, Hepatitis A IgM antibody, Hepatitis B surface antigen, Hepatitis B Core Antibody (IgM), Hepatitis C RNA, Cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or heterophile antibody or monospot testing), and Hepatitis E IgM antibody.

- Re-testing of LFTs every 2 weeks until improvement to Grade 1 or lower if alternative cause is not found

Of note, lapatinib may ***not*** be restarted following the toxicities described above regardless of the results of imaging and laboratory tests, or other attributable cause.

Dose interruptions and dose reductions may also be appropriate following other abnormal liver function tests. For NCI CTCAE v.4.0 Grade 1 abnormal liver function tests, no change is necessary but may be undertaken at the discretion of the treating physician. See Figure 3 for management of NCI CTCAE Grade 2 abnormal liver function tests.

Figure 3: Algorithm for management of Grade 2 abnormal liver function tests with lapatinib



6.4 **Dermatologic toxicity**

For NCI-CTCAE v.4.0 Grade 4 rash manifested as toxic epidermal necrolysis (i.e. Stevens-Johnson Syndrome), lapatinib must be permanently discontinued**.**

Subjects with poorly tolerated skin adverse events may undergo a brief (up to 14 day) therapy interruption at the discretion of the patient and investigator. The daily dose of lapatinib should then be reinstated. However, this is not mandated, as the rash may improve without the need for interrupting therapy, and is left up to the discretion of the treating physician.

Of note in current studies, many subjects were able to resume lapatinib therapy at the same dose after resolution of rash, and they then had less extensive and/or less severe rashes. A variety of agents can be used to manage skin rashes. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, or topical or systemic antihistamines.

There is no standard, known, or established treatment proven effective for drug-related skin rashes or changes due to lapatinib. If the rash is severe (1-3%) then most commonly, a papular/pustular rash has been observed, which frequently improves even though the same dose of lapatinib therapy is continued uninterrupted. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation. Oral retinoids should not be given because of theoretical concerns about negatively affecting the lapatinib mechanism of action. Oral steroids are also strongly discouraged. Other options for treatment of significant rashes may be determined upon consultation with dermatologist.

6.5 **Gastrointestinal Toxicity**

If GI events are not appropriately managed, they may be associated with the development of dehydration. Management of gastrointestinal adverse events is discussed in detail below.

6.5.1 Nausea, Vomiting, or Both

In subjects who have emesis and are unable to retain lapatinib, every attempt should be made to obtain control of nausea and vomiting. If a subject vomits after administration of lapatinib, the subject should be instructed not to retake the dose. Subjects should take the next scheduled dose. If vomiting persists, then the subject should contact the investigator.

6.5.2 Diarrhea

These broad general management principles are recommended to proactively try and avoid more serious complications by active management of diarrhea syndrome. Guidelines such as these should never replace sound clinical judgment. Experience thus far suggests that when lapatinib is used as monotherapy, uncomplicated Grade 1 or 2 diarrhea is most prevalent. These general management principles do not address comprehensive management of more serious or protracted diarrhea syndromes.

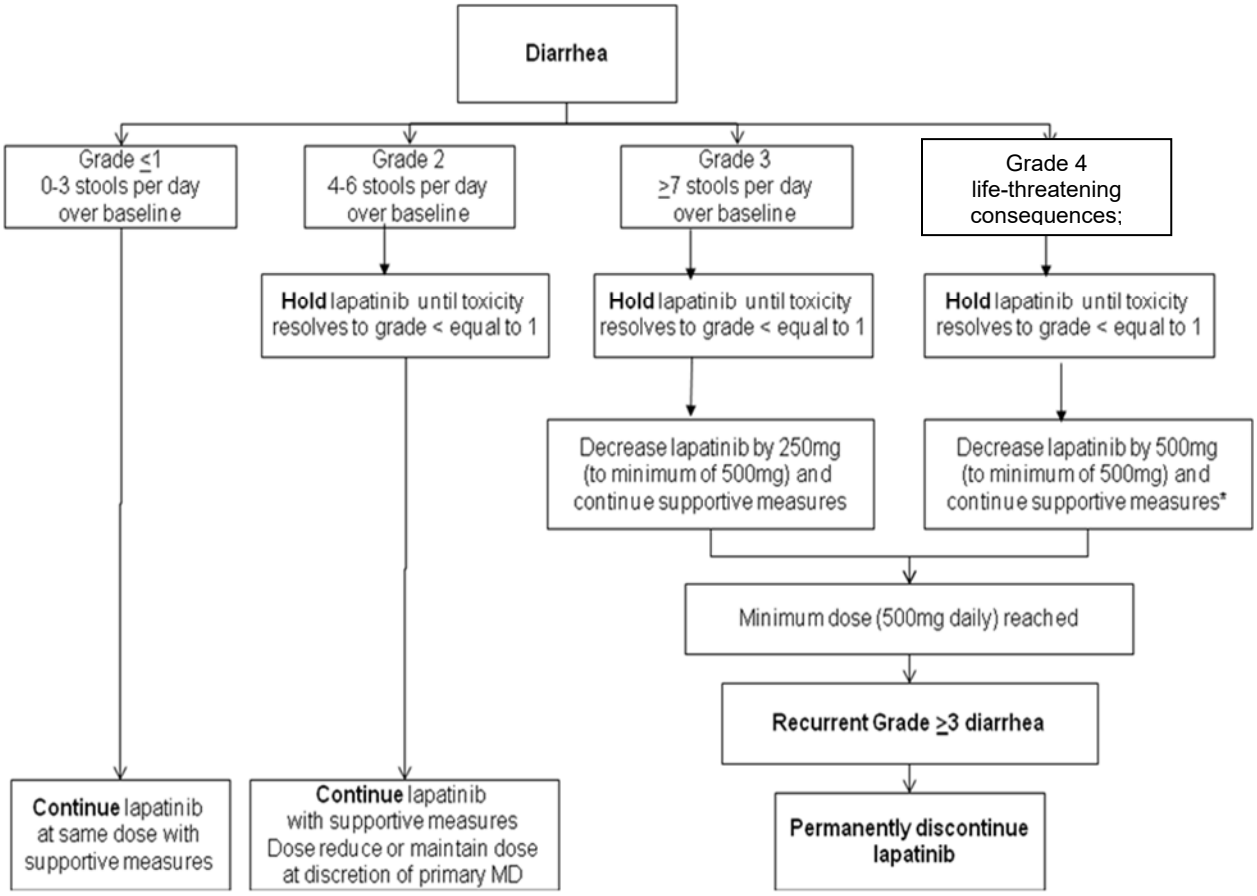
Common clinical sense with the onset of uncomplicated Grade 1-2 diarrhea: stop all lactose containing products: drink 8-10 large glasses of clear liquids a day; eat frequent small meals;

For Grade 1 or 2 diarrhea**;** administer standard doses of loperamide: initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool. It is suggested to continue loperamide until the subject is free from diarrhea for 12 hours.

For Grade 2-4 diarrhea or Grade 1 diarrhea with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration) hold lapatinib until diarrhea resolved. Use intravenous fluids as appropriate, consider hospital administration. Use prophylactic antibiotics as needed (example: fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is a fever or Grade 3-4 neutropenia.

See figure 4 for an algorithm for managing diarrhea with lapatinib.

Figure 4: Dose modifications for lapatinib GI toxicity



*Note: A patient may only resume lapatinib at a 500mg dose reduction if he/she had been on the full dose prior to the episode (1000mg daily). If a patient on 750mg daily of lapatinib experiences Grade 4 diarrhea, lapatinib must be permanently discontinued. Doses of lapatinib less than 500mg daily are not permitted.

6.6 **Pulmonary Toxicity**

If a patient develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, lapatinib and trastuzumab therapy should be interrupted and a thorough evaluation performed.

If NCI-CTCAE v4.02 Grade 3 or 4 pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to lapatinib and/or trastuzumab cannot be excluded), lapatinib and trastuzumab must be permanently discontinued. All incidences of interstitial lung disease/ interstitial pneumonitis regardless of grade must be reported as serious adverse events (SAEs).

6.7 **Summary of Modifications due to Toxicity**

A summary of dose holding, delays, and dose reduction recommendations for lapatinib and trastuzumab is described in Table 4.

Table 6: Summary of dose holding and dose de-escalation recommendations for lapatinib in case of lapatinib related adverse events

Adverse events	Action
Cardiotoxicity (↓ LVEF)	**NYHA Class I or II and/or asymptomatic LVEF drop:** see algorithm (Figure 2) **NYHA Class III or IV: Permanently discontinue both lapatinib and trastuzumab**
Hepatotoxicity (↑ LFTs)	**Grade 1 abnormal LFTs**: Adjust per MD discretion **Grade 2 abnormal LFTs**: See specific algorithm (Figure 3) **Grade 3 abnormal LFTs**: **Permanently discontinue lapatinib**
Diarrhea	**See specific algorithm (Figure 4)**
Other Non-heme Grade 1	Continue lapatinib therapy at full dose prescribed. Apply maximum supportive care recommendations.
Other Non-heme Grade 2	MD discretion as to whether to continue lapatinib, interrupt therapy until resolution, or continue with dose reduction. Continue trastuzumab. Continue maximum supportive care recommendations.

Other Non-heme Grade ≥3	**Hold lapatinib and trastuzumab.** If toxicity resolves to grade 1 or less within 4 weeks, dose reduce lapatinib by one dose level before resuming (max 2 dose reductions of lapatinib allowed). If toxicity does not resolve within 4 weeks, **permanently discontinue both drugs. If more than one full cycle of trastuzumab is missed, reloading of trastuzumab is required upon resuming the drug. For grade 3 toxicities deemed unrelated to cancer or cancer treatment (such as hypertension, hyperglycemia, decrease lymphocyte count, non-cancer related pain, fractures, or orthopedic surgery) treatment may be continued at the current dose at the discretion of the treating physician unless meeting other stopping criteria (see specifically section 6.2, 6.3, 6.5.2).**
Hematologic toxicity	No required dose modification. Treatment discontinuation or dose adjustment at the discretion of treating MD.

7.0 Data and Safety Monitoring

7.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

7.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Expanded Access Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS

4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted according to the timelines in Table 1 above. Protocol specific data collection will include the following items: After 30 patients have completed one full cycle of therapy, the study team will review the data and assess the toxicity profile and rates of dose reduction, delays, interruptions and hospitalization related to the combination of agents. Within this interim analysis a specific review will be made of the data for the patients over 75 years of age. Additional guidelines and will be used to flag an unexpected number of patients that experience symptomatic cardiac toxicity (NYHA Class III or IV if cardiac failure, or Grade 3 or higher by NCI NCTAE v4.0 for other cardiac events)safety of lapatinib given in combination with trastuzumab in older adults (using CRFs based on CTCAE v.4.02), efficacy of lapatinib plus trastuzumab in older adults (based on imaging using RECIST 1.1 criteria), geriatric assessment of older adults, adherence of the population to the oral medication, cardiac safety in the study population (using cardiac imaging). Reporting of data and safety to the DSMC will occur at the time of enrollment of 20 subjects, or after an unexpected number of severe adverse cardiac events (see section 13) using the PMT report.

7.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a)] - An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

7.1.1.1 *Serious Adverse Event (SAE) [21 CFR 312.32] - defined as any expected or unexpected adverse event that results in any of the following outcomes:*

- Death

- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.4 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems - Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/policy/Policies%20and%20Procedures/REVIEWING_AND_REPORTING_UNANTICIPATED_PROBLEMS.pdf. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

7.1.1.2 Serious Adverse Events - **All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/policy/Policies%20and%20Procedures/REVIEWING_AND_REPORTING_UNANTICIPATED_PROBLEMS.pdf and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org).**

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of *serious* OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

DSMC Risk Level 3 and Risk Level 4 Protocol Reporting Timelines

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
Death while on active treatment or within 30 days of last day of treatment		
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
Death after 30 days of last active treatment/therapy		
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
Within 30 days of last active treatment/therapy		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days
After 30 days of last active treatment/therapy		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

DSMC Risk Level 1 and Risk Level 2 Protocol Reporting Timelines

Required Reporting Timeframe to DSMC		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

COH IRB Adverse Event Reporting Timelines

Required Reporting Timeframe to COH IRB		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment/therapy or within 30 days of the last day of active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2	
Possibly, Probably, Definitely	5 calendar days[1]	Annual[2]
Unlikely, Unrelated	Annual[2]	Annual[2]

[1] These events must be reported in the time frame if they meet the definition of an unanticipated problem.

[2] For studies that are not first in human, Phase I and first in pediatric trials, only grades 3-5 must be reported at annual review.

PLEASE NOTE: If additional reporting guidelines are required due to a sponsor's requirement or for any other reasons, please add those reporting requirements here, below the City of Hope reporting requirements.

Additional SAE Reporting Requirements:

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) ***(For patients taking Lapatinib / Novartis drugs)***.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure patient safety, every SAE, regardless of suspected causality, occurring

- after the patient has provided informed consent and until atleast 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment

must be reported to Novartis within 24 hours of learning of its occurrence Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form by fax to (fax: 877-778-9739) within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets**.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it

was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Lapatinib Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

7.5 Reporting Adverse Events (Occurring at Participating Institutions)

The guideline is to provide a procedure for accurate and timely reporting of

serious adverse events (SAEs) from the participating institution to the Principal Investigator (PI) at City of Hope (COH). The participating institution, participating PI and/or study coordinators are responsible for reporting all serious adverse events immediately (within 24 hours after learning of the event) to their local IRB, the PI at City of Hope, the Data Coordinating Center at COH as well as follow the protocol specific SAE reporting requirements (per Section 7.2.9, 7.2.10 and 7.2.11 below). The participating investigator must report each serious adverse event, regardless of attribution, to the Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event..

Report serious adverse events by telephone and facsimile to:

Dr. Arti Hurria **Phone: 626-471-9200** Fax: 626-301-8233

- The participating institution will notify the Data Coordinating Center of any serious adverse event (defined in Section 7.2.13) via a telephone call to (626) 256-4673 ext. 63968.
- The participating institution will notify their local IRB as per their local established guidelines.
- As this study will not involve an IND, reporting to FDA is voluntary. Guidelines can be found at http://www.fda.gov/cder/aers/fr07oc97.htm and http:///www.fda.gov/medwatch/index/html. All relevant events may be voluntarily reported to the FDA using the MedWatch system.
- In addition to being reported to the participating institutions' local IRB and to the FDA (voluntary reporting), the Data Coordinating Center will

need to send a copy of the participating institutions serious adverse event report to GSK Oncology MDC.

- A copy of the participating institutions serious adverse event report submitted to their local IRB, as well as a copy of the MedWatch form (if applicable) must be sent to the Data Coordinating Center in the Department of Clinical Research Information Support at City of Hope by fax to (626) 301-8422 within 24 hours. The Notification of Toxicity Form (see Appendix F) should also be sent to the Data Coordinating Center within 24 hours. Any supporting documentation to the reports (i.e., laboratory, pathology, progress notes, discharge summary, autopsy, etc.) explaining the adverse event should also be submitted to the Data Coordinating Center at City of Hope. The Data Coordinating Center will then submit to our COH IRB as well as submit to the Novartis Drug Safety and Epidemiology Safety Desk in a timely manner.

7.5.1 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. In addition, NYHA Class III and IV heart failure will be captured. Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Principal Investigator.

Definitions

- Adverse Event: Any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.
- Serious Adverse Event: Any expected or unexpected adverse event that is related or unrelated to either the intervention or the study agents(s) that results in any of the following outcomes:
    - Death
    - A life-threatening event
    - Inpatient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization
    - A persistent or significant disability/incapacity
    - A congenital anomaly/birth defect
    - Causes cancer
    - Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

- Unexpected Adverse Event: Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

- Expected Adverse Event: Any event in which the severity or specificity is consistent with the risk information described in the protocol, or is consistent with the subject's medical history.
- Follow-up to Adverse Event: Any new information obtained following the initial report of the event (e.g. lab result(s) for pending test(s)).
- Attribution: For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator (PI) after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded electronically in iRIS (http://iris.coh.org/) in one of five categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related, and 1=unrelated. The attribution is subject to change as follow-up information becomes available, and can be changed by the DSMB or by the IRB during the process of review.

8.0 Agent Information

8.1 Drug Information for Lapatinib (Tykerb®)

Other Names: NSC # 727989, Tyverb®

Mode of Action: Dual inhibitor of epidermal growth factor receptor (EGFR or ErbB1) and ErbB2 tyrosine kinases.

Availability: Lapatinib is commercially available

8.1.1 Risks and Contraindications

Table 7: Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for lapatinib alone

Metabolism and nutrition disorders	
Common (≥10%)	Anorexia
Cardiac disorders	
Less common (≥1%)	Decreased left ventricular ejection fraction
Gastrointestinal disorders	
Common (≥10%)	Diarrhea, which may lead to dehydration

	Nausea Vomiting
Skin and Subcutaneous Tissue Disorders	
Common (>10%)	Rash
General disorders	
Common (>10%)	Fatigue

Serious Adverse Events:
Decreases in Left Ventricular Ejection Fraction: Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular cardiac function that are ≥Grade 3or a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal. Among 198 patients who received lapatinib/capecitabine combination treatment, 3 experienced Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTCAE v3.0).
Hepatotoxicity: Lapatinib has been associated with hepatotoxicity though very rarely
Interstitial Lung Disease/Pneumonitis: Lapatinib has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies, but also very rarely.

8.1.2 Supplier

Study drug is being provided by the drug manufacturer, GlaxoSmithKline.

8.1.3 Concomitant Medications/Precautions

See section 5.5 and Appendix A

8.1.4 Dose and Administration

Dose: 1000mg (4 tablets)

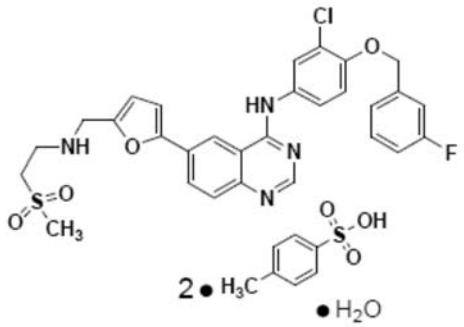
Route of Administration: Orally on an empty stomach (either 1 hour before or 1 hour after meals).

8.1.5 Storage

Storage: The intact bottles should be stored at controlled room temperature (15°C-30°C).

8.1.6 Structure and Molecular Weight

The structural formula is:



Molecular formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$
Molecular weight: 581.05 g/mol

Chemical Name: N-(3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl)-6-[5-(([2-(methylsulfonyl)ethyl]amino}methyl)-2 furyl]-4-quinazolinamine

8.1.7 Formulation/Agent Preparation

How Supplied: lapatinib is supplied as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. The tablets contain 410 mg of lapatinib Ditosylate Monohydrate, equivalent to 250 mg lapatinib free base per tablet. The tablets are packaged into HDPE bottles with child-resistant closures.

Excipients present in the tablet include: Microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate.

The film-coat contains: Hydroxypropyl methylcellulose, titanium dioxide, triacetin/glycerol triacetate, and yellow iron oxide.

Kool-Aid Flavored Suspension

Prepare Lemonade or Tropical Punch Kool-Aid as directed on the package. Place 2 or 4 oz of Kool-Aid (room temperature or refrigerated) in a glass container, then add four 250 mg lapatinib tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10-20 minutes or until the tablets are completely broken up. Stir the container for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and administer (total of 4-6 oz of liquid is dispensed).

Suspension in Water

Place 4 oz of water in a glass container, then add four 250 mg lapatinib tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10-20 minutes or until it is fully dispersed. Stir the container for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and administer (total of 6 oz of liquid is dispensed).

8.1.8 Stability

Stability: Shelf life surveillance studies of the intact bottle are on-going. Current data indicates lapatinib is stable for at least 2 years at controlled room temperature (15°C - 30°C).

8.1.9 Agent Accountability

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from Novartis.

8.1.10 Agent Ordering

Lapatinib will be ordered directly from the manufacturer, Novartis.

8.2 **Drug Information for Trastuzumab (Herceptin©)**

The below information is largely duplicated from the Herceptin package insert.[94] Relevant points are summarized as follows.

Other names: none

Mode of Action: recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.

Availability: Trastuzumab is commercially available

8.2.1 Risks and Contraindications

Cardiotoxicity:

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction, have been observed in patients treated with trastuzumab. Congestive heart failure associated with trastuzumab therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The clinical status of patients in the trials who developed congestive heart failure was classified for severity using the New York Heart Association classification system (I-IV, where IV is the most severe level of cardiac failure). (See Table 8)

Table 8: Incidence and Severity of Cardiac Dysfunction

	Trastuzumab alone[38] n = 213	Trastuzumab + Paclitaxel[28] n = 91	Paclitaxel[28] n = 95	Trastuzumab + Anthracycline+ cyclophosphamide[28] n = 143	Anthracycline+ cyclophosphamide[28] n = 135
Any Cardiac Dysfunction	7%	11%	1%	28%	7%
Class III-IV	5%	4%	1%	19%	3%

38 (see reference): Open-label, single-agent Phase II study (94% received prior anthracyclines).
28 (see reference): Randomized Phase III study comparing chemotherapy plus trastuzumab to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

Candidates for treatment with trastuzumab should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at

risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving trastuzumab should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) may decrease the ability to tolerate trastuzumab therapy; however, the data are not adequate to evaluate the correlation between trastuzumab-induced cardiotoxicity and these factors.

Discontinuation of trastuzumab therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of trastuzumab. The safety of continuation or resumption of trastuzumab in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of trastuzumab therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

Precautions

General: Trastuzumab therapy should be used with caution in patients with known hypersensitivity to trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

Drug Interactions: There have been no formal drug interaction studies performed with trastuzumab in humans. Administration of paclitaxel in combination with trastuzumab resulted in a two-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in trastuzumab serum levels in clinical studies.

Benzyl Alcohol: For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic Water for Injection) reconstitute trastuzumab with Sterile Water for Injection (SWFI), USP. DISCARD THE SWFI-RECONSTITUTED TRASTUZUMAB VIAL FOLLOWING A SINGLE USE.

Immunogenicity: Of 903 patients who have been evaluated, human anti-human antibody (HAHA) to trastuzumab was detected in one patient, who had no allergic manifestations.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Trastuzumab has not been tested for its carcinogenic potential.

Mutagenesis: No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 µg/mL trastuzumab. Human peripheral blood lymphocytes treated *in vitro* at concentrations of up to 5000 µg/plate trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential.

In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg trastuzumab.

Geriatric Use: Trastuzumab has specifically evaluated in 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients.

Adverse Reactions

Cardiac Failure/Dysfunction: For a description of cardiac toxicities, see above.

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in treatment groups receiving trastuzumab and chemotherapy, especially in those receiving trastuzumab with AC The majority of these cytopenic events were mild or moderate in intensity and reversible

Hematologic toxicity is infrequent following the administration of trastuzumab as a single agent, with an incidence of Grade III toxicities for WBC, platelets, hemoglobin all <1%.

Diarrhea: Of patients treated with trastuzumab as a single agent in various studies, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving trastuzumab in combination with chemotherapy.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed in patients receiving trastuzumab in combination with chemotherapy.

Infusion Reactions: During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). Trastuzumab discontinuation is rarely necessary. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. The symptoms occur infrequently with subsequent trastuzumab infusions.

Table 9: Adverse Events Occurring in ≥ 5% of Patients or at Increased Incidence in the Trastuzumab Arms of Various Randomized Studies (Percent of Patients)[94]

	Single Agent n = 352	Trastuzumab + Paclitaxel n = 91	Paclitaxel Alone n = 95	Trastuzumab + AC n = 143	AC Alone n = 135
Body as a Whole					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34

Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15
Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic Reaction	3	8	2	4	2
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Heme & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2

Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	<1
Urogenital					
Urinary tract infection	5	18	14	13	7

Other serious adverse events

The following other serious adverse events occurred in at least one patient on trastuzumab being treated in clinical trials:

Body as a Whole: cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia

Cardiovascular: vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock, arrhythmia

Digestive: hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis

Endocrine: hypothyroidism

Hematological: pancytopenia, acute leukemia, coagulation disorder, lymphangitis

Metabolic: hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

Musculoskeletal: pathological fractures, bone necrosis, myopathy

Nervous: convulsion, ataxia, confusion, manic reaction

Respiratory: apnea, pneumothorax, asthma, hypoxia, laryngitis

Skin: herpes zoster, skin ulceration

Urogenital: hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

8.2.2 Supplier

Trastuzumab will be ordered from the individual study site's pharmacy.

8.2.3 Concomitant Medications/Precautions

See section 5.5.2

8.2.4 Dose and Administration

Usual Dose

The recommended initial loading dose is either 4 mg/kg trastuzumab administered as a 90-minute infusion (if planning weekly dosing) or 8 mg/kg trastuzumab administered as a 90-minute infusion (if planning every three week dosing). The recommended weekly maintenance dose is 2 mg/kg trastuzumab and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. The recommended every three week maintenance dose is 6mg/kg trastuzumab and can be administered as a 30 minute infusion if the loading dose was well tolerated. Trastuzumab may be administered in an outpatient setting. Trastuzumab is to be diluted in saline for IV infusion. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS** (see **Administration**). There is no change in dosage for obese patients.

Administration

Treatment may be administered in an outpatient setting by administration of either a 4 mg/kg trastuzumab loading dose by intravenous (IV) infusion over 90 minutes or 8mg/kg trastuzumab loading dose by intravenous infusion. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg trastuzumab may be administered over 30 minutes, or subsequent doses of 6mg/kg trastuzumab may be administered every three weeks.

Trastuzumab should not be mixed or diluted with other drugs. Trastuzumab infusions should not be administered or mixed with Dextrose solutions.

8.2.5 Storage

Vials of trastuzumab are stable at 2-8°C (36-46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, may be stored at 2-8°C (36-46°F) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24 hours at room temperature (2-25°C).

However, since diluted trastuzumab contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2-8°C).

8.2.6 Structure and Molecular Weight

Formula: $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$

Molecular Mass: 14531.5 g/mol

Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

8.2.7 Formulation/Agent Preparation

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The nominal content of each Herceptin vial is 440 mg trastuzumab, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, 400 mg trehalose dihydrate, and 1.8 mg polysorbate 20, USP. Reconstitution with **only 20 mL of the supplied Bacteriostatic Water for Injection (BWFI), USP,** containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.

Preparation

The diluent provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. Other diluents have not been shown to contain effective preservatives for HERCEPTIN. Each vial of Herceptin should be reconstituted with **ONLY 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied,** to yield a multi-dose solution containing 21 mg/mL trastuzumab. Use of all 30 mL of diluent results in a lower-than-intended dose of HERCEPTIN. THE REMAINDER (approximately 10 mL) OF THE DILUENT SHOULD BE DISCARDED. Immediately upon reconstitution with BWFI, the vial of Herceptin must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, Herceptin must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). HERCEPTIN WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.

Shaking the reconstituted Herceptin or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of Herceptin that can be withdrawn from the vial.

Use appropriate aseptic technique when performing the following reconstitution steps:

a. Using a sterile syringe, slowly inject **20 mL** of the diluent into the vial containing the lyophilized cake of trastuzumab. The stream of diluent should be directed into the lyophilized cake.

b. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE.**

c. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent, and colorless to pale yellow.

Determine the number in mg of trastuzumab needed, based on a loading dose of 4 mg trastuzumab/kg body weight or a maintenance dose of 2 mg trastuzumab/kg body weight. Calculate the volume of 21 mg/mL trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between Herceptin and polyvinylchloride or polyethylene bags have been observed.

8.2.8 Stability

A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2-8°C (36-46°F), and the solution is preserved for multiple use.

9.0 Correlative/Special Studies

One blood sample for lapatinib trough pharmacokinetics will be drawn on the day of trastuzumab administration immediately prior to taking the lapatinib dose for that day. This sample will be drawn weeks 3, 4, and 5 only, provided that the patient has taken lapatinib at the same dose level for each of the seven days prior to this study. In the event that the lapatinib dose is held or the dose level is changed, pharmacokinetic sample will be rescheduled accordingly.

At each of the required timepoints (Days 15/22/29), 2 mL venous blood will be collected into a tube containing EDTA (to be provided by GSK). Samples will be inverted several times and kept on ice until processing can begin. Plasma will be separated from whole blood by centrifugation at 1,500 x g for 10 minutes at 4° C and transferred to appropriately-labeled polypropylene tubes (to be provided by GSK) and frozen at < -20°C until shipping. Specimens will be batched at each participating site and stored in freezers at each site. If sites do not have sufficient storage space to keep these samples, sites not at City of Hope can ship frozen plasmasamples to City of Hope/Beckman Research Institute, Shapiro Building Room 1043, 1500 E. Duarte Rd, Duarte Ca. 91010. At City of Hope, the specimens will be stored in this same freezer accessible only to members of the City of Hope pharmacokinetic staff working under the auspices of Tim Synold, PharmD.

Each tube will be labeled with the study number, patient registration number, time point, and the date and time the sample was drawn.

Frozen plasmasamples at each site will be packed in the shipping container (provided by GSK) in sufficient dry ice to last at least 3 days (typically 6-8 kg), this shipment will occur yearly. The container will be sealed and shipped along with the packing worksheet via courier to:

PharmaNet Canada, Inc

Sample Controller

2500 rue Einstein

Quebec (Quebec), Canada G1P 0A2

Phone: 1-418-527-40000
Fax: 1-418-688-5242
E-mail : vcholette@anapharm.com

Analytical Methods

Lapatinib concentrations will be determined in all samples by GSK using a validated LC/MS/MS assay. Assay methodologies are based on previously reported methods, and the limits of detection for lapatinib is 1 ng/ml.

Pharmacokinetic Data Analysis

Lapatinib trough levels will be calculated by GSK using standard noncompartmental methods and WinNonlin software.

10.0 Study Calendar

	Pre-Study (up to 14 days prior to enrolling)[j]	Cycl 1 Day 1 (21 day cycle)	Cycl 1 Day 8	Cycl 1 Day 15	Cycl 2 Day 1	Cycl 2 Day 8	Cycl 3 Day 1	Cycl 4 Day 1	Cycl 5 Day 1	Every cycle There-after	Every 4 cycles	Off Study[i]
Lapatinib (day 1-7 of each wk)[a]		X	X	X	X	X	X	X	X	X		
Trastuzumab (±1 day if qwk, ±3 days if q3wk)[a,b]		X			X		X	X	X	X		
Informed consent	X											
Demographics	X											
Medical history	X											
Concurrent meds (± 1 wk)	X	X			X		X	X	X	X		
Physical exam (± 1 wk)	X	X			X		X	X	X	X		X
Vital signs (± 1 wk)	X	X			X		X	X	X	X		X
Height	X											
Weight (± 1 wk)	X				X		X	X	X	X		X
Performance Status (± 1 wk)	X	X			X		X	X	X	X		X
CBC w/diff, plts (± 1 wk)	X	X[c]			X		X	X	X	X		X
Complete Metabolic Panel[d] (± 1 wk)	X	X[c]	X		X		X	X	X	X		X
Nurse brief toxicity evaluation			X	X		X						
EKG	X											
Pharmacokinetic samples (± 1 days)[k]				X	X	X						
Adherence evaluation (pill count, diaries) (± 1 wk)					X		X	X	X		X	
Adverse event evaluation (± 1 wk)					X		X	X	X		X	X
Tumor measurements using CT or PET-CT (± 1 wk)	X[e]								X		X[f]	X[g]
LVEF Assessment	X[e]								X		X[f]	X[g]
Geriatric Assessment Survey (±1 wk)	X								X		X	X[h]

a: Dose as assigned; lapatinib 1000mg orally daily; trastuzumab 4mg/kg IV cycle one day 1, 2mg/kg IV every week thereafter; OR trastuzumab 8mg/kg cycle 1, day 1, 6mg/kg each cycle (3 wks) thereafter. Doses held due to toxicity will not be made up.

b: X in schema for trastuzumab applies to q3 week schedule.

c: If baseline laboratory tests are done within 14 days of start of treatment, these labs do not need to be repeated prior to day 1.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

e: Baseline radiologic imaging may be done up to 30 days prior to start of treatment

f: Tumor measurements and LVEF assessment are repeated every 4 cycles ± 1 wk until patient comes off study. Documentation (radiologic or clinical) must be provided for patients removed from study for progressive disease.

g: Off-study radiologic evaluation will only be done if clinically indicated

h: Geriatric assessment should be repeated off study ONLY if it had not been administered within the previous month

i: Patients will be followed for 30 days following discontinuation of therapy in order to capture toxicity attributable to therapy

j. Chart review data must be within 14 days to determine if patient meets study criteria. Once patient is deemed to meet study criteria, then all criteria must be within window specified in protocol from Day1 as indicated in column one in the schema above.
k: Phamacokinetic samples will be drawn after the patient has been taking lapatinib at the same dose level for a period of at least 7 days.

11.0 Evaluation Criteria/Measurement of Effect

For the purposes of this study, patients should be reevaluated for response every 12 weeks.

Response and progression will be evaluated in this study using the new updated international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1.[102] Per the new RECIST criteria, as disease response is not the primary endpoint of this trial, confirmatory scans following documentation of progression or response will not be required. Rather, progression/response will be determined based on results of the single scan.

11.1 **Definitions**

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with lapatinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of 10mm with conventional techniques (CT, MRI, or caliper measurement) or ≥20mm by chest X-ray (if clearly defined and surrounded by aerated lung.) To be considered pathologically enlarged and measurable, lymph nodes must be greater than 15mm on short axis and considered measureable can be used as target lesions when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm by chest X-ray or <10 mm using CT, MRI or caliper measurement), are considered non-measurable disease. Leptomeningeal disease, blastic bone lesions, ascites, pleural or pericardial effusion inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable. Lymph nodes measuring between 10 to <15mm are also considered non-measurable.

Target 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. Lymph nodes less than 15mm in the short axis can not be used as target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest axis of non-lymph target lesion and the shortest axis of target lymph nodes will be calculated and reported as the baseline sum longest diameter (LD). The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.4 **Response Criteria**

11.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Lymph node CR is when the lymph node has decreased to less than 10mm in the short axis.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including the baseline scan if that is the smallest), and at least a 5mm increase or the appearance of new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. However, unequivocal progression should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

11.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of measurement criteria, but confirmation is not necessary.

Table 10: Assessment of Best Overall Response Using Target and Non-Target Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

11.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.6 **Progression-Free Survival**

Progression-free survival is defined as the length of time between the start of treatment and when objective evidence of disease progression is documented.

11.7 **Overall Survival**

Overall survival is defined as the length of time between the start of treatment and death.

12.0 Data Reporting/Protocol Deviations

12.1 **Data Reporting**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1.1 Method

This study will be monitored by the City of Hope. Reports are due quarterly on the 15th of each month. **Note**: **All** adverse events that have occurred on the study must be reported to the study sponsor.

Reporting will conform to the COH policy on reporting of AEs (http://www.infosci.coh.org/ocrqa/forms/guidance.doc) and to all FDA requirements. As this study will not involve an IND, voluntary reporting requirements will conform to policies as described at http://www.fda.gov/cder/aers/fr07oc97.htm and http:///www.fda.gov/medwatch/index/html, and all relevant events will also be voluntarily reported to the FDA using the MedWatch system.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting data and/or data forms to the Study Sponsor quarterly by the 15th day of the month. The Principal Investigator will then review, and timely submit data to the IRB.

The City of Hope PI is responsible for compiling and submitting data to all data review authorities for all participants and for providing the data to each Principal Investigator for review.

12.1.3 Confidentiality of and Storage of Records

The original data collection forms will be stored in password protected databases. Hard copy forms will be stored in locked cabinets. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

The original data collection forms will be submitted into Medidata Electronic Data Collection (EDC). Data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

12.1.4 Subject Consent Form

At the time of registration, the original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights (for the medical record) and three copies (for the subject, the research record, and the Coordinating Center) must be available. All Institutional, NCI, Federal, and State of California requirements will be fulfilled.

12.1.5 **Data Collection Forms and Submission Schedule (for COH Patients)**

All data will be collected in a timely manner using Case Report Forms (Paper or via Medidata Electronic Data Collection (EDC). , Geriatric Assessment Surveys, medication adherence forms, Adverse/Serious Event logs, Pharmacokinetics Worksheet, and Tumor Measurement Logs. Data will be sent to the Primary Investigator and stored in a secure location.

12.1.5.1Eligibility Checklist

The Eligibility Checklist (see Appendix D) must be completed by a protocol nurse or clinical research associate and signed by an authorized investigator prior to registering the subject. See Section 4.3 for the registration procedure.

12.1.5.2Prior Therapy and On-Study Forms

Before the first dose of study agents are given, the clinical research associate must submit the Eligibility Checklist, the baseline Geriatric Assessment Form, baseline report of cardiac ejection fraction form, and baseline tumor measurement form.

12.1.6 **Data Collection Forms and Submission Schedule (for Participating Institutions)**

All data will be collected in a timely manner using Case Report Forms (Paper or via Medidata Electronic Data Collection (EDC). Other forms that may be used include: Geriatric Assessment Surveys (Paper or

touchscreen computer survey), medication adherence forms, Adverse/Serious Event logs, Pharmacokinetics Worksheet, and Tumor Measurement Logs.

The participating institutions will be provided with a complete forms set specific to this protocol, along with forms instructions and the timepoints when data is to be collected and submitted to the Data Coordinating Center at City of Hope.

12.1.6.1 The participating institution will complete the Eligibility Checklist Worksheet at the time of registration.

12.1.6.2 Patient Consent Form: The original consent form will reside with the participating institution and a copy will be kept at the Data Coordinating

12.1.6.3 Center at City of Hope.

12.1.6.4 Data collection forms will be submitted to the Data Coordinating Center *via FAX at (626) 301-8422 or online (if applicable),* along with all corresponding source documentation. All forms will remain in a secure location in the Department of Clinical Research Information Support (CRIS).

12.2 **Multicenter Guidelines**

This protocol will adhere to the policies and requirements of the Study Sponsor's Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Study Sponsor (Coordinating Center) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Study Sponsor is responsible for distributing all IND Action Letters or Safety Reports received from the study sponsor to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order the investigational agent lapatinib directly from the manufacturer. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the City of Hope to GSK.

12.3 **Protocol Deviations**

12.3.1 Deviation Policy

In accordance with the COH Policy on Clinical Research Protocol Deviation, there will be a "no deviations" rule for this protocol. However, for subject safety or unforeseen scheduling problems, planned deviations may be permitted following IRB approval. These planned deviations, considered Single Subject Exception, are considered an Amendment to the Protocol. In addition, if contractually obligated, the sponsor must also approve any planned deviations.

12.3.2 Reporting of Unplanned Deviations

All unplanned deviations will be reported to the COH DSMB who will forward to the IRB following review.

12.3.3 Resolving Disputes

If there is a dispute among the persons involved in the provision of research treatment, in regard to whether a treatment deviates from the protocol, the facts of the case will be reported to the DSMB which will serve as the arbiter of whether a deviation exists.

13.0 Statistical Considerations

13.1 **Study Design**

The primary objective of this study is to determine the safety & tolerability of lapatinib (1000mg orally daily) in combination with trastuzumab given either weekly (first as a loading dose of 4mg/kg intravenously during week 1, and then at a maintenance dose of 2mg/kg intravenously weekly), or every three weeks (loading dose of 8mg/kg intravenously during week 1, then at a maintenance dose of 6mg/kg every three weeks thereafter) for patients 60 years of age and older.

13.1.1 Primary Endpoints

Grade 3 or higher non-hematological toxicities in patients taking the combination of lapatinib and trastuzumab, and symptomatic congestive heart failure

13.1.2 Secondary Endpoints

1. All toxicities associated with the combinations as measured by NCI CTCAE v.4.0
2. Dose reductions, interruptions, and discontinuations
3. Pharmacokinetic parameters
4. Response as determined by RECIST criteria
5. Progression-free survival
6. Overall survival

13.1.3 Methods for Stratification and Randomization

None.

13.2 **Sample Size and Accrual Rate**

Given a sample size of 40 subjects the widest half-width of the 95% confidence limits for the rate of grade 3 or higher toxicities will be less than or equal to 0.16. For example if we saw a toxicity rate of 0.2 (8 subjects/40) the 95% lower and upper confidence limits would be .09 and .36, respectively. As of December 2014, the accrual for this study has been approximately 8 participants per year. Given the current sample size of 27 evaluable participants, we should reach our accrual goal of 40 patients within 24 additional months making the full accrual period 72 months.

13.3 **Interim Analyses and Stopping Rules**

Interim Analyses: After 20 patients have completed one full cycle of therapy, the study team will review the data and assess the toxicity profile and rates of dose reduction, delays, interruptions and hospitalization related to the combination of agents. Within this interim analysis a specific review will be made of the data for the patients over 75 years of age. In response to the DSMB review of the planned interim analysis results, we are adding a second interim analysis after 30 patients have completed one full cycle of therapy.

Stopping Rules: As cardiac toxicity has been seen with this combination, we have established additional guidelines and criteria which will be used to flag an unexpected number of patients that experience symptomatic cardiac toxicity (NYHA Class III or IV if cardiac failure, or Grade 3 or higher by NCI NCTAE v4.0 for other cardiac events).

The risk set to be used in the safety monitoring decision (to trigger a review of the protocol) will include all patients that have received the combination of lapatinib and trastuzumab.

Every time a patient experiences a symptomatic cardiac toxicity, we will look at the column for the total number of patients that have experienced symptomatic cardiac toxicity (X), and compare the number of patients, N, who are in the risk set to N_X. If the number of patients, N, is greater than N_X, the number given in the bottom row of the table below, then accrual will continue. If N is less than or equal to N_X, then the monitoring boundary will have been crossed and a careful review of the trial data will be mandated.

Table 11: Criteria for Suspending Accrual to Evaluate Safety			
X: # pts who experience a symptomatic cardiac toxicity	**2**	**3**	**4**
N_x: safety boundary crossed if # patients in risk set (N) is less than or equal to N_x (if N ≤ N_x)	**≤10**	**≤ 33**	**≤ 40**

These rules were selected to ensure a low probability that the safety boundary would be crossed, indicating excessive cardiac toxicity, if the true chance of symptomatic cardiac toxicity were less than 2% and a high probability that the boundary would be crossed if the true chance of symptomatic cardiac toxicity reached 8%. Criteria for flagging an excessive number of patients that have symptomatic cardiac toxicity are based on the sequential probability ratio test with α=0.10, β=0.05, p_o=0.02 and p_a=0.08. The table below summarizes these probabilities. The values in the table below are based on 10,000 simulations.

	Table 12: Probability of Crossing the Safety Boundary (i.e. too many patients have TOX)				
True Chance of Experiencing Symptomatic Cardiac Toxicities	**2%**	**4%**	**8%**	**12%**	**16%**
Probability of Crossing the Safety Boundary	0.04	0.18	0.54	.81	0.94

13.4 **Analysis of Toxicity Data:**

Tables will be created to summarize the toxicities and side effects for each dose schedule by dose, course, organ and severity for all patients. We will describe all serious adverse events and other serious toxicities on a patient by patient basis. Numbers of cycles received and dose reductions will be tabulated by dose. Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 3 or higher toxicities, 2) all grade nausea, diarrhea and vomiting, 3) all grade cardiac events including SAEs and otherwise, 4) dose reductions, delays, interruptions and hospitalizations. Descriptive statistics will be provided for study patient demographics.

The primary analysis will be on all patients who receive the first dose of the combination of lapatinib and trastuzumab. Sub-analyses will then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

13.5 **Secondary analyses:**

13.5.1 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.] Response rate (CR + PR) and clinical benefit rate (CR+PR+SD) and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated. .

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories

4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

Primary analysis will be on all patients who are evaluable for toxicity. Sub analyses will then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

13.5.2 Pharmacokinetic parameters:

We will measure trough levels of lapatinib in each patient who is eligible for such measure (has been on a stable dose of lapatinib for at least 7 days) at three different time periods as described earlier. Each sample will be processed at the participating study site, and will be batched and sent to GSK for assay. AUC will be calculated and reported using standard descriptive statistics.

13.5.3 Factors other than chronologic age that can affect outcomes:

We will perform a geriatric assessment analysis on all patients enrolling in the study. This assessment will be given at baseline, at the end of every four cycles, and once the study is over. A comprehensive cancer-specific geriatric assessment includes an evaluation of functional status, comorbidity, cognition, psychological status, social functioning and support, and nutritional status.[1] This assessment has been piloted in the CALGB. We will also collect data on the subjects regarding number at type of prior treatments, and collect baseline laboratory values, baseline tumor burden, and baseline ejection fraction. General linear models and graphical methods will be used to explore factors other than chronologic age that can predict toxicity, efficacy and/or pharmacokinetic parameters of interest.

14.0 Human Subject Issues

14.1 **Institutional Review Board**

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

14.2 **Recruitment of Subjects**

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team, from the pool of patients seen by the study center with locally advanced or metastatic breast cancer. Potential subjects will be contacted by their treating physician and will be referred to the investigator/research staff of the study at their institution.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at the participating institution, provided that the investigator/research team is only reviewing records at their home institution, in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patients regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information

collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted by the treatment team, investigator, or the research staff working in conjunction with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons we seek a limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable). Treating physicians will be contacted regarding potentially eligible patients, and may then choose whether to offer eligible patients the opportunity to participate in the study. The goals of the study will be described and the patient will be given a copy of the informed consent to review. The interested patient will sign the consent form and retain a copy.

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Blood tests that were performed within 14 days and radiologic tests performed within 28 days for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained.

14.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

14.4 Study location and Performance Sites

This study will be performed at COH. Other sites may enroll patients onto the research protocol provided that this protocol, with site-specific changes only, is approved by each site IRB. All data analysis will be performed at City of Hope.

14.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual response to the study drugs and any side effects, and this will be linked to the subject's identity using a coded study number. The principal investigator, co-investigators, and laboratory technicians will have access to this information, but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.

14.6 Financial Obligations and Compensation

The study drug lapatinib will be provided by the manufacturer free of charge to patients on this study. *Note: For patients enrolling at Roswell Park Cancer Institute, lapatinib will be provided as Standard of Care and this drug will be billed to the insurance. (It is anticipated that lapatinib related costs will be covered wholly or in part by most insurances due to the fact that lapatinib is FDA approved in HER2 overexpressing breast cancer.) Pharmacokinetic lab draws, processing, and results will also be free of charge as a part of research. Routine standard of care clinic visits, laboratory tests, and tumor imaging will be billed to the patient and/or the patient's insurance. Cardiac imaging will be provided free of charge. The study drug trastuzumab, infusion center time, and routine nursing care involved in administering

trastuzumab and supportive medications during infusion will be billed to the patient and/or the patient's insurance. It is anticipated that trastuzumab related costs will likely be covered wholly or in part by most insurances due to the fact that trastuzumab is FDA approved in HER2 overexpressing breast cancer. Medication and/or treatment needed for side effects of either study drug will be billed to the patient and/or the patient's insurance.

If there is a serious medical complication of the research, treatment will be available at City of Hope, but there will be no compensation to the subject for this injury.

14.7 **Informed Consent Processes**

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, the research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

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APPENDIX A*:* Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Multicenter Guidelines

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with sponsoring organization. The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to the FDA and Novartis are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Data Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Data Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- The Data Coordinating Center is responsible for central patient registration of patient's from participating institutions. The Data Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Data Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair that has been received by the participating institutions.
- The Data Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to the FDA and Novartis with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to Novartis and the FDA. The Data Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Routine monitoring of data quality will take place for all data received from participating institutions. The participating institution will be asked to provide the Data Coordinating Center source documentation pertaining to the data collected. This information should be de-identified by the participating institution prior to faxing to the Data Coordinating Center.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are sent from participating sites to the Data Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the study sponsor chooses to have an audit at the Data Coordinating Center, then the Data Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Data Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Data Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions through the Data Coordinating Center.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order lapatinib directly from Novartis

APPENDIX C: Lapatinib Prohibited Medication List

Lapatinib is a substrate for CYP3A4. Inducers and inhibitors of CYP3A4 may alter the metabolism of lapatinib. The following list of CYP3A4 inducers and inhibitors are prohibited from screening through discontinuation from study.

Drug Class	**Agent**	**Wash-out[1]**
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)	
Antiretrovirals	efavirenz, nevirapine, tipranivir, etravirine	
Glucocorticoids (oral)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone[2] (>1.5 mg)	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin, **flucloxacillin**	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir, atazanivir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant[3]	
Other	red wine, Seville oranges, grapefruit or grapefruit juice and/or kumquats, pomegranate or pomegranate juice, pomelos, exotic citrus fruit (i.e., star fruit, bitter melon), grapefruit hybrids or fruit juices, or other foods and juices known to inhibit CYP3A4	
	amiodarone	6 months
Miscellaneous		
H2 blockers	cimetidine	7 days
Antacids	Mylanta, Maalox, TUMS™, Rennies	1 hour before and after dosing
Herbal supplements[4]	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	14 days
Study Specific Medications		
Potent Pgp inhibitors	resperine	14 days
	tacrolimus	3 days
	cyclosporine	5 days

1. At baseline, if a subject is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of study drug and throughout the study period in order for the subject to be eligible to participate in the study.
2. Glucocorticoid daily doses (oral) ≤1.5 mg dexamethasone (or equivalent) are allowed. Glucocorticoid conversions are provided in parentheses.
3. Emetogenic chemotherapy may require 3-4 daily doses of aprepitant. CYP3A4 inhibition by oral (not IV) aprepitant may require a concurrent dose reduction of 1-2 lapatinib tablets.
4. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact a GSK medical monitor.

NOTE: If future changes are made to the list of prohibited medications, formal documentation will be created and stored with the study file. Any changes will be communicated to the investigative sites in the form of a letter.

APPENDIX D: Eligibility Checklist

Question	Yes	No
Does this patient have locally advanced or metastatic breast cancer?		
Does this patient have documented HER2 positive disease (defined as IHC 3+ or FISH ratio ≥2.0)?		
	IHC:	
	FISH ratio:	
Is the patient age 60 or older?		
Does the patient have a life expectancy of ≥12 weeks?		
Is the patient's ECOG Performance Status ≤ 2?	PS:	
Has the patient had resolution of all grade 2 or higher toxicities from previous treatments?		
Can the patient understand and sign a written informed consent document?		
Is the absolute neutrophil count ≥ 1,500/mm^3?		
	ANC:	
	Date:	
Is the platelet count ≥ 100,000/ mm^3?		
	Plts:	
	Date:	
Is the hemoglobin ≥ 10g/dL?		
	Hgb:	
	Date:	

Question	Yes	No
Is the total bilirubin within the normal institutional limits (or does the patient have known chronic but stable liver disease such as Gilbert's syndrome)?	Bilirubin: Date:	
Are the ALT and AST $\leq$ 2.5 times the institution's upper limit of normal? (Or does the patient have known chronic but stable liver disease?)	ALT/AST: Date:	
Is the creatinine clearance $\geq$ 30ml/min?	Cr clearance:	
Were the above tests performed within 14 days of study enrollment?		
Does the patient have the ability to swallow and retain oral medication?		
Will the patient be receiving any other investigational agents?		
Has the patient ever received trastuzumab and lapatinib *concurrently*?		
Does the patient have untreated CNS metastases or symptomatic CNS metastases requiring doses of corticosteroids?		
History of allergic reactions attributed to compounds of similar chemical or biologic composition to lapatinib or trastuzumab. However patients with a history of infusion reaction to trastuzumab which was controlled with premedication on subsequent infusions without a recurring infusion reaction are eligible.		
Does the patient have the presence of any serious or uncontrolled infection (including HIV)?		
Does the patient have psychiatric illness or a social situation that would limit compliance with study medications?		

Question	Yes	No
Is the patient currently taking any of the medicines listed in Appendix C?		
If the patient is sexually active and not post-menopausal, does he/she agree to use appropriate contraception during the trial?		
Does the patient have a left ventricular ejection fraction greater than 50%?		
	EF:	
	Date:	
Does the patient have problems with GI absorption that may limit her ability to retain the drug?		
Does the patient have active hepatic or biliary disease?		
Has the patient had a documented myocardial infarction in the past six months?		
Does the patient have angina pectoris requiring anti-anginal medication?		
Does the patient have clinically significant valvular heart disease?		
Does the patient have a *history* of congestive heart failure or decreased left ventricular ejection fraction <50%?		
Does the patient have evidence of transmural infarction, ventricular tachycardia, high-grade AV-block, and/or supraventricular tachycardia which is not adequately rate-controlled on EKG?		
Does the patient have poorly controlled hypertension (systolic BP >180mm Hg or diastolic BP >100mm Hg?		
	BP:	

Signatures:

Consenting MD:_____ Date:_____

Protocol RN:_____ Date:_____

**Shaded boxes must be checked for patient to be eligible*

APPENDIX E: Geriatric Assessment Survey

Completed via touchscreen computer survey (preferable) or paper assessment forms (Attached)

APPENDIX F

Data Coordinating Center

Department of Clinical Research Information Support

City of Hope

NOTIFICATION OF TOXICITY

THIS FORM ALONG WITH A COPY OF LOCAL IRB REPORT, NOVARTIS SAE NOTIFICATION AND MEDWATCH (IF APPLICABLE) FORM MUST BE FAX'D (626-301-8422) TO THE DATA COORDINATING CNETER WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF ADVERSE EVENT

COH IRB #10112

INSTITUTIONAL IRB # _____

TOLERABILITY OF THE COMBINATION OF LAPATINIB AND TRASTUZUMAB IN ADULTS AGED 60 OR OLDER WITH HER2 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER

Participating/Treating Institution: _____

Reporter: _____ Phone #:_____

Email: _____

PATIENT INFORMATION

Patient Name_____ Pt Study ID: _____

ADVERSE EVENT INFORMATION

Adverse Event: _____ Start Date of AE: ____/____/____

REPORTING INFORMATION

Has the event been reported to the following?

Via Phone/Fax to Dr. Arti Hurria? __ No __ Yes Date: __ __ / __ __ / __ __

Phone: 626-471-9200/Fax: 626-301-8233

Institutional IRB? __ No __ Yes Date: __ __ / __ __ / __ __

FDA (if applicable)? __ No __ Yes Date: __ __ / __ __ / __ __

Novartis? __ No __ Yes Date: __ __ / __ __ / __ __

Report sent to Data Coordinating Center (COH)? __ No __ Yes Date: __ __ / __ __ / __ __

Fax: 626-301-8422