The Feasibility of Paclitaxel with Trastuzumab and Lapatinib in HER2-Positive Early Stage Breast Cancer

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

~~**Participating Institutions**~~	~~**PI's Name**~~	~~**Site's Role**~~
~~University of Pennsylvania~~	~~Bonnie Ky, PhD~~	~~Specimen Analysis~~

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a feasibility trial of dose-dense adjuvant chemotherapy for patients with node-negative, HER-2/neu-overexpressed/amplified breast cancer. The regimen consists of paclitaxel (T) at 175 mg/m^2 q 2 weeks x 4 with filgrastim/pegfilgrastim + trastuzumab (H) + daily oral lapatinib (L), followed by trastuzumab q 3 weeks x 15 doses + daily oral lapatinib (HL). Pegfilgrastim 6mg will be given subcutaneously (SQ) on day # 2 of each paclitaxel administration. Filgrastim may be used in lieu of pegfilgrastim at the physician's discretion. Trastuzumab will be administered weekly (4 mg/kg bolus followed by 2 mg/kg weekly) starting with paclitaxel treatment cycle # 1. After completion of 4 cycles of paclitaxel, patients will receive trastuzumab on a q 3 week schedule x 15 doses. A total of 15 infusions of trastuzumab will be given q 3 weeks after the completion of paclitaxel (during the HL phase). Lapatinib will be given orally at 1000 mg daily, starting with paclitaxel during the THL phase and continued for the remaining year during the HL phase for about a year.

Study blood will be collected serially for cardiac biomarker analysis [troponin I (cTnI), brain type natriuretic peptide (BNP), neuregulin-1ß (NRG-1ß)]. We will also assess the left ventricular ejection fraction (LVEF) at baseline and at months 2, 6, 9, 12 and 18 of treatment with an echocardiogram (ECHO) with a strain imaging analysis (+/- 4 weeks). When an ECHO cannot be done, a multi-gated acquisition scan (MUGA) may be done.

The primary objective is to determine the feasibility of a dose-dense adjuvant paclitaxel with HL in patients with node-negative, HER-2/neu-overexpressed/amplified breast cancer.

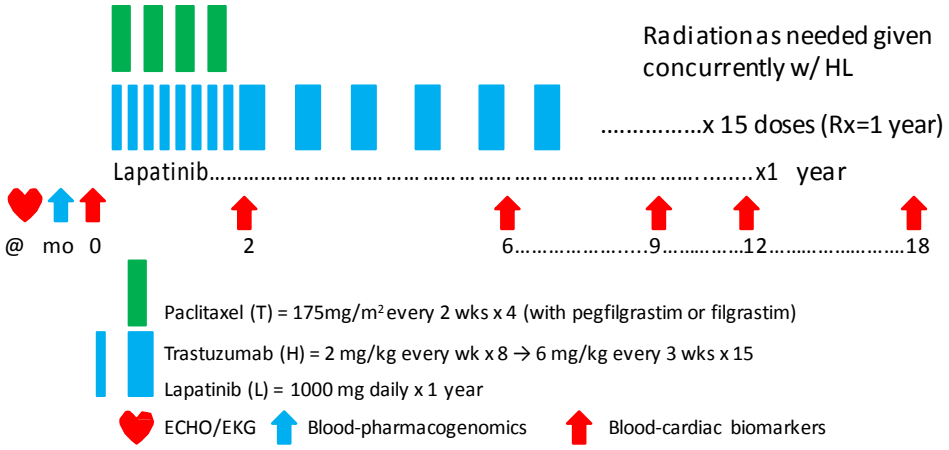
The regimen is considered feasible if patients are able to complete the paclitaxel, trastuzumab, and lapatinib (THL) portion of the regimen without a dose delay or reduction or grade 3 or greater QTc prolongation. An early stopping rule that terminates the trial if the overall cardiac event (CE) rate is greater than 4% or if there is excessive grade 3 gastrointestinal toxicity has been incorporated. The incidence of cardiac events will be closely monitored. A CE is defined as 1) cardiac death or 2) symptomatic congestive heart failure (CHF) defined as dyspnea with normal activity or at rest and "absolute" decline in LVEF by > 10% to < 50 % by echocardiogram or MUGA. A cardiac event will result in discontinuation of trastuzumab and lapatinib.

The secondary objectives are to evaluate the toxicities of this regimen, to explore the use of cardiac biomarkers as predictors of cardiac toxicity and to explore the use of single-nucleotide polymorphism (SNP) genotyping in evaluation of pharmacogenetic determinates of gastrointestinal toxicity.

We plan to accrue 55 evaluable patients with HER-2/neu overexpressed/amplified breast cancer (node-negative, tumor size ≤ 3 cm) to this trial within 12 months. Endpoints for removal from the study are unacceptable toxicity, progression of disease while on study drugs, death, major protocol violation, and patient withdrawal from study.

Schema

Accrual Goal = 55 pts



Research bloods (TnI, BNP, NRG-1ß) every cycle (pre- and post-infusion of cycles 1-4 during THL pre- and post-infusion during months 6 and 9 (cycles)(+/- a cycle) and month 18 (after completeion of HL).

Post-Chemotherapy

Hormonal therapy such as tamoxifen or an aromatase inhibitor will be given to patients with hormone receptor positive disease at the physician's discretion. Radiation therapy to the breast or chest is recommended to patients as appropriate.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

To determine the feasibility of a dose-dense adjuvant paclitaxel in patients with node-negative, HER2-positive breast cancer using dual anti-HER2 inhibition with trastuzumab and lapatinib (1000 mg).

The regimen is considered feasible if patients are able to complete the paclitaxel, trastuzumab, and lapatinib (THL) portion of the regimen without a dose delay or reduction or grade 3 or greater QTc prolongation. We have incorporated an early stopping rule that terminates the trial if the overall cardiac event (CE) rate is greater than 4% or if there is excessive grade 3 gastrointestinal toxicity.

Secondary Objectives

- Safety
- To explore certain allele frequencies of CYP3A4, CYP3A5, CYP2C8, CYP2C19, ABCB1, and ABCG2 (genes known to be involved in taxane and lapatinib metabolism) and their association relative to gastrointestinal toxicity
-To explore the use of serial troponin I, and B-type natriuretic peptide, as potential predictors of cardiac toxicity of this regimen
-To explore serial ECHOs with strain imaging

3.0 BACKGROUND AND RATIONALE

Background

Adjuvant Chemotherapy

Adjuvant chemotherapy with combinations of cytotoxic agents reduces the risk of recurrence and has an important role in the treatment of early breast cancer. The 2005 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrated a survival advantage for anthracycline-based adjuvant regimens compared with non-anthracycline based therapies.[1] Given the rare but serious long-term effects of anthracycline exposure including congestive heart failure and secondary hematologic malignancies, tailoring adjuvant regimens to minimize the cumulative exposure to anthracyclines and optimize efficacy has been a focus for medical oncologists. Over the past 25 years, taxanes have been studied in the treatment of breast cancer and are well established agents in the metastatic setting. Paclitaxel and docetaxel, when administered as single agents have similar efficacy to anthracyclines in chemotherapy naïve patients.[2-3] Several randomized controlled trials have evaluated the benefit of a taxane to an anthracycline-based regimen in the treatment of early breast cancer. A recent meta-analysis demonstrated that taxane-based regimens provide both a disease free survival (DFS) and overall survival benefit (OS) with an absolute 5-year risk reduction of 5% for DFS and 3% for OS when compared to standard anthracycline regimens. The benefit risk reduction for recurrence was seen irrespective of estrogen receptor (ER) status, lymph node status, and age with a magnitude of benefit that remained nearly constant across subgroups of patients.[4]

Dose Dense Therapy

In an attempt to optimize taxane delivery in the adjuvant setting, the Cancer and Leukemia Group B (CALGB) 9741 trial explored the concept of dose density or the administration of chemotherapy with shortened inter-treatment intervals.[5] This strategy was developed from the Norton-Simon mathematical model of tumor cell growth which shows that a given dose of chemotherapy kills a certain fraction rather than a certain number of cancer cells. Additionally, breast cancer cells demonstrate non-exponential Gompertzian kinetics, and regrowth of cancer cells between cycles of therapy is more rapid in these cancer models than exponential models.[6-7] Thus, the fixed cell kill achieved with each cycle of therapy may be optimized by delivering each subsequent cycle in quick succession. The limitation of dose-dense therapy is the impact on rapidly proliferating cells, including bone marrow progenitor cells though this is mitigated by the administration of G-CSF. The CALGB 9741 trial randomized 2,005 patients to one of four treatment arms: 1) sequential doxorubicin (A) x 4 cycles, paclitaxel (T) x 4 cycles, cyclophosphamide (C) x 4 cycles (A-T-C) delivered three weeks apart; 2) sequential A-T-C delivered every two weeks with G-CSF; 3)

concurrent AC x 4 cycles followed by 4 cycles of T (AC-T) delivered every three weeks; 4) concurrent AC-T delivered every two weeks with G-CSF. At a median 6.5 years of follow-up, there is a statistically significant improvement in DFS and OS in favor of dose-dense chemotherapy administration.[8].

Anti-HER2 Therapies

Trastuzumab

In an effort to improve upon these outcomes, biologic therapeutics have been incorporated into adjuvant regimens. Amplification of the human epidermal growth factor receptor 2 (HER2/*neu*) gene is observed in 20% to 30% of invasive breast carcinomas and portends a poor prognosis with increased risk of disease progression and decreased overall survival.[9] Given that HER2 overexpression mediates the transformed phenotype, therapeutic strategies targeting HER2 activation are a logical approach. Trastuzumab (Herceptin®), a humanized, recombinant monoclonal antibody, binds to the extracellular domain of HER2 inhibiting kinase activity and leading to cell cycle arrest and apoptosis.[10] The pivotal phase III clinical trial, which led to FDA approval of trastuzumab for the treatment of metastatic HER2-positive breast cancer, randomized 469 women who had not received chemotherapy for metastatic HER2-amplified disease to receive chemotherapy plus trastuzumab or chemotherapy alone. Women were treated with an anthracycline- or taxane-based regimen based on their prior exposures. The addition of trastuzumab to chemotherapy led to statistically significant improvements in time to progression, duration of response, objective response rate, and overall survival. These results were tempered by cardiac toxicity documented with trastuzumab especially in combination with anthracycline therapy (27% incidence with anthracycline and trastuzumab, 13% with paclitaxel and trastuzumab, and 8% with anthracycline therapy alone).[11]

Motivated by the proven benefits of trastuzumab in the metastatic setting, four international studies initiated in 2000-2001 with over 13,000 women examined the safety and efficacy of adjuvant trastuzumab: the Herceptin Adjuvant (HERA)[12-13] trial, the National Surgical Adjuvant Breast and Bowel Project B-31 (NSABP B-31) trial, the North Central Cancer Treatment Group 9831 (N9831)[14] trial, and the Breast Cancer International Research Group 006 (BCIRG 006)[15-16] trial. Two smaller trials, the Finland Herceptin (FinHER)[17] trial and the Protocole Adjuvant dans le Cancer du Sein 04 (PACS 04)[18] trial followed soon after (Table 1). With the exception of PACS 04, the adjuvant trials collectively demonstrated trastuzumab reduced the risk of breast cancer recurrence by approximately 40-50% despite differences in patient population and trial design. Although trastuzumab has been widely accepted in the adjuvant setting, there remain several uncertainties regarding administration including possible cardiac toxicity.

Cardiac Toxicity

Reports of trastuzumab-related cardiac toxicity during pivotal trials of data collected from seven phase II and III clinical trials for trastuzumab are available.[19-20] The analysis performed independently by the Cardiac Review and Evaluation Committee, evaluated the risk and severity of cardiac dysfunction, baseline risk factors, and the role of cumulative doses of anthracyclines and trastuzumab relative to the development of cardiac dysfunction. The severity of these events was categorized using the New York Heart Association functional classification system. The

incidence of class III or IV cardiac dysfunction was 2% for those receiving first-line trastuzumab, 4% for those receiving trastuzumab in the refractory setting, 2% for those receiving concurrent paclitaxel plus trastuzumab, 1% for those receiving paclitaxel alone, 16% for those receiving concurrent AC and trastuzumab, and 4% for those receiving AC alone. The incidence and severity of cardiac dysfunction was greatest among patients receiving concurrent AC and trastuzumab. The risk of cardiac toxicity was lower in those receiving concurrent paclitaxel and trastuzumab or paclitaxel alone, despite prior anthracycline exposure in most of these patients. The four large adjuvant trials have shown that the incidence of cardiac toxicity attributable to treatment with anthracycline-taxane based regimen followed by trastuzumab is acceptable with rates of congestive heart failure below 4% and very rare cardiac deaths.[13, 16, 21-24]

Given the superiority of dose-dense AC-T over conventionally scheduled AC-T in terms of DFS and OS, and the benefit and safety of trastuzumab with conventionally scheduled AC-T, our group examined the feasibility of dose-dense AC followed by T and trastuzumab in HER2-amplified breast cancer. The primary end point of the study was cardiac safety. In our study, the addition of trastuzumab to dose-dense AC-T was well tolerated with only 1/70 patients (1.4%) experiencing symptomatic LVEF decline with congestive heart failure; there were no cardiac deaths.[25]

Lapatinib

Having shown the safety of dose-dense AC-T plus trastuzumab, our attention turned to further improving adjuvant regimens and their outcomes for patients with HER2-overexpressing breast cancer. Lapatinib, a dual inhibitor of epidermal growth factor and HER2/*neu* kinase activity has demonstrated activity as a single agent, combined with trastuzumab, as well as with capecitabine in patients with progression after prior anthracycline, taxane, and trastuzumab therapy.[26-28] This motivated the inclusion of lapatinib into adjuvant regimens including the large multicenter phase III ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial. We conducted a phase II study to establish safety data for one arm of ALTTO: dose-dense AC followed by paclitaxel, weekly trastuzumab, and lapatinib, followed by trastuzumab and lapatinib. The dose of lapatinib selected was 1,000 mg daily based on phase I studies that established the feasibility of the combination of trastuzumab and lapatinib (EGF10023) and weekly paclitaxel and lapatinib (EGF10009/EGF105764).[27, 29]

Our phase II study of dose-dense AC followed by paclitaxel, trastuzumab, and lapatinib (THL) followed by trastuzumab, lapatinib was not feasible at a lapatinib dose of 1000 mg given excessive diarrhea. Diarrhea was experienced by 84 (88%) patients and 27 (29%) patients had grade 3 diarrhea. The study was closed early as 43% of patients required a lapatinib dose reduction due to grade 3 or unacceptable grade 2 or less diarrhea.[30] Two trials with similar designs demonstrated high rates of diarrhea for the combination of weekly paclitaxel, trastuzumab, and lapatinib dosed at 1,000 mg daily. Johnson and colleagues reporting the Mayo Clinic experience found that 43% of patients had grade 3 or greater diarrhea.[31] The neoadjuvant CHERLOB (Chemotherapy Plus Trastuzumab, Lapatinib, or Both in HER2-Positive Operable Breast Cancer) reports 41% of patients experienced grade 3 or greater diarrhea in the arm receiving weekly paclitaxel, trastuzumab, and lapatinib.[32]Institution of proactive diarrhea management in our study could explain the lower rate of grade 3 diarrhea reported in our phase II study.

Diarrhea

Diarrhea is a known side-effect of lapatinib therapy; a pooled analysis of eleven studies with lapatinib monotherapy or in combination with capecitabine or taxanes demonstrated a less than 10% rate of grade 3 or 4 diarrhea. Diarrhea rates in the two phase I studies examining combination lapatinib with taxane therapy were higher than that for lapatinib monotherapy. In EGF10009 (lapatinib 1,250 or 1,500 mg with paclitaxel at 135 to 225 mg/m2 every 3 weeks or 80 mg/m2 weekly) and in EGF10021 (lapatinib 1,000 or 1,500 mg with docetaxel at 50 to 75 mg/m2 every 3 weeks) incidence of all grade diarrhea were 82% and 71%, respectively.[33] Pharmacokinetic studies for EGF10009 demonstrated a greater than 20% increase in systemic exposure for both lapatinib and paclitaxel when paclitaxel was administered every three weeks. Diarrhea rates were higher for patients who received lapatinib with weekly paclitaxel than those on every three week paclitaxel, 50% versus 7%, respectively.[29]

There are several possible explanations for the excessive diarrhea seen in our phase II safety trial of dose-dense AC followed by paclitaxel, trastuzumab, lapatinib, followed by trastuzumab and paclitaxel. First, paclitaxel, trastuzumab, and lapatinib can all individually lead to diarrhea although this is usually grade 1 or 2.[34-36] Second, paclitaxel therapy may affect the intestinal crypt cells and lead to a loss of absorption leading to worsening diarrhea with lapatinib and trastuzumab therapy.[37] Third, the schedule of paclitaxel administration influences diarrhea rates. There is a higher incidence of grade 3 diarrhea reported with weekly than every three week paclitaxel administration.[35] Examination of every two week versus every three week dosing of paclitaxel (CALGB 9741) showed no significant difference in diarrhea rates.[5] The findings of our phase II safety trial of dose-dense AC followed by paclitaxel, trastuzumab and lapatinib followed by trastuzumab and lapatinib influenced the design of the ALTTO trial. The dose of lapatinib was adjusted from 1000 mg to 750 mg daily when combined with paclitaxel and lapatinib. In terms of cardiac toxicity, three patients (3%) had symptomatic congestive heart failure and there were no cardiac deaths on study.[30] The rate of cardiac toxicity is similar to the Mayo Clinic experience with paclitaxel, trastuzumab, and lapatinib.[31] A recent review of the cardiac safety data from 3,689 patients on lapatinib determined a symptomatic CHF rate of 0.2% and an asymptomatic cardiac event rate of 1.4%.[38] Although our study reported higher rates of cardiac toxicity, this may be explained by enhanced cardiac toxicity with concurrent administration of lapatinib and trastuzumab. In support of this hypothesis, the phase III study comparing lapatinib and trastuzumab with lapatinib monotherapy, more cardiac events were reported for combination illustrating the potential of greater cardiac toxicity for lapatinib and trastuzumab in combination.[39]

Adjuvant Therapy for Node Negative HER2 Positive Patients

There is much less data on the treatment of patients with node-negative HER2-positive breast cancer than those with node-positive disease. We have recently completed accrual of a single-arm phase II efficacy trial designed to evaluate the role of 12 doses of adjuvant weekly paclitaxel and trastuzumab followed by trastuzumab monotherapy for an additional 40 weeks in about 400 patients with node-negative HER2-positive breast cancers measuring $\leq$ 3cm. The DFS and OS outcomes of this study are forthcoming. There are now data showing that dual anti-HER2 therapy is more effective than single anti-HER2 treatment. In the metastatic setting, Blackwell et al showed that in a heavily pre-treated population, lapatinib combined with trastuzumab led to a improvement in progression-free survival over just lapatinib alone.[39] In the neoadjuvant setting, the Neo-ALTTO trial showed that the pathologic complete response (pCR) rate was higher in the

group that received THL (51.3%) at the time of surgery when compared to those who received TH (29.5%) or TL (24.7%).[40] One of the major side effects was a higher grade ≥ 3 diarrhea in those receiving lapatinib containing arms, with 23% in TL arm and 21% in THL group, but only 2 % in TH arm. Of note, paclitaxel in this study was given weekly and the diarrhea toxicity data is consistent with our findings when weekly paclitaxel is used with lapatinib and trastuzumab.[30] However, the DFS and OS results for both Neo-ALTTO and ALTTO are pending.

It is possible that dual anti-HER2 therapy (ie: THL) may lead to improved DFS and/or OS over time. However, the limitation with the THL combination with weekly paclitaxel is the occurrence of significant ≥ G 3 diarrhea. Thus, it is important to establish an optimal THL schedule with a different paclitaxel schedule (dose-dense) and study it in a lower risk, node negative population.

Pharmacogenomics Studies of Drug Toxicity

Chemotherapy associated toxicity differs greatly between patients. Genetic variation may contribute to the differences in severity and frequency with which chemotherapy associated toxicities occur. A genetic polymorphism is defined as a minor allelic variant present in >1% of the population.[41] Genetic polymorphisms can occur as single nucleotide polymorphism in coding, non-coding and promoter regions, deletions, insertions, or gene copy number variant, all of which can result in altered functional pharmacokinetic and pharmacodynamic activity of the affected protein.[42] Functional polymorphisms resulting in altered drug metabolism of chemotherapeutic agents have been identified and may contribute to the variability of toxicities observed. Table 1 lists the candidate genes and the partial rationale for inclusion in this study.

Table 1. Candidate SNPs for Toxicity Association Assessment

Gene	Polymorphism	Allele Freq[43]	Partial Rationale For Inclusion

CYP2C8	*2, rs11572103	0.16	Result in lower metabolism of paclitaxel[44-48]
CYP2C19	*2, rs4244285	0.20	Leads to "slow metabolizer" phenotype[49-51]
CYP3A4	*1B, rs2740574	0.22	Involved in taxane metabolism/clearance[52-55]
CYP3A5	*3, rs776746	0.34	Results in a splicing defect that reduces CYP enzyme activity[56-57]
ABCG2	421(C>A) rs2231142	0.14	Gastrointestinal toxicity with TKI [58-59]
ABCB1	3435 (C>T) rs1045642	0.39	Multi-Drug resistance transporter[60]
	1236 (C>T) rs1128503	0.41	
	2677(G>T/A) rs2032582	0.34	

Polymorphisms in ATP-binding cassette (ABC) transporters have been shown to result in altered toxicity in those receiving tyrosine-kinase inhibitors (TKI) and taxanes. ATP-binding cassette transporter B1 (ABCB1, Multidrug resistance-1) polymorphism may change the function of P-glycoprotein, by which taxanes can be extruded through the cell membranes. The prevalence and severity of mucosal inflammation and dermatologic toxicity has been shown to be higher in patients with variant haplotypes of ABCB1 efflux transporter genes receiving tyrosine kinase inhibitors. The ABCB1 haplotype P-gp*2 includes 3435(C>T), 1236(C>T), 2677(G>T/A); and has been associated with grade 3 diarrhea in those treated with taxanes.[60] Another relevant polymorphism for this study is ABCG2 at position 421(C>A), which has been associated with diarrhea in those treated with TKIs.[59]

Functional polymorphism in genes encoding for the enzymes responsible for paclitaxel and lapatinib metabolism have also been identified within the hepatic CYP450 family. For instance, paclitaxel is converted to *p*-3′-hydroxypaclitaxel by CYP3A4 and CYP2C8 catalyzes the formation of 6α-hydroxypaclitaxel.[62] We will evaluate these and other CYP genes involved in paclitaxel and lapatinib metabolism including CYP2C19 and CYP3A5 for the presence of previously identified polymorphisms.

Determining of the extent to which functional polymorphism in drug metabolism results in altered toxicity has the potential to be applicable in multiple regimens and malignancies and in the future may allow us to identify a sub-population that is at increased for toxicity, thus helping to inform treatment decisions.

Cardiac Biomarkers

Cardiac toxicity is a potentially grave toxicity of certain cytotoxic chemotherapy agents, particularly the anthracycline drugs. In the adjuvant setting where cure is the goal, potential long- term cardiac sequelae of treatment are particularly relevant. Early detection of evolving cardiac damage and the institution of medical management may help to decrease the morbidity associated with cardiac toxicity. The use of angiotensin converting enzyme (ACE) inhibitors has been shown in studies to reduce the risk of developing symptomatic heart failure or cardiac death in patients with asymptomatic left ventricular dysfunction.[62] Research has focused on the development and validation of cardiac biomarkers that might identify subclinical cardiac damage

and patients who may benefit from cardioprotective measures. Preliminary data suggests that the use of ACE inhibitors may prevent cardiac toxicity in patients receiving high-dose chemotherapy identified as increased risk on the basis of cardiac biomarkers.[63] To date, the majority of experience with cardiac biomarkers has been in the setting of anthracycline chemotherapy.[64]

Cardiac Troponins

The incidence of elevation of cardiac troponins I or T (cTnI or cTnT) with each chemotherapy cycle may be as high as 30-34% in patients treated with potentially cardiotoxic (primarily anthracycline) chemotherapy across studies. The etiology of the troponin rise appears to be non- ischemic as it is not associated with symptoms or classical EKG changes, and it predates LV dysfunction rather than accompanying it. Troponin determination in breast cancer patients has been found to predict the occurrence of clinically significant LV dysfunction as well as the degree and severity of future LV dysfunction. Cardinale and colleagues studied 211 patients receiving high dose therapy for breast cancer (mean age 46) using cardiac troponin I (cTnI) measurements at six time points before and after each chemotherapy cycle (up to 72 hours after) and correlated these to ECHO findings at 1,2,3,4,7 and 12 months.[65] A close relationship was found between the maximal cTnI value obtained and maximum LVEF decrement seen in follow up. In addition, there was a significant correlation between the number of positive cTnI values and the LVEF maximal decrement. The presence of normal cTnI levels after therapy was associated with no significant decline in LVEF in follow-up. A study in 79 patients with leukemia measured cTnI at various intervals during induction therapy, and found elevated cTnI levels at day 7-14 correlated with reversible decreases in LVEF.[66] Reports of smaller patient cohorts ranging from 15 to 31 patients showed more variable levels of cTnI detection after anthracycline therapy.[67-69] There are now emerging data on the utility of cardiac biomarkers in patients treated with anti-HER2 agents after an anthracycline based treatment, and the data are mixed. [70-71]At MSKCC, we recently showed that 67% of patients had an elevated cTNI during the THL phase (after dd AC) but these patients were asymptomatic. This may reflect a subtle cardiac injury related to the treatment.[70] Cardinale et al, on the other hand, reported in their group of patients, treated with trastuzumab after an anthracycline-based treatment, that those with elevated TNIs are at risk for trastuzumab induced cardiac toxicity.[71]

B-type natriuretic peptide (BNP)

Natriuretic peptides are rapidly produced by the heart in response to hemodynamic stress. Both BNP and NT-proBNP are widely tested in heart failure as markers of heart failure diagnosis, prognosis, and overall risk assessment.[64] Several studies examined BNP levels at prolonged intervals from chemotherapy. A Dutch study evaluated BNP and NT-BNP levels at two time points after anthracycline chemotherapy: a median of 2.7 years later, and a median of 6.5 years afterwards.[72] Elevated BNP levels were found in 14 out of 54 patients 6.5 years after chemotherapy. The BNP levels were significantly higher in patients receiving 450 mg/m^2 epirubicin than those who received 360 mg/m^2. Cardiac function was not assessed. However, a similar study evaluating BNP levels in 63 patients at least 1 year from anthracycline therapy found cardiac dysfunction in 41% and significantly higher mean BNPs in this group.[73] Similar results of elevated BNP levels in association with reduced left ventricular function have been documented in the pediatric literature after anthracycline exposure.

Cardiac biomarkers with trastuzumab

Limited data exist regarding the use of cardiac biomarkers as predictors of cardiac toxicity in patients treated with trastuzumab. Plasma cTnI and NT-proBNP levels were assayed in 15 patients taking part in a study of an imaging modality (indium-111 labeled trastuzumab scintigraphy) as a predictor of cardiac toxicity.[74] Patients received trastuzumab as part of a non-anthracycline containing regimen. While the imaging test was not shown to be of value, pre-treatment plasma NT-proBNP levels were found to be higher in patients who developed cardiac toxicity. A pilot study examined and established novel measures of metabolic and vascular risk factors for cardiovascular disease (including BNP) in a small subset of patients participating in the BCIRG 006 adjuvant trastuzumab study.[75] Patients entered the study a median of 20 months after the completion of chemotherapy and trastuzumab. In this study, 38.4% of patients had an LVEF value 10% or more below their baseline assessment; BNP was significantly elevated in 40% of patients and was a predictor of LVEF on univariate analysis. In N9831, an adjuvant study of anthracycline and taxane-based chemotherapy with trastuzumab vs chemotherapy alone, a study correlating cardiac biomarkers including BNP, C-reactive peptide (CRP), and troponin T and I with LVEF was conducted. Elevations in BNP and cTnI at baseline and doubling of BNP during trial were seen as possibly predictive of cardiac toxicity in a small subset of patients.[76]

Neuregulin

Neuregulin-1 (NRG-1) is a cardioprotective, paracrine growth factor released by microvascular endothelial cells. This pathway, which is necessary for the maintenance of cardiac function and survival during states of increased stress, is believed to be an important mediator of heart failure and chemotherapy-induced cardiac dysfunction.[77] In vitro studies demonstrate that NRG-1 administration protects doxorubicin-treated cardiomyocytes from myofibrillar disarray and death, and NRG-1 or ErbB2 deficient mice have dramatically worse survival with anthracycline exposure.[78-80] Trastuzumab, and pertuzumab, specifically target the ErbB2 receptor, a mediator of NRG-1 activity, and its association with clinical cardiac dysfunction may be related to effects on this signaling pathway.[80]

In order to define the mechanistic and translational significance of NRG-1 signaling in humans, Ky and colleagues recently quantified serum NRG-1ß levels in a large cohort (N=899) of patients with chronic heart failure in the Penn Heart Failure Study.[81] Elevated NRG-1ß levels were significantly associated with more advanced heart failure (NYHA Class IV median 6.2 ng/ml versus those with Class I CHF 4.4 ng/ml, p=0.002). Furthermore, NRG-1ß was independently associated with an elevated risk of all-cause death or cardiac transplantation over a median follow-up of 2.4 years (adjusted HR 1.58, 95% C.I of 1.04-2.3, p=0.003), comparing the 4th vs the 1st quartile of NRG-1ß. Associations differed according to heart failure cause and severity, with stronger relationships observed in those with ischemic heart failure (interaction p=0.008) and advanced NYHA Class III/IV symptoms (interaction p=0.01). In addition, patients with chemotherapy-induced cardiac dysfunction had significant alterations in their circulating NRG-1 ß levels compared to all other etiologies (p=0.02).

Our goal is to extend these findings and provide further insight of the potential clinical relevance of cTnI, BNP ~~and NRG-1ß~~ on chemotherapy-induced cardiac dysfunction. ~~We will quantify the relationship of these cardiac biomarkers with incident cardiac dysfunction by serial echocardiogram imaging. We hope to develop an understanding of the predictive utility of these biomarkers.~~

As of A(6), we will no longer be quantifying the relationship between NRG-1ß cardiac biomarkers and incident cardiac dysfunction by serial echocardiogram imaging since the incidence of cardiac dysfunction based on the LVEF data has been minimal.

Echocardiograms (and Strain Imaging Analysis for research purposes):

Echocardiograms will be performed at months 2, 6, 9, 12 and 18 of treatment as defined in the study. Strain imaging will be analyzed off-line using 2D image loops from the routine echocardiographic examination. The ECHO machine for the strain imaging analysis should be the Vivid 7 or E9 machine (GE healthcare, Milwaukee, WI). In addition to being stored in the main ECHO PACS system, these studies will also be stored in an external GE workstation which contains the software needed to perform the strain imaging analysis. To calculate strain and strain rate, the LV myocardium is traced in a click-to-point approach. Subsequently, the software automatically defines an epicardial and myocardial line and processes all frames of the loop. The myocardium in each of the 3 standard apical views is divided into 6 segments. The software will automatically calculate strain and strain rate for each of the 18 segments plus a global value for the entire myocardium. These measurements will be made by a designated investigator (Dr. Jennifer Liu) blinded to patient identification, demographics and clinical characteristics at the end of the study. When possible any ECHOs done outside of MSKCC are requested to be done on the GE Vivid 7 or E9 machine (GE healthcare, Milwaukee, WI), and the disc to be sent to Dr. Jennifer Liu for the strain imaging analysis.

Rationale

With great advances made with chemotherapy combinations in breast cancer outcomes and trastuzumab in HER2-positive breast cancer cells, there is always room for improvement. Most patients enrolled onto clinical trials for the treatment of HER2-positive breast cancer had node-positive disease, and the majority received an anthracycline and taxane-based treatment with trastuzumab. This led to a significant improvement in DFS and OS with an acceptable 2-4% risk of cardiac events. The optimal treatment for a lower risk group, such as those with node-negative HER2-positive disease, needs to be studied further. With emerging data demonstrating better outcomes with dual anti-HER2 therapy in metastatic breast cancer and improved pCR rates in the neoadjuvant setting ,[39, 40] it is important to study a dual anti-HER2 treatment with a taxane in this lower risk group, but omit the anthracycline (such as AC) to avoid the added risk of cardiac toxicity.

Lapatinib is one of the most exciting targeted drugs and the simultaneous inhibition of HER2 with lapatinib and trastuzumab has shown to be effective in the metastatic setting[39] and may allow for more potent inhibition of cell growth than one line of anti-HER2 therapy. Previous studies showed that the rate of G 3 diarrhea was only 7 % when lapatinib (1250-1500mg) was given with paclitaxel (135-225 mg/m^2) every 3 weeks, but it was 50% when given with weekly paclitaxel (80 m/m^2).[39] Citron et al showed that the incidence of G 3 diarrhea was extremely low at 2 % versus 1% with paclitaxel (175 mg/m^2) given every 3 versus 2 weeks (dose dense), respectively.[5] It remains unanswered if lapatinib at 1,000 mg with trastuzumab, as established by Storniolo[27], can be better administered with dose-dense paclitaxel as part of adjuvant therapy for early HER2-amplified breast cancer. Based on previous data, we hypothesize that dose-dense paclitaxel may be better tolerated when combined with lapatinib (1000 mg) and trastuzumab.

We seek to address this in a phase II trial of adjuvant chemotherapy with dose-dense paclitaxel every two weeks with weekly trastuzumab and daily lapatinib (1,000 mg) followed by the completion of a year of trastuzumab (administered every three weeks) and lapatinib therapy. We choose paclitaxel every two weeks as it is may be the more optimal taxane schedule to combine with a full dose of lapatinib (1000 mg) and trastuzumab, with possibly a lower diarrhea toxicity risk than what has been reported with weekly paclitaxel. However, we may still uncover significant G3-4 diarrhea with this new THL combination. There may be an interaction between paclitaxel and lapatinib and both drugs are metabolized by CYP3A4, CYP3A5, and CYP2C8, and lapatinib is additionally metabolized by CYP2C19. Toxicities of these 2 drugs may also be influenced by variants of drug transporter genes, such as ABCB1 and ABCG2. Thus, we will perform exploratory analyses on allele frequencies of these candidate genes.

Since the incidence of G3-4 cardiac events of a previous adjuvant taxane and trastuzumab study (BCIRG 006)[16] was reported as < 1%, we anticipate that we will observe a low cardiac event (symptomatic CHF or cardiac death) rate with this study regimen as an anthracycline is omitted. However, it is still unknown the long-term cardiac event rate as well as the implication of asymptomatic LVEF declines over time. Thus, it will be important to explore cardiac biomarkers and correlate them with LVEF declines (both symptomatic and significant asymptomatic drops as defined by our study). Thus, as a correlative study we will evaluate potential cardiac biomarkers (cardiac troponin I, and B-type natriuretic peptide (BNP)) to assess if there is a correlation between elevated markers and decline in left ventricular ejection fraction (LVEF) on echocardiogram (ECHO) imaging. Additionally, for research purposes cardiac strain imaging will be done with each ECHO when possible.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II trial of dose-dense adjuvant chemotherapy for patients with node-negativeHER-2/neu overexpressed/amplified breast cancer. The regimen consists of paclitaxel (T) at 175 mg/m^2 q 2 weeks x 4 with filgrastim/pegfilgrastim + trastuzumab (H) + daily oral lapatinib (L), followed by trastuzumab q 3 weeks x 15 doses + daily oral lapatinib (HL). Pegfilgrastim 6mg will be given subcutaneously (SQ) on day # 2 of each paclitaxel administration. Filgrastim may be used in lieu of pegfilgrastim at the physician's discretion. Trastuzumab will be administered weekly (4 mg/kg bolus followed by 2 mg/kg weekly) starting with paclitaxel treatment cycle # 1. After completion of 4 cycles of paclitaxel, patients will receive trastuzumab on a q 3 weeks x 15 doses (to complete about one year). The q 3 week trastuzumab may be started at the last dose of paclitaxel infusion or from 1-3 weeks after the last dose of paclitaxel. A total of 15 infusions of trastuzumab will be given q 3 weeks after the completion of paclitaxel during the HL phase. Lapatinib will be given orally at 1000 mg daily, starting with paclitaxel during the THL phase and continued for the remaining year during the HL phase for about a year.

We plan to accrue 55 evaluable patients with HER2-amplified breast cancer to this trial within 12 months. Endpoints for removal from the study are unacceptable toxicity, progression of disease while of study drugs, death, and patient withdrawal from study.

One sample of blood (10 ml in EDTA) will be collected for pharmacogenomics analysis. This may be done at any point during the study regimen, but preferably at the beginning of the treatment.

Cardiac biomarkers (troponin I, B-type natriuretic peptide, neuregulin-1ß) will be serially followed throughout the study period. Baseline values will be obtained and biomarker testing will occur pre- and post-infusion of each paclitaxel and trastuzumab administration every 2 weeks x 4 (during THL phase). Biomarkers will then be drawn pre- and post- infusion of trastuzumab at every other cycle (approximately every 6 weeks) x 7 draws (during HL phase).

Echocardiograms (with strain) and EKGs will be obtained at baseline and at months 2, 6, 9, 12, 18 (+/- 4 weeks) following the start of chemotherapy.

4.2 Intervention

T (175mg/m2) q 2 week x 4 + trastuzumab + lapatinib (THL) → HL

↑ECHO/EKG (0 mo) ↑ECHO/EKG (2 mo) ↑ECHO/EKG (6 mo, 9 mo, 12 mo,18mo)

↑Bloods for pharmacogenetic analysis

(0 mo)

Bloods for cardiac biomarkers will be collected pre-and post- each paclitaxel/trastuzumab infusion (q 2 weeks) X 4, then every other cycle (q 6 weeks) during trastuxumab monotherapy X7.

This is a phase II study of lapatinib in combination with trastuzumab and paclitaxel for the treatment of patients with early-stage node negative HER2 (+) breast cancer. Based on promising results of the combination of lapatinib and trastuzumab in a metastatic population and better responses seen in the neoadjuvant setting[39-40] it makes sense to test this combination with paclitaxel given in a dose-dense every 2 week regimen in the treatment of patients with low-risk node negative HER2-positive breast cancer. With the superiority of every 2 week over every 3 week schedule of paclitaxel[5, 8] and since there are less toxicities seen with every 3 week paclitaxel than weekly paclitaxel,[29] it is worthwhile to combine dose-dense every 2 week paclitaxel with trastuzumab and lapatinib.

The regimen will consist of paclitaxel (175 mg/m^2) every 2 weeks x 4 + trastuzumab weekly (4 mg/kg loading dose → 2 mg/kg) both given intravenously (IV) + lapatinib 1000mg orally daily. After the completion of paclitaxel, trastuzumab (6 mg/kg IV q 3 weeks) x 15 and lapatinib (1000 mg daily) will be given to complete the year's duration. Pegfilgrastim SQ is given on day # 2 of each paclitaxel cycle and may be dropped at the last paclitaxel infusion. Filgrastim may be used in lieu of pegfilgrastim at the physician's discretion.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Paclitaxel (Taxol®)

a. Dosage

Paclitaxel is an antimicrotubule agent that promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions. The dose of paclitaxel is 175 mg/m^2 IV every 2 weeks.

Paclitaxel is commercially available.

b. Preparation

Paclitaxel will be prepared as per MSKCC chemotherapy guidelines (MSKCC and affiliates).

c. Administration

Treatment may be administered in an outpatient setting by administration of 175 mg/m^2 IV every 2 weeks. If paclitaxel is being administered concomitantly with trastuzumab, chemotherapy administration may be given before or after either antibody. A strict sequence of administration of paclitaxel relative to trastuzumab is not mandated. Patients should be observed for fever and chills or other infusion associated symptoms.

d. Storage

Unopened vials of paclitaxel are stable until the date as indicated on the package. Vials of paclitaxel should be stored at 20-25º C (68-77º F) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components of paclitaxel may precipitate but will re-dissolve upon reaching room temperature with little or no agitation.

e. Safety

Side-effects include myelosuppression, hypersensitivity (hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, bronchospasm, and tachycardia), sinus bradycardia, complete heart block, sinus tachycardia, premature ventricular beats, ventricular tachycardia, bigeminy, syncope, myocardial infarction, hypotension, hypertension, peripheral neuropathy, taste changes, arthralgia, myalgia, seizures, mood alterations, neuro-encephalopathy, motor neuropathy, autonomic neuropathy, alopecia, radiation recall dermatitis, nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, pancreatitis, elevated liver function, hepatic failure, fatigue, headache, light-headedness, elevated creatinine, elevated triglyceride, and blurred vision.

Trastuzumab (Herceptin®)

a. Dosage

The recommended initial loading dose is 4 mg/kg (for weekly dosing schedules) or 8 mg/kg (for every 3 weeks) Herceptin administered as a 90-minute infusion. The recommended maintenance Herceptin dose is 2 mg/kg weekly or 6 mg/kg every 3 weeks and can be administered as a 30-minute infusion if the initial loading dose was well

tolerated. Herceptin may be administered in an outpatient setting. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS (see ADMINISTRATION).

b. Preparation

Use appropriate aseptic technique. Each vial of Herceptin should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multidose solution containing 21 mg/mL Herceptin. 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.

Determine the dose of Herceptin needed. Calculate the correct dose using 21 mg/mL Herceptin solution. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, 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.

c. Administration

Treatment may be administered in an outpatient setting by administration of a 4 mg/kg Herceptin loading dose for weekly dosing schedules (OR 8 mg/kg Herceptin loading dose for q3wk dosing schedules) by intravenous (IV) infusion over 90 minutes. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. If Herceptin is being administered concomitantly with chemotherapy, Herceptin administration may be given before or after chemotherapy administration. Patients should be observed for fever and chills or other infusion associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated subsequent doses of 2 mg/kg Herceptin weekly (OR 6 mg/kg Herceptin q3wk) may be administered over 30 minutes.

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

d. Storage

Vials of Herceptin are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted Herceptin solution should be used immediately and

any unused portion must be discarded. DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.

The solution of Herceptin for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted Herceptin has been shown to be stable for up to 24 hours at room temperature 15°C–25°C; however, since diluted Herceptin contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).

e. Safety

Infusion-Associated Symptoms. During the first infusion with Herceptin, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent Herceptin infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine.

Serious Infusion-Associated Events. Serious adverse reactions to Herceptin infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of Herceptin as indicated.

Hematologic Toxicity. In the clinical trials, an increased incidence of anemia was observed in patients receiving Herceptin plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible; none resulted in discontinuation of Herceptin therapy. In the clinical trials, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. In the post marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving Herceptin and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of Herceptin on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated. The observed incidence of leukemia among Herceptin-treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer. Therefore, the contribution of Herceptin to the etiology of acute leukemia or myelodysplastic syndrome in these cases is unclear.

Lapatinib Ditosylate (Tykerb®)

a. Dosage

Lapatinib is a dual inhibitor of epidermal growth factor receptor (EGFR or ErbB1) and ErbB2 tyrosine kinases. Lapatinib is supplied as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side de-bossed 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.

The dosage for this study is 1000 mg orally daily.

Lapatinib is commercially available.

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).

b. Administration

Lapatinib 1000 mg is taken orally on an empty stomach (either 1 hour before or 1 hour after meals).

c. Storage

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

d. Safety (See Treatment/Intervention Section 9.0 below for details regarding management of toxicity)

Cardiotoxicity. Decreases in left ventricular ejection fraction (LVEF) have been reported (usually within the first 3 months of treatment); baseline and periodic LVEF evaluations are recommended. Interrupt therapy or decrease dose with decreased LVEF ≥ grade 2 or LVEF < LLN. Use with caution in conditions which may impair left ventricular function and in patients with a history of or predisposed (prior treatment with anthracyclines, chest wall irradiation) to left ventricular dysfunction. Interruption of therapy is recommended with decreased LVEF ≥ grade 2.

Diarrhea. Diarrhea is common, may be severe. Management with antidiarrheal agents is recommended and severe diarrhea may require hydration, electrolytes, dose reduction or interruption of therapy.

Hepatotoxicity. [U.S. Boxed Warning]: Hepatotoxicity (ALT or AST >3 times ULN and total bilirubin >2 times ULN) has been reported with lapatinib and may be severe and/or fatal. Onset may occur within days to several months after treatment initiation. Monitoring liver

function is recommended (at baseline and during treatment); with permanent discontinuation recommended with severe changes in liver function during treatment. Caution is advised in patients with hepatic impairment.

Pulmonary toxicity. Interstitial lung disease (ILD) and pneumonitis have been reported with lapatinib monotherapy and combination chemotherapy. Monitoring for pulmonary symptoms which may indicate ILD or pneumonitis is recommended. Discontinuation of therapy is recommended for grade 3 (or higher) pulmonary symptoms indicative of ILD or pneumonitis.

QT_c prolongation. QT_c prolongation has been observed. Caution is advised in patients with a history of QT_c prolongation or with medications known to prolong the QT interval. Baseline and periodic 12-lead ECG are recommended.

Concurrent drug therapy issues:

High potential for interactions. Avoid use with strong CYP3A4 inhibitors or inducers.

QT_c-prolonging agents. Concurrent use with other drugs which may prolong QT_c interval may increase the risk of potentially-fatal arrhythmias.

Pegfilgrastim (Neulasta®)

Pegfilgrastim (Neulasta® is a covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol. Both pegfilgrastim and filgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that Filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to Filgrastim.

Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

The standard dose of pegfilgrastim is 6 mg SQ given on the day after (day # 2) chemotherapy cycle. This may be dropped at the last infusion of paclitaxel.

Clinical Experience

Pegfilgrastim was evaluated in two randomized, double-blind, active-control studies, using doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 administered every 21 days for up to 4 cycles in the treatment of patients with high-risk stage II or stage III/IV breast cancer (68-69). Study 1 investigated the utility of a fixed dose of pegfilgrastim. Study 2 used a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 x 10^9/L) with a mean duration of 5 to 7 days, and a 30 to 40% incidence of febrile neutropenia (70).

In study 1, 157 subjects were randomized to receive a single SC dose of 6 mg of pegfilgrastim on day 2 of each chemotherapy cycle or filgrastim 5 ug/kg/day SC beginning on day 2 of each cycle.

In study 2, 310 subjects were randomized to receive a single SC injection of pegfilgrastim at 100 ug/kg on day 2 or filgrastim 5 ug/kg/day SC beginning on day 2 of each cycle of chemotherapy. Both studies met the primary objective of demonstrating that the mean days of severe neutropenia (ANC < 0.5 x 10^9/L) of pegfilgrastim-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The rates of febrile neutropenia were 13% and 9% for pegfilgrastim vs. 20% and 18% for Filgrastim in studies 1 and 2, respectively. Other secondary endpoints included days of severe neutropenia in cycles 2 to 4, the depth of ANC nadir in cycles 1 to 4, and the time to ANC recovery after nadir. In both studies, the results for the secondary endpoints were similar between the two treatment groups (68, 69).

The safety and efficacy of once-per cycle pegfilgrastim was also found to be comparable to daily Filgrastim in studies in patients with non-small cell lung cancer being treated with carboplatin and paclitaxel and patients with NHL or Hodgkin's lymphoma being treated with ESHAP or CHOP chemotherapy (71-73). Pegfilgrastim has also been found to be safe when given in dose-dense AC → T q 2 weekly regimen (74).

Filgrastim (Neupogen®)

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. G-CSF is a 175 amino aid protein produced by *E. Coli* bacteria into which has been inserted human G-CSF gene. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens.

G-CSF is a sterile, clear, colorless, preservative-free liquid for parenteral administration (subcutaneous). Each vial of G-CSF contains 300 mcg/ml of filgrastim. Intact vials must be stored under refrigeration at 2-8°C. Prolonged exposure of G-CSF to temperatures outside this range can inactivate the drug.

The standard dose of filgrastim is 5 mcg/kg given SQ daily over the course of several days depending on the chemotherapy regimen.

Side-effects include chills, fever, nausea, anorexia, myalgia, bone pain, local injection site pain or inflammation, elevated liver function, thinning of hair, enlargement of spleen, and rarely fluid retention.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patients must have histologically confirmed adenocarcinoma with HER2/neu immunohistochemistry 3+ or FISH-amplified breast cancer with a ratio of ≥ 2.0
- Tumor size of ≤ 3 cm and node-negative disease. Nodes with single cells or tumor clusters < 0.2 mm by H&E or IHC are considered node-negative. Patients with micrometastasis (nodes with tumor clusters between 0.02 and 0.2cm) are allowed. Further axillary dissection will be determined by the patient's surgeon as per standard of care.
- Patients must be ≥18 years of age.

- Patients must have an ECOG performance status of 0 or 1.

- Treatment should be started within 90 days of the final surgical procedure for breast cancer.

- Patients may have bilateral synchronous breast tumors.

- Patients may have received hormonal therapy for the purpose of chemoprevention but must be willing to discontinue prior to enrollment and while participating in this trial.

- If patients have peripheral neuropathy, it must be $\leq$ grade 1.

- Patients must be willing to discontinue sex hormonal therapy e.g., birth control pills, ovarian hormonal replacement therapy, etc., prior to enrollment. Women of childbearing potential must be willing to consent to using effective contraception while on treatment and for a reasonable period thereafter.

- Hematologic parameters: absolute neutrophil count (ANC) $\geq$1500/μL and platelet count $\geq$100,000/μL.

- Non-hematologic parameters: total bilirubin must be $\leq$ 1.5 X institutional upper limit of normal (ULN), transaminases (SGOT or SGPT) $\leq$ 3.0 x ULN.

- Negative HCG pregnancy test for premenopausal women of reproductive capacity and for women less than 12 months after the menopause.

- LVEF by ECHO (with strain if possible) with LVEF of $\geq$ 50%. If an ECHO cannot be done, a MUGA may be performed.

- Patients must give written, informed consent indicating their understanding of and willingness to participate in the study.

6.2 Subject Exclusion Criteria

- Patients with stage IV breast cancer or undergoing chemotherapy, radiation therapy, immunotherapy, or biotherapy for current breast cancer.

- Pregnant or breastfeeding patients.

- Patients with a concurrently active second malignancy, other than adequately treated non-melanoma skin cancers or *in situ* cervical cancer.

- Patients with unstable angina, congestive heart failure, or with a history of a myocardial infarction within 12 months. Patients with high-risk uncontrolled arrhythmias (ventricular tachycardia, high-grade AV block, supraventricular arrhythmias which are not adequately rate-controlled). Patients are excluded if they have grade 3 QT prolongation (Appendix F) (>500 ms) or require drugs that may prolong the QT.

- Subjects who have current active hepatic (including hepatitis B or C) or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones).

- Subjects who are concomitantly using certain CYP3A4 Inducers and Inhibitors listed in APPENDIX F
- Patients with active, unresolved infections.
- Patients with a sensitivity to E. coli derived proteins.

7.0 RECRUITMENT PLAN

This study is open to patients with HER2 amplified carcinoma of the breast histologically confirmed at MSKCC or MSKCC satellites. These patients will be identified and recruited from the breast cancer patients seen at the Breast Cancer Center at MSKCC or MSKCC satellites.

Patients who are potentially eligible will be evaluated at the Breast Cancer Center at MSKCC or MSKCC satellites. This initial encounter will include a discussion of the proposed treatment and the rationale for its use. Eligible patients will be required to review and sign an informed consent.

8.0 PRETREATMENT EVALUATION

The following must be completed within 2 weeks prior to starting protocol therapy:

- Complete medical history
- Physical examination findings to include blood pressure, weight, height, and calculation of body surface area (BSA)
- Assessment of ECOG performance status (**Appendix A**)
- Pregnancy test for females of child-bearing potential
- Contraceptive counseling for females of childbearing potential and also for men

The following must be obtained within 1 month prior to starting protocol therapy:

- Complete blood count including hemoglobin, WBC with differential, and platelet count
- Serum chemistries to include potassium and magnesium
- Liver function test to include bilirubin, SGPT (ALT), SGOT (AST)
- Signed informed consent

The following must be obtained within 3 months prior to starting protocol therapy

(Study Table):

- Assessment of LVEF by echocardiogram (if not feasible will accept MUGA scan). When possible, a baseline ECHO with strain imaging is preferred.

- EKG

9.0 TREATMENT/INTERVENTION PLAN

Paclitaxel (175 mg/m^2) IV every 14 days x 4 and trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly) IV and lapatinib (1000 mg oral daily); followed by trastuzumab (6 mg/kg IV every 3 weeks) x 15 doses and lapatinib (1000 mg oral daily) to complete about a year of treatment. Trastuzumab at a q 3 week dosage may be given at final paclitaxel infusion. A total of 15 infusions of trastuzumab will be given q 3 weeks during the HL phase.

During treatment with paclitaxel, pegfilgrastim will be given 24 hours after the completion of chemotherapy and may be stopped at the last paclitaxel infusion. Filgrastim may be used in lieu of pegfilgrastim at physician's discretion.

Note: Physicians may omit pegfilgrastim (or filgrastim) after cycle # 4 of paclitaxel.

Total duration of trastuzumab and lapatinib therapy is one year.

Paclitaxel

Paclitaxel (175 mg/m^2) IV every 2 weeks x 4 will be administered.

Premedications for paclitaxel: Patients should receive the standard IV dexamethasone 10-20 mg (or a steroid equivalent), diphenhydramine 50 mg (or another H1-blocker), and an H2-blocker about 30 minutes before paclitaxel infusion. If patients do not experience a hypersensitivity reaction after the first 2 doses of paclitaxel, premedications can be altered at physician's discretion.

Dose Modifications:

This study will use the NCI Common Toxicity Criteria (CTC) AE version 4.0 for toxicity.

After each paclitaxel treatment, dose adjustments of the taxane should be based on hematologic and nonhematologic toxicities. Patients experiencing neutropenic fever (ANC <1,000/μL and body temperature ≥38.5°C) will have a 25% dose reduction. Only one dose reduction is allowed. (ie: 175 mg/m2 →130 mg/m2). Physicians may use antibiotics as secondary prophylaxis as deemed appropriate.

- If on the day that paclitaxel is due, platelet counts are <100,000/μL and/or ANC <1000/μL and/or non-hematologic toxicities (excluding alopecia and neuropathy) have not recovered to ≤Grade 1, treatment should be delayed by up to 1 week and CBC and toxicity grading repeated weekly. If platelet count and ANC and non-hematologic toxicity have not recovered to ≤Grade 1, a further delay of up to1 week is required. If LFTs are checked, paclitaxel can be given at full dose without delay if SGOT/SGPT are at ≤ Grade 2, and bilirubin is at ≤ Grade 1. If the SGOT/SGPT are at ≥ Grade 3 or

bilirubin is at ≥ Grade 2, LFTS should be checked weekly and paclitaxel can be held until the SGOT/SGPT have recovered to ≤ Grade 2 and bilirubin ≤ at Grade 1. Up to 3 weeks (21 days) are allowed for the appropriate recovery. If the SGOT/SGPT have not recovered to ≤ Grade 2 and bilirubin at ≤ Grade 1 within 3 weeks, the patient will be taken off study treatment. Of note, even if the toxicity is felt to be due to lapatinib, paclitaxel treatment will not resume unless all of the appropriate hematologic and nonhematologic parameters are met..

- Hypersensitivity reactions: Please see **Appendix B** for treatment. Treatment should be discontinued for Grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions. Consider discontinuation of taxane therapy if patient experiences 2 episodes of Grade 3 hypersensitivity reaction.

Trastuzumab

Trastuzumab loading dose (4 mg/kg) IV will be administered on same day as paclitaxel cycle # 1 and is continued weekly at the dose of 2 mg/kg IV for the duration of paclitaxel treatment. Trastuzumab may also be administered at a dose of 6mg/kg during the last dose of paclitaxel in the THL phase. At the completion of paclitaxel, patients will receive trastuzumab on a q 3 week schedule at 6 mg/kg IV. Each trastuzumab q 3 week cycle at 6 mg/kg is equivalent to 3 trastuzumab weekly treatments at 2 mg/kg. The duration of trastuzumab from beginning to end is about a year.

Note: Patients should not miss more than one q 3 week dose of trastuzumab consecutively (except when those missed doses are associated with a HOLD and REPEAT for asymptomatic LVEF declines as per table below). Patients do not have to make up missed doses.

Premedications for trastuzumab
For the first (loading) dose of trastuzumab, premedication with acetaminophen 650 mg po will be given.

Dose Modifications
Dose modification of trastuzumab is **not** permitted.

For Adjuvant Breast Cancer Protocols: Asymptomatic Decrease LVEF Percentage Points from Baseline

RELATIONSHIP OF LVEF TO THE LOWER LIMIT OF NORMAL (LLN)	ABSOLUTE DECREASE OF < 10 PERCENTAGE POINTS	ABSOLUTE DECREASE OF 10 TO 15 PERCENTAGE POINTS	ABSOLUTE DECREASE OF ≥ 16 PERCENTAGE POINTS
Within radiology facility's normal limits	Continue H + L	Continue H + L	Hold H + L and repeat ECHO within 3-4 weeks
1 to 5 percentage points below the LLN	Continue H + L	Hold H + L and repeat ECHO within 3-4 weeks	Hold H + L and repeat ECHO within 3-4 weeks
≥ 6 percentage points below the LLN	Continue H + L and repeat ECHO within 3-4 weeks	Hold H + L and repeat ECHO within 3-4 weeks	Hold H + L and repeat ECHO within 3-4 weeks

H=Herceptin

L=Lapatinib

Rules for interpreting and applying "repeat" ECHO scan results:

- H + L must be permanently discontinued when two consecutive "hold" categories occur.
- H + L must be permanently discontinued when three intermittent "hold" categories occur. (At the investigator's discretion, H + L may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories.)
- If LVEF is maintained at a "continue and repeat ECHO" or improves from a "hold" to a "continue and repeat ECHO" category, additional ECHOs prior to the next scheduled ECHO will be at the investigator's discretion.

Patients who experience significant "asymptomatic" LVEF decline while on trastuzumab + lapatinib which results in permanent discontinuation of H + L will be followed long-term. These patients will be seen in the cardiology clinic. Follow-up ECHOs or MUGAs will be performed every 3-6 months until 6 months since the last H + L exposure. If any of these patients experiences CHF or cardiac death later during follow-up, the event will be considered a true cardiac event and will be counted towards the stopping rule as defined in section 13.0.

Note: If an ECHO cannot be done, a MUGA may be performed.

Note: If patients are restarted on trastuzumab and > 2 weeks have lapsed since the last intended "q 3 week" dose of trastuzumab, then patients should have a re-loading dose of trastuzumab at (8 mg/kg followed by q 3 week dose of 6 mg/kg).

Note: Patients will receive 15 doses of trastuzumab every 3 weeks during the HL phase. If trastuzumab dose is held for cardiac toxicity, this dose does not need to be made up once the patient is re-started on anti-HER2 therapy. In other words, the duration of therapy should be about a year from beginning to end.

Lapatinib

Lapatinib Administration

Patients should be advised to take lapatinib on an empty stomach (either 1 hour before or 1 hour after meals). The starting dose is 1000 mg orally daily.

DOSING DELAYS/DOSE MODIFICATIONS

Starting dose and dose modifications for unacceptable toxicity are listed in Table 2.
For toxicity that is thought to be related to lapatinib, the daily dose of lapatinib will be decreased according to the schedule displayed in the Table 3.

Dose adjustments are to be made according to the greatest degree of toxicity. Toxicities will be graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 2. Lapatinib Starting Dose and Dose Reduction Schedule

Starting dose	**1000 mg/day**
One dose reduction	**750 mg/day**

Table 3. Dose Reduction Criteria and Guidelines for Management of lapatinib Associated Toxicity

Toxicity	**Grade**	**Guideline for management**	**Lapatinib dosage modification***

Diarrhea (Please see APPENDIX I)	**1**	**Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs unti diarrhea free for 12 hrs**	**None**
	2	**Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs unti diarrhea free for 12 hrs)**	**None; If unacceptable to patient or medically concerning then hold** **until recovery to ≤ grade 1, up to 21 days*. Restart at same dose**.**
	≥ 3 (despite optimal use of loperamide)		**Hold until recovery to ≤ grade 1, up to 21 days*. And then reduce 1 dose level.**
Rash	**1**	**No intervention**	**None**
	2	**Any of the following: minocycline+, topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)**	**None; If unacceptable to patient or medically concerning then hold** **until recovery to ≤ grade 1, up to 21 days*. Restart at same dose**.**
	≥ 3		**Hold until recovery to ≤ grade 1, up to 21 days*. And then reduce 1 dose level.**
Other **Toxicity (excluding left ventricular dysfunction and pneumonitis see below)**	**1**	**No Intervention**	**None**
	2	**Treatment as appropriate**	**None; If unacceptable to patient or medically concerning then hold** **until recovery to ≤ grade 1, up to 21 days*. Restart at same dose **.**
	2 prolonged or clinically significant and grade ≥ 3	**Treatment as appropriate**	**Hold until recovery to ≤ grade 1, up to 21 days an then reduce** **1 dose level***

* if no recovery after 3 weeks of holding drug, patients should go off study

** if dose has been previously held for grade 2 toxicity and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level

\+ recommended dose: 200mg po bid (loading dose), followed by 100mg po bid for 7-10 days

Note: Only one dose reduction of lapatinib is allowed.
If grade 3 toxicity recurs (ie: diarrhea, rash,) with lapatinib at 750 mg daily, then lapatinib should be held and no further dose reduction is allowed. Patient is then taken off study.

Experience thus far suggests that when lapatinib is used as monotherapy most diarrhea

presents as uncomplicated NCI CTCAE Grade 1 or 2 (G1 54%, G2 20%, G3 15%, G4<1%).

In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea [Benson, 2004]. Presented in the sections below are the recommended guidelines for the management of diarrhea in subjects receiving lapatinib-based therapy; these guidelines were derived from the recommendations published by the ASCO panel [Benson, 2004].

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below.

Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhea history.

If subjects present with diarrhea of any Grade, check they are taking lapatinib correctly, i.e. single daily dose, rather than splitting it through the day. . Obtain information on food (solid and liquid) and over the counter (OTC) medication, including herbal supplements, taken during the lapatinib treatment period.

Definitions
National Cancer Institute (NCI) guidelines define diarrhea compared to baseline (APPENDIX H).

Lapatinib hepatotoxicity

Lapatinib can cause abnormal liver function tests (LFTs), but the incidence is rare. A crude incidence of 0.4% has been reported for liver dysfunction (predominantly liver enzyme abnormalities) in over 8700 patients who have received lapatinib in clinical trials as of December 2007. Recently, there is a report of a small number of liver toxicity-related deaths, possibly due to lapatinib. These patients were being treated for metastatic breast

and other cancers, including some cases with liver cancer, so it was difficult to determine what role lapatinib may have played.

Due to the rare liver toxicity-related deaths in the metastatic population, the following suggestions are recommended:

1) LFTs (SGOT, SGPT, bilirubin) will be checked serially while patients are actively taking lapatinib. LFTs are checked every 2 weeks during concurrent chemotherapy phase (THL) and then every 3-6 weeks after chemotherapy completion (HL).

2) Lapatinib dose modifications are recommended for the following LFT abnormalities:

   a) If SGOT, SGPT, or bilirubin is at ≥ Grade 3, the patient should "stop" lapatinib altogether and not resume it.

   b) If SGOT, SGPT, or bilirubin is at Grade 2, the patient may hold the lapatinib until the SGOT, SGPT, or bilirubin is at ≤ Grade 1. The patient may have up to 21 days to hold the lapatinib and LFTs may be checked within 3 weeks (or sooner at the physician's discretion). The patient may then resume the lapatinib at one dose reduction (from 1000 mg to 750 mg).

      i. If the lapatinib dose is already at 750 mg when SGOT, SGPT, or bilirubin is at ≥ Grade 2, the patient may hold the lapatinib until the SGOT, SGPT, or bilirubin is at ≤ Grade 1. The patient may have up to 21 days to hold the lapatinib and LFTs may be checked within 3 weeks (or sooner at the physician's discretion). The patient may then resume the lapatinib at the same dose of 750 mg. If a Grade 2 event occurs again, then patient must "stop" lapatinib altogether and "not" resume it.

   c) If SGOT, SGPT, or bilirubin is at ≤ Grade 1, the patient may continue lapatinib at the same dose.

Note: During the concurrent chemotherapy, trastuzumab, and lapatinib phase (THL) when LFTs are checked every 2 weeks, paclitaxel can be given at full dose without delay if the SGOT/SGPT are at ≤ Grade 2, and bilirubin is at ≤ grade 1. If the SGOT/SGPT are at ≥ Grade 3 or bilirubin is at ≥ Grade 2, LFTS should be checked weekly and paclitaxel can be held until the SGOT/SGPT have recovered to ≤ Grade 2 and bilirubin ≤ Grade 1. The patient can have up to 3 weeks (21 days) for this recovery. If not, then the patient will come off study treatment.

Lapatinib Dosing based on LFTs

SGOT/SGPT/bilirubin	Grade 1	Grade 2	Grade > 3
Lapatinib	Continue	Hold up to 21 days and resume at one dose reduction (from 1000 mg to 750 mg)* until the SGOT/SGPT/bilirubin have	Stop and not resume

		recovered to ≤grade 1	

*If the lapatinib dose is already at 750 mg when SGOT, SGPT, or bilirubin is at ≥ Grade 2, the patient may hold the lapatinib until the SGOT, SGPT, or bilirubin is at ≤ Grade 1. The patient may have up to 21 days to hold the lapatinib and LFTs may be checked within 3 weeks (or sooner at the physician's discretion). The patient may then resume the lapatinib at the same dose of 750 mg. If a Grade 2 event occurs again, then patient must "stop" lapatinib altogether and "not" resume it.

Paclitaxel Dosing based on LFTs

	SGOT/SGPT ≤ Grade 2 and bili < Grade 1	**SGOT/SGPT ≥ Grade 3 And bili > Grade 2**
Paclitaxel	Full dose	*Hold until SGOT/SGPT ≤ Grade 2 and bili ≤ Grade 1

*LFTS should be checked weekly and patients can have up to 3 weeks (21 days) for SGOT/SGPT to recover to ≤ Grade 2 and bili to ≤ Grade 1.Supportive care guidelines for lapatinib toxicities are in **Appendix C**.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

- Every 2 weeks during THL phase and every 3-6 weeks during the HL phase:
    - History and physical examination with vital signs, ECOG performance status.
    - Recording of the adverse events
    - Labs
        - CBC and differential count will be done prior to (within - 3 days) each paclitaxel infusion (paclitaxel can be given +/- 3 days). Labs can be done within -3 days of each treatment.
        - LFTs will be performed every 2 weeks (within - 3 days) during the THL phase and every 3-6 weeks (+/- 3 days) during the HL phase.
        - Magnesium and potassium levels will be performed every 2 weeks (within - 3 days) during the THL phase and every 3-6 weeks (+/- 3 days) during the HL phase.
- Patients may have their treatment schedule modified as follows:
    - Patients may have a delay of treatment for up to 3 weeks (for any reason).
    - If there is a delay of > 2 weeks since the last infusion of trastuzumab, then a re-loading of trastuzumab is advised.
- A lapatinib pill diary will be given to the patient and a pill count will be conducted every 4-6 weeks (**Appendix D**).

- Patients should be educated about medications that are prohibited (ie: CYP3A4 inducers or inhibitors) while on lapatinib (**Appendix E**).

- Assessment of left ventricular ejection fraction by echocardiogram (with strain when possible) will be performed at baseline and at months 2, 6, 9, 12 and 18 (+/- 4 weeks).

- Assessment of EKG will be required at baseline and months 2, 6, 9, 12 and 18 (+/- 4 weeks).

  If QTc prolongation is noted as Grade 3 or greater (> 500 ms) at any time on EKG monitoring, lapatinib should be held and a repeat EKG should be done within 4 weeks. If the repeat EKG shows that the QTc is < or equal to 500 ms, then lapatinib can be given with one dose reduction (from 1000 mg to 750 mg daily). If the repeat EKG still shows that the QTc as Grade 3 or greater (>500 ms), then lapatinib is still held and patient should be removed from study. If the patient is already taking lapatinib at a lower dose of 750 mg daily (for any reason) and the QTc is prolonged at Grade 3 or greater (> 500 ms), lapatinib should then be held and the patient from study. The patient will then be treated as deemed appropriately by the treating physician. Serial potassium and magnesium levels should be followed (and corrected if low) while the patient is on lapatinib (**Appendix F**).

- Evidence of disease evaluation by CT of the chest, abdomen, and pelvis, PET scan, and/or bone scan will be conducted if clinically indicated by the patient's symptomatology, by abnormal laboratory values, or at the physician's discretion.

- Correlative blood work consisting of a cardiac troponin I, BNP, and neuregulin-1ß will be measured every 2 weeks during THL phase (pre- and post- infusion of paclitaxel, trastuzumab) and during months 6, 9, and 18.

- Blood for SNP analysis will be drawn once during study, preferably either prior to or the day of cycle #1 of paclitaxel.

Biomarker Evaluations:

Troponin

From each patient at every 2 weeks during THL phase (pre- and post- infusion of paclitaxel, trastuzumab) and during months 6, 9, and 18 (7 time-points in total) five mL of peripheral blood will be collected pre- and post-infusion in a green top (heparin) tube for the measurement of TnI. For the troponin assay, plasma will be separated from peripheral blood and samples will be frozen for analysis and will not be known to the investigator until the patient has completed the study. The TnI samples will be evaluated by Dr. Martin Fleisher's laboratory at MSKCC. At all MSKCC sites, blood samples should be clearly labeled before transfer to Main campus. This labeling should include the study identifier (IRB-assigned protocol number), MSKCC-assigned patient identifier (once available), test ("troponin") and the time point of sample measurement.

TnI concentrations will be determined by a fluorometric enzyme immunoassay analyzer (Tosoh Bioscience, Inc., San Francisco, CA) with a low end sensitivity of 0.06 ng/ml. TnI levels will be classified as <0.06 ng/mL ("undetectable"), 0.06-0.31 ng/mL ("minimal elevations"), or >0.31 ng/mL ("above normal range"). In addition to categorizing TnI values in

this way, the absolute change (represented by the difference between the baseline value and the maximum value observed during follow-up) will be calculated for each patient.

Brain Natriuretic Peptide

From each patient at every 2 weeks during THL phase (pre- and post- infusion of paclitaxel, trastuzumab) and during months 6, 9, and 18 (7 time-points in total) , five mL of peripheral blood will be collected pre- and post-infusion into a lavender top (EDTA) tube for measurement of BNP. The BNP assay will be performed within 24 hours of blood collection. The BNP samples will be evaluated by Dr. Martin Fleisher's laboratory at MSKCC. BNP specimens can be refrigerated following collection. Samples from MSKCC Regional Network sites will be delivered to the MSKCC Main Campus at least once daily per usual Regional practice for preparation and frozen storage. At all MSKCC sites, blood samples should be clearly labeled before transfer to Main campus. This labeling should include the study identifier (IRB-assigned protocol number), MSKCC-assigned patient identifier (once available), test ("BNP") and the time point of sample measurement.

BNP is assayed in the Clinical Chemistry STAT lab. The BNP assay is performed on a Biosite Triage analyzer (Biosite, San Diego, California) using fluorescence immunoassay on EDTA anticoagulated whole blood. Average within day imprecision is 8.5% at 71 pg/ml and 11% at 630 pg/ml. BNP results less than or equal to 100 pg/ml are representative of normal values in patients without CHF. BNP will be classified as ≤100 pg/mL ("within normal range") or >100 pg/mL ("above normal range"). In addition to categorizing BNP values in this way, the absolute change (represented by the difference between the baseline value and the maximum value observed during follow-up) will be calculated for each patient.

Neuregulin 1ß

From each patient at every 2 weeks during THL phase (pre- and post- infusion of paclitaxel, trastuzumab) and during months 6, 9, and 18 (7 time-points in total) , five mL of peripheral blood will be collected pre- and post-infusion in a lavender top (EDTA) tube for the measurement NRG-1ß. For the NRG-1ß assay, plasma will be separated from peripheral blood and samples will be frozen for analysis and will not be known to the investigator until the patient has completed the study. A reproducible assay for assessing serum NRG-1ß levels using an indirect sandwich ELISA technique has been developed and validated in the Sawyer Lab at Vanderbilt University. The monoclonal capture antibody used in this assay is against a biologically active and cardiac-specific peptide sequence, which has been studied extensively by Sawyer et al. This peptide has been shown to play an important role in the activation of the ErbB receptor and downstream signaling pathways in ventricular myocytes. The coefficient of variation (CV) of this assay is 5.6-13%.

The first generation form of this assay was used in a pilot study performed by Dr. Sawyer's group which sought to define the effects of exercise on circulating NRG-1ß levels in humans [94]. This study demonstrated that there was no significant difference in serum NRG-1ß levels pre- and post- exercise in healthy human subjects, but these levels were associated with cardiopulmonary exercise capacity.

A second generation ELISA assay with lower detection limits has since been developed with NRG-1ß being detected in >98% samples tested to date. This assay was used to quantitate NRG-1ß from serum samples in 899 subjects with chronic heart failure. [82] NRG-1ß levels were

detected in all non-heart failure samples and all but 12 heart failure patients. Extensive validation of the second generation form of this assay has been performed. The effects of multiple freeze/thaw cycles and the differences between plasma and serum NRG-1ß levels have also been assessed. NRG-1ß is detectable in both serum and plasma with a strong correlation (R^2=0.91), with plasma levels being 50% higher than serum. Repeated measures of NRG-1ß levels after exposure to multiple freeze/thaw cycles are highly correlated (R^2=0.92), but decrease 25.7% per freeze/thaw cycle. Because of these findings, we will use frozen, previously unthawed plasma for our study.

A third generation form of this assay has also been developed and validated at the University of Pennsylvania Translational Core Lab led by Theodore Mifflin, PhD and Stephen Master, MD, PhD under Dr. Ky's direction and Dr. Sawyer's collaboration. This assay has lower detection limits and an improved coefficient of variation

Neuregulin-1β Assay: Plasma will be collected, banked, and stored at -80°C at various time-points immediately prior to and after specific cycles serially during the course of chemotherapy as outlined above. ~~We will measure NRG-1β from previously unthawed plasma samples using a reproducible, established 2nd generation ELISA for assessing NRG-1β (CV 5.6-13%) (82). This monoclonal capture antibody targets a biologically active peptide that is relevant to the cardiac system and able to induce ErbB receptor activity. Importantly, as new candidate biomarkers arise, we will also test these using robust assays.~~

As of A(6), we will no longer be measuring NRG-1β from previously unthawed plasma samples using ELISA, given the scarce incidences of cardiac dysfunction based on the LVEF data.

Note: As the clinical significance of an elevated TnI, BNP, or NRG-1ß in an asymptomatic patient is unknown, the TnI and NRG-1ß samples drawn at various time intervals as described previously for each patient will be analyzed but the results will be blinded to the treating physician until the end of the study, "not in real time". Patients and their treating physicians will not have the results in real time and thus, treatment decisions will not be affected. The BNP assay will be performed within 24 hours of sample collection, but the results will not be released to the treating oncologist until the end of the study, as the significance of an elevated BNP in an asymptomatic patient is not known. The results will instead be stored for interpretation at the end of the study.

Note: The TnI and BNP samples will be collected at the BAIC and will be picked up by the courier and delivered to Dr. Fleisher's lab, as per standard MSKCC's standard practice. The NRG-1ß samples will be frozen and stored at the BAIC. ~~and will be sent to Dr. Bonnie Ky at the end of the study for the exploratory analysis.~~

As of A(6), NRG-1β samples will no longer be sent to Dr. Bonnie Ky's laboratory for exploratory analysis. They will be discarded.

Pharmacogenomics Determinants of Toxicity to Therapy

Hepatic oxidative drug metabolism is carried out by the cytochrome (CYP) P450 system. Sequencing of the genome has revealed 58 different human CYP genes. Polymorphisms in CYP genes may contribute to either diminished or absent metabolism, or excessive metabolism of a compound. Within the CYP system, enzyme families CYP 1, CYP2, and CYP3 are responsible for

the metabolism of paclitaxel and lapatinib. Specifically, CYP2C8, CYP3A5, CYP3A4, and CYP2C19 have been shown to be involved in metabolism of both drugs. Inherited variations in drug transport proteins are also of interest when considering pharmacogenetics. Members of the adenosine triphosphate (ATP)-binding cassette (ABC) family of membrane transporters modulate drug action at the cellular level. Genes relevant to lapatinib and paclitaxel metabolism include ABCB1, ABCG2, CYP2C8*2, CYP2C19*2, CYP3A5*3, CYP3A4*1B and can be identified using SNP assay analysis.

These samples will be collected at the BAIC and frozen until they are analyzed at the end of the study for each patient. Samples will be analyzed by Sequenom MassArray in the Sequenom Core (Diagnostic Molecular Pathology). Assay design, sample plating and preparation will be performed in the Clinical Genetics Service laboratory under the direction of Vijai Joseph, Ph.D. Quality control will be assessed by inclusion of random duplicates and blanks, per standard protocol. In the unlikely event that a SNP cannot be included in the assay design, we will either perform a TaqMan assay for that particular SNP or use a more tractable SNP in LD (r2 = 1) with the SNP of interest. Genotype calls will be made by V. Joseph and M. Robson by inspection of the Sequenom output. For ABCB1, the results of genotyping of rs1045642, rs1128503, and rs2032582 will be used to construct haplotypes, and it will be the haplotypes that will be used in the analysis rather than the individual genotypes

Echocardiograms (and Strain Imaging Analysis for research purposes):

Echocardiograms will be performed at months 2, 6, 9, 12 and 18 of treatment as defined in the study. Strain imaging will be analyzed off-line using 2D image loops from the routine echocardiographic examination. The ECHO machine for the strain imaging analysis should be the Vivid 7 or E9 machine (GE healthcare, Milwaukee, WI). In addition to being stored in the main ECHO PACS system, these studies will also be stored in an external GE workstation which contains the software needed to perform the strain imaging analysis. To calculate strain and strain rate, the LV myocardium is traced in a click-to-point approach. Subsequently, the software automatically defines an epicardial and midmyocardial line and processes all frames of the loop. The myocardium in each of the 3 standard apical views is divided into 6 segments. The software will automatically calculate strain and strain rate for each of the 18 segments plus a global value for the entire myocardium. These measurements will be made by a designated investigator (Dr. Jennifer Liu) blinded to patient identification, demographics and clinical characteristics at the end of the study. When possible any ECHOs done outside of MSKCC are requested to be done on the GE Vivid 7 or E9 machine (GE healthcare, Milwaukee, WI), and the disc to be sent to Dr. Jennifer Liu for the strain imaging analysis.

STUDY TABLE: SCHEDULE OF EVENTS ACTIVITY

	Pre-Treatment	Prior to each chemo-therapy treatment	Every 2 weeks during THL and every 3-6 weeks during HL	Months 2, 6, 9, 12, 18	After Treatment Completion[9]
Medical History	X (w/i 2 weeks)		X		X
Physical examination[1]	X (w/i 2 weeks)		X		X
ECOG PS	X (w/i 2 weeks)		X		
CBC[2]	X (w/i 4 weeks)	X	X		
Chemistry [3]	X (w/i 4 weeks)		X		
Pregnancy test[4]	X (w/i 2 weeks)				
Contraceptive counseling[4]	X (w/i 2 weeks)				
ECHO[5] and EKG	X (w/i 3 months)			X	
Cardiac correlative blood-work[6]			X		
Blood-work for genetic analysis[7]	X				
Signed informed consent	X (w/i 4 weeks)				
Adverse event/toxicity assessment			X		X
Pill diary			X[8] (every **4 weeks** during THL, every 3-6 weeks during HL)		

1. Prior to the first cycle of treatment, a height and weight must be obtained.
2. CBC includes hemoglobin, hematocrit, white cell count, platelets (within -3 days during THL and +/- 3 days during HL).
3. Chemistry profile includes potassium, magnesium, SGOT (AST), SGPT (ALT), total bilirubin (within -3 days during THL and +/- 3 days during HL)
4. Females of child-bearing potential.
5. LVEF determined via an ECHO with strain imaging. When an ECHO by the GE Vivid 7 or E9 system (GE Healthcare, Milwaukee, WI) is not available for strain imaging analysis, then an LVEF by a standard ECHO machine per facility may be done. If an ECHO cannot be done, a MUGA scan may be done. This can be done within +/- 4 weeks.

6. Correlative cardiac blood-work will consist of TnI, BNP, and NRG-1ß. These will be done pre- and post-infusion on day 1 of every THL cycle (4 times, every 2 weeks) and at months 6, 9 and 18 (7 time-points in total).

7. Blood for genetic analysis will be done prior to receipt of cycle # 1 paclitaxel (but can be done at any time during study if not done at baseline).

8. A lapatinib pill diary will be collected every 4 weeks during THL phase and every 3-6 weeks during HL phase of the study.

9. Evidence of disease (EOD) evaluation should be considered (CT of chest, abdomen, and pelvis and bone scan) if clinically indicated by the patient's symptomatology or by abnormal laboratory values, at the physician's discretion.

11.0 TOXICITIES/SIDE EFFECTS

Assessment of Adverse Events:

Investigators will assess the occurrence of AEs at all patient evaluation time points during the study. All AEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be recorded in the patient's medical record and on the appropriate AE CRDB page. Each recorded AE will be described by its duration (i.e., start and end dates), severity and suspected relationship to the investigational product. Since this trial's primary outcome is to measure safety and feasibility of the intervention by assessing toxicity, suspected relationships or attributions of non-hematological adverse events will only be collected if assessed as grades ≥ 2 except for the following events: rash and diarrhea. Additionally, laboratory toxicities will be collected for assessment if the results are considered grades ≥ 2. AE grading (severity) scale found in the NCI CTCAE, Version 4.0 will be used for AE reporting.

Trastuzumab (Herceptin®)

Infusion-Associated Symptoms. During the first infusion with Herceptin, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent Herceptin infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine.

Serious Infusion-Associated Events. Serious adverse reactions to Herceptin infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of Herceptin as indicated.

Hematologic Toxicity. In the clinical trials, an increased incidence of anemia was observed in patients receiving Herceptin plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible; none resulted in discontinuation of Herceptin therapy. In the clinical trials, the per-patient incidences of moderate to severe neutropenia and of

febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. In the post marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving Herceptin and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of Herceptin on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated. The observed incidence of leukemia among Herceptin-treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer. Therefore, the contribution of Herceptin to the etiology of acute leukemia or myelodysplastic syndrome in these cases is unclear.

Paclitaxel (Taxol®)

Side-effects include alopecia, myelosuppression, fatigue, neuropathy, arthralgia, myalgia, onycholysis, taste changes, amenorrhea, teratogenesis, hypersensitivity (hypotension, flushing, chest pain, abdominal or extremity pain, skin reactions, pruritus, dyspnea, bronchospasm, and tachycardia), fever, sinus bradycardia, complete heart block, sinus tachycardia, premature ventricular beats, ventricular tachycardia, bigeminy, syncope, myocardial infarction, hypotension, hypertension, dizziness, visual changes, headaches, radiation recall, nausea and vomiting, mouth sores, abdominal pain, diarrhea, typhlitis, ischemic colitis, abnormal liver function, pancreatitis, abnormal triglyceride, and seizures.

Lapatinib

The most common toxic effects of lapatinib are:

Diarrhea, nausea, vomiting, rash, anorexia, and fatigue.

Information on Hepatotoxicity

Lapatinib can cause abnormal liver functions (LFTs), predominantly transaminase elevations, but the incidence is rare. A crude incidence of 0.4% of hepatotoxicity has been reported for liver dysfunction in over 8700 patients who have received lapatinib in clinical trials as of December 2007. Recently, there is a report of a small number of liver toxicity-related deaths, possibly due to lapatinib. These patients were being treated for metastatic breast and other cancers, including some cases with liver cancer, so it was difficult to determine what role lapatinib may have played.

Information on pregnancy

As of 28 February 2006 there have been three pregnancy reports within the lapatinib clinical program. Study EGF10004 subject 402 was found to be pregnant at an unknown time after the first dose of lapatinib. The subject gave birth to a normal female baby at 36 weeks gestation by caesarean section. Study EGF20002 subject 2655 was found to be pregnant at an unknown time after receiving lapatinib and zoledronic acid. Treatment with lapatinib was discontinued. The patient experienced a spontaneous/missed abortion at 9 weeks gestational age which was reported as related to lapatinib by the investigator. Another subject in study EGF100642 subject 101 became pregnant in the first month following her last dose of lapatinib. She later underwent an elective abortion due to progression of her underlying cancer.

Cardiac and pulmonary toxicity

Potential risks for the lapatinib program include cardiac toxicity and pulmonary toxicity which are known risks associated with other ErbB1 or ErbB2 inhibitors. Cardiac and pulmonary events are monitored closely in all lapatinib clinical trials and reviewed regularly by GSK. An Independent Data Monitoring Committee (IDMC) comprising oncologists, a cardiologist and a pulmonologist meet quarterly to assess the benefit-risk ratio in ongoing trials. Cardiac safety and interstitial pneumonitis are reviewed as part of this responsibility.

Decreased Left Ventricular Ejection Fraction (LVEF)

Left Ventricular Ejection Fraction (LVEF) has been evaluated using MUGA scans or echocardiogram during lapatinib phase I, II and III trials. As of 28 February 2006 a total of 60 subjects on the lapatinib program have experienced 62 events of decreased LVEF, giving an approximate incidence for this event of 1.5% for the program as a whole. Of these 62 events, 57 events (55 subjects) met the protocol specific serious definition included in lapatinib phase II and III protocols:

NCI CTC Grade 3 or 4 left ventricular systolic dysfunction (NCI CTC version 4.0) or LVEF decrease ≥20% relative to baseline value and below the institutions lower limit of normal. Age range for subjects experiencing decreased LVEF was 31 to 81 years, with a median of 59 years. Seventy three 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. Sixty percent of the decreased LVEF events occurred within nine weeks of treatment onset. In 37 subjects, (62%) the event resolved or improved.

Forty two of the 55 subjects whose LVEF decrease met the protocol specific serious definition are known to have received lapatinib, giving an incidence of 1.3%. For the remaining 13 subjects: 5 remain blinded, 4 occurred on placebo, and 4 subjects received comparator (capecitabine or medroxy-progesterone) only.

Of the 42 subjects on lapatinib, 33 LVEF decreases were assessed as related to investigational product by the investigator. Twenty three subjects (55%) were participating in monotherapy studies. Of the 42 lapatinib subjects, 29 experienced asymptomatic LVEF decreases which were complicated by pre-existing conditions and/or previous/concurrent medications. Examples included: previous episodes of decreased LVEF, myocardial infarction, arrhythmia, left-chest radiation, and exposure to anthracyclines, trastuzumab, or paditaxel, all of which have been associated with cardiac adverse events.

A further nine lapatinib subjects experienced LVEF decreases which resolved or improved on discontinuation of lapatinib. Eight subjects received lapatinib monotherapy, one subject received lapatinib in combination with capecitabine. Three of the eight monotherapy cases were symptomatic. The symptoms observed were dyspnea and cardiac failure, which resolved on discontinuation of lapatinib. The remaining five monotherapy cases and one combination therapy report were asymptomatic. All nine of these cases were complicated by pre-existing conditions and/or previous/concurrent medications which may have contributed to the observed LVEF decrease and make assessment of the event complex.

The remaining four subjects had no contributing factors, three subjects were receiving lapatinib monotherapy, and one subject received combination therapy with cisplatin. Two of the subjects died due to disease progression whilst an asymptomatic LVEF decrease was ongoing. In one case lapatinib was discontinued, the second subject had remained on lapatinib. The third subject experienced a symptomatic (palpitations) LVEF decrease. Lapatinib was interrupted and the event was ongoing at the time of reporting. The subject who received combination therapy experienced an asymptomatic decrease in LVEF three weeks after completing treatment with lapatinib. The event resolved.

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 paclitaxel or capecitabine, both of 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 has been included in the DCSI for lapatinib.

QT prolongation

QT prolongation measured by an EKG was observed in uncontrolled, open-label dose escalation study of lapatinib in patients with advanced cancer (81). In this study 81 patients received lapatinib at doses ranging from 175 to 1800 mg daily. Serial EKGs were collected on days 1 and 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of 81 patients were found to have either QTcF (corrected by the Friedericia method) of > 480 msec or an increase in QTcF by > 60 msec by an automated machine-read evaluation of the EKG. Thus, there may be a relationship between lapatinib concentration and QTc interval. Lapatinib should be administered with caution in those at risk for QTc prolongation. These patients include those with hypokalemia, with hypomagnesemia, with congenital long QT syndrome, taking anti-arrhythmic drugs or medications that lead to QT prolongation (Appendix E), and who had a high cumulative anthracycline exposure. Thus, hypokalemia and hypomagnesemia should be corrected prior to administering lapatinib. Baseline and on-treatment EKG monitoring with QT measurement and monitoring of potassium and magnesium should be done on patients who are receiving lapatinib.

Interstitial Pneumonitis

Current phase II and III lapatinib protocols include specific requirements for reporting of signs or symptoms of pneumonitis: subjects who have pulmonary symptoms which are NCI CTC version 3.0 Grade 3 or greater will be removed from study and the events documented as an SAE. As of 28 February 2006, 9 pulmonary events have been reported: 5 subjects experienced interstitial lung disease, 4 subjects experienced pneumonitis. Given current enrolment of 4084 subjects in the lapatinib program, this gives an approximate incidence of 0.2% for 'pneumonitis type' events. Seven of these events were reported as related to investigational product. Six subjects were participating in combination studies and one of these subjects did not receive lapatinib. The remaining three reports were from lapatinib monotherapy studies.

Age range for subjects experiencing signs or symptoms of pneumonitis was 48 to 73 years, with a median of 66 years. The majority of the reports (6/9) were for female subjects which may be attributed to the fact that there are a large number of breast cancer subjects in the lapatinib program. Five subjects (55%) who experienced pulmonary events recovered. Three of these 5 subjects required treatment, commonly methylprednisolone or prednisolone. For the remaining four subjects: two events were fatal, one event was

ongoing at the time of the subject's death due to disease progression, and one event was ongoing at the time of reporting. Both subjects who died were participating in monotherapy studies. The first subject died due to interstitial lung disease which the investigator attributed to disease progression. The second subject developed interstitial lung disease and died approximately seven months after the last dose of lapatinib. The subject had recently completed radiotherapy and the investigator felt that lapatinib may have affected the subject's tolerance to radiotherapy.

In addition to the reports received from the lapatinib program, a report of interstitial pulmonary infiltrates was received for a subject participating in study VEG10006 (lapatinib and pazopanib). The final diagnosis for this event was bilateral pneumonia, which was reported as unrelated to the investigational products. Reports of signs/symptoms of pneumonitis are closely monitored and current data do not support the addition of this term to DCSI for lapatinib.

Pegfilgrastim (Neulasta®)

The most common adverse event attributed to pegfilgrastim in clinical trials was medullary bone pain, reported in 26% of subjects, which was comparable to the incidence in Filgrastim-treated patients. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patients withdrew from the study due to bone pain. Reversible elevations in LDH, alkaline phosphatase and uric acid have been observed in clinical trials. Pegfilgrastim has been associated with leukocytosis (defined as WBC > 100 x 10^9/L) in < 1% of 465 subjects with non-myeloid malignancies, when observed it was not associated with any adverse event.

The maximum amount of pegfilgrastim that can be safely administered in single or multiple doses has not been determined. Single doses of 300 mcg/kg have been administered SC to 8 normal volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These subjects experienced a mean maximum ANC of 55 x 10^9/L, with a corresponding mean maximum WBC of 67 x 10^9/L. The absolute maximum ANC observed was 96 x 10^9/L with a corresponding absolute maximum WBC observed of 120 x 10^9/L. The duration of leukocytosis ranged from 6 to 13 days. Leukapheresis should be considered in the management of symptomatic individuals.

Pegfilgrastim is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, pegfilgrastim, Filgrastim, or any other component of the product.

Rare cases of splenic rupture have been reported with pegfilgrastim in the post-marketing setting. Similar events have been reported following the administration of the parent compound of pegfilgrastim, Filgrastim, for PBPC mobilization in both healthy donors and patients with cancer. Some of these cases with Filgrastim were fatal. Pegfilgrastim has not been evaluated in this setting, therefore, pegfilgrastim should not be used for PBPC mobilization. Patients receiving pegfilgrastim who report left upper abdominal or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Rare cases of allergic-type reactions have been experienced by patients receiving pegfilgrastim in the post-marketing setting. This is similar to allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatments that have been reported with the parent compound of pegfilgrastim, filgrastim. In some cases, symptoms have recurred with re-challenge with Filgrastim, suggesting a causal relationship. If a serious allergic reaction or anaphylactic reaction occurs, appropriate therapy should be administered and further use of pegfilgrastim should be discontinued.

Severe sickle cell crisis has been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle+ thalassemia) who received filgrastim, the parent compound of pegfilgrastim, for PBPC mobilization or following chemotherapy. One of these cases was fatal.

Filgrastim (Neupogen®)

Side-effects include chills, fever, nausea, anorexia, myalgia, bone pain, local injection site pain or inflammation, elevated liver function, thinning of hair, enlargement of spleen, and rarely fluid retention and pericardial effusion.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

At the time of each re-evaluation, patients will be classified in the following manner:

- No evidence of disease.
- Breast cancer recurrence: Local/regional breast cancer recurrence is defined as the development of tumor (except LCIS) in the ipsilateral breast (after lumpectomy); in the soft tissue/chest wall and/or skin of the ipsilateral chest wall; or tumor in the ipsilateral internal mammary, supraclavicular, infraclavicular, or axillary nodes or soft tissue of ipsilateral axilla. Suspected tumor recurrence in the ipsilateral breast, chest wall structures, supraclavicular, or lower (level I ± II) axillary nodal areas must be confirmed by biopsy or cytology. Histologic or cytologic confirmation of tumor is recommended for internal mammary or infraclavicular/high axillary nodal recurrence. A distant recurrence is defined as development of tumor in areas other than the local/regional area that is documented by a positive cytology aspirate, biopsy, or imaging studies.
- New primary: A new primary is defined as the development of contralateral breast cancer or a second cancer other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix or LCIS of the breast that is histologically confirmed.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Cardiac Death
- Symptomatic CHF
- Grade 3 or greater QTc prolongation on EKG on 2 consecutive EKGS within 4 weeks apart
- 2 “consecutive” or 3 “intermittent” H + L hold categories for “asymptomatic” LVEF decline

- More than one dose reduction of paclitaxel due to toxicities
- More than one dose reduction of lapatinib
- More than 3 consecutive weeks of holding lapatinib due to toxicities (except when holding lapatinib due to an asymptomatic LVEF decline)
- Disease recurrence
- Unacceptable toxicity
- Intercurrent, non-cancer related illness that prevents continuation of protocol therapy or follow-up
- Major protocol violation that would render the patient inevaluable for efficacy (ie: the initiation of non-protocol antineoplastic therapy or the discovery of information that, if known, would have rendered the patient ineligible for the study)
- Repeated non-compliance by the patient with protocol requirements
- Changes in the patient's condition or study drug related toxicity such that, in the opinion of the investigator, continued participation in the protocol would compromise patient well-being
- Withdrawal of patient's consent
- Any signs or symptoms of pneumonitis that are ≥Grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen). Refer to NCI CTCAE grading of pneumonitis/pulmonary infiltrates.

14.0 BIOSTATISTICS

This is a feasibility trial of a dose-dense adjuvant chemotherapy regimen that consists of paclitaxel (175 mg/m^2) q 14 days x 4 with pegfilgrastim + trastuzumab (4 mg/kg bolus → 2 mg/kg) + daily lapatinib followed by q 21 day trastuzumab (6 mg/kg) + daily lapatinib. The primary objective of this trial is to determine the feasibility of this regimen in patients with node-negative HER-2/neu overexpressed /amplified breast cancer with a tumor size of ≤ 3 cm. The regimen is considered feasible for patients who are able to complete the paclitaxel, trastuzumab, and lapatinib (THL) portion of the regimen without a dose delay or reduction or grade 3 or greater QTc prolongation. If the trial stops early for serious cardiac toxicity or excessive grade 3 gastrointestinal toxicity, the regimen will be deemed not feasible. The allowable incidence of cardiac events (CHF, cardiac death) is set to be ≤ 4% and the acceptable incidence of grade 3 gastrointestinal toxicity is set at 20%. A cardiac event (CE) is defined as 1) cardiac death or 2) symptomatic congestive heart failure (CHF) defined as dyspnea with normal activity or at rest and "absolute" decline in LVEF by > 10% to < 50 %. A cardiac event will result in discontinuation of trastuzumab and lapatinib.

We will accrue 55 patients for this study. Based on the accrual rate from prior studies, accrual is expected to take 12 months. Any patient who receives treatment on study, regardless of the ability to complete treatment, is evaluable. Any patient who is removed from the study for any reason prior to the 12 month mark will be classified as not being able to complete the regimen.

Greater than 85% of the patients on standard adjuvant trials complete the intended study regimens without a dose-delay or reduction. As the incidence of QT prolongation was reported in 13/81 (16%) in a group of patients followed with serial EKG monitoring, we anticipate that the incidence of QT prolongation on this study to be $\leq$ 20%. Thus, for this study, we would like to be able to discriminate between feasibility rates of 65% (unpromising) and 80% (promising). If a patient has more than one dose delay or dose reduction for any reason, these events are collectively counted as one entity in the same patient. With 55 patients, this design discriminates between true completion rates of $\leq$ 65% and $\geq$ 80% at a Type I error of 5% and a Type II error of 20%. A feasibility rate of $\leq$ 65% will indicate that this regimen is not feasible and not worthy for further investigation. The paclitaxel, trastuzumab, and lapatinib (THL) portion of the regimen will be considered feasible and warrant further clinical study if 42 or more patients are able to complete this portion of the regimen without a dose delay or reduction.

We have incorporated two early stopping rules. First, the study design includes early termination in the event of excessive grade 3 diarrhea. The allowable grade 3 diarrhea rate is set at 20% and the unacceptable rate is set at 40%. The boundaries are based on a maximum accrual of 55 patients. The below table provides the stopping boundary based on repeated significance testing:

First 10 patients	stop if 5 grade 3 GI toxicities are observed
20 patients	stop if 8 grade 3 GI toxicities are observed
30 patients	stop if 10 grade 3 GI toxicities are observed
40 patients	stop if 13 grade 3 GI toxicities are observed
50 patients	stop if 15 grade 3 GI toxicities are observed
55 patients	stop if 17 grade 3 GI toxicities are observed

If the true toxicity rate is 20%, the probability the study will be stopped is 12%, while if the true toxicity rate is 40%, the probability the study will be stopped is 97%. The study will not be halted after each set of 10 patients is accrued.

For the second stopping rule, the study design includes an early stopping rule to account for the possibility of cardiac events. The allowable incidence of cardiac events (CHF, cardiac death) is set to $\leq$ 4%, to be consistent with the reported adjuvant trastuzumab trials (19-21). Since the clinical significance of asymptomatic LVEF decline is unknown, patients will be followed long-term. The study will be stopped if there are 3 cardiac events that occur at any time as one of the following two scenarios: 1) if there is 1 cardiac death and 2 symptomatic CHF events 2) if there are 3 symptomatic CHF events. The probability of stopping the trial is 38% if the true cardiac event rate is 4% and 83% if the true cardiac event rate is 8%.In addition, if there are any cardiac deaths at any time, the trial will be terminated.

Patients from the terminated trial will receive care according to the discretion of their treating physicians.

Upon completion of the study, the rate of patients who complete the paclitaxel, trastuzumab, and lapatinib portion of the regimen without a dose delay or reduction will be estimated via the observed completion rate and an exact confidence interval will be constructed.

Selected non-hematologic and hematologic toxicities will be described by frequency and grade, by cycle and over all cycles, with the maximum grade over all cycles used as the summary measure per patient.

There are several secondary analyses planned. Serial blood measurements of cardiac markers (cTnI, and BNP) will be examined. We will also assess the LVEF at baseline at months 2, 6, 9, 12 and 18 with an ECHO. When an ECHO cannot be done, a multi-gated acquisition scan (MUGA) may be done. EKG will also be done at months 2, 6, 9, 12 and 18.To assess cardiac safety of this regimen, analysis of the cardiac biomarkers and changes seen on echocardiogram/EKG will be correlated. In a descriptive, graphical analysis, changes in cardiac biomarkers will be examined in patients who develop cardiac toxicity and compared to changes seen in patients who did not develop a cardiac toxicity. We will also explore the use of single-nucleotide polymorphism (SNP) genotyping in evaluation of pharmacogenetic determinates of gastrointestinal toxicity.

All toxicities following chemotherapy will be graded using the National Cancer Institute – Common Toxicity Criteria version 4.0. We will use logistic regression models to estimate the odds ratio and 95% confidence intervals for the association of each SNP with the incidence of grade 3 or higher diarrhea. The major endpoint in this clinical pharmacogenomics study is to determine the association between variant genotypes and toxicity.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The Clinical Research Database (CRDB) will be used for data collection. The data will be reported to the institution (IRB) and the sponsor (Roche) as appropriate.

It is estimated that 5-7 patients will be accrued per month and it will take 12 months to accrue.

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSKCC.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals, protocol compliance, eligibility verification, informed consent procedure, data accuracy, and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of 2 times a year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Every effort will be made to keep study records private. Neither the patient's name nor anything else that could identify the patient will be used in any reports or publications that result from this study. Trained staff at Memorial Hospital will be able to review the medical records if necessary. The patient may terminate her participation in the study at any time during the trial.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number

written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Reporting SAEs:

All SAE reports must also be forwarded as soon as possible to:

Study Coordination Center/Principal Investigator: Chau Dang, M.D.

Contact Information phone: 646-888-4554 fax: 646-888-4555

All SAEs that are serious and reasonably or probably related to the use of lapatinib (this applies to both expected and unexpected events) should be recorded on an MSK CRDB SAE report and faxed as soon as possible to:

Stephen Rubin, M.D., Office: (610) 917-5235 Mobile: (484) 620-9545

or

Rob Friedman, B.Sc. Office: (610) 917-7456 Mobile: (484) 802-4002

or

Allitia DiBernardo Office fax: (610) 675-2602 Mobile: (484) 620-9545

Toll Free Number: (800) 877-7074, ext. 5731 or 6862

After Hours or Weekends: (800) 366-8900, ask for physician on call

GlaxoSmithKline UP4420

1250 S. Collegeville Road,

P.O. Box 5089

Collegeville, PA 19426-0989

Adverse Event Reporting Definitions:

A serious treatment emergent adverse event (STEAE) is any sign, symptom or medical condition that emerges during lapatinib treatment or during a post-treatment follow-up period that (1) was not present at the start of lapatinib treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of lapatinib treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death

- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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APPENDIX A: ECOG PERFORMANCE STATUS SCALE

Grade	Description
0	Fully active, able to carry out all normal activity without restriction (Karnofsky 100)
1	**Restricted in physically strenuous activity but ambulatory and able to carry out light work (Karnofsky 90-80)**
2	Ambulatory and capable of all self-care but unable to carry out any work.

	Up and about more than 50% of waking hours (Karnofsky 70-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 50-40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 30-20)
5	Death

APPENDIX B: MANAGEMENT OF ACUTE HYPERSENSITIVITY

Severity of Symptoms	Treatment Guidelines
Mild **symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash**	· **consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient** · **then, complete taxane infusion at the initial planned rate**
Moderate **symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg**	· **interrupt taxane infusion** · **give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms** · **resume taxane infusion after recovery of symptoms; depending on the physician's assessment of the patient, taxane infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate*, (eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, and then finally, resume at the 3-h infusion rate)*** · **depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the initial planned rate, *(eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, and finally, administer at the 3-h infusion rate)***
Severe symptoms: **any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema**	· **immediately discontinue taxane infusion** · **give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms** · **the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.**
Anaphylaxis (NCI grade 4 reaction)	· NO FURTHER STUDY DRUG THERAPY

APPENDIX C: Supportive Care Guidelines for Lapatinib

Rash: Skin rash (usually grade 1-2) has been observed during the first several days of treatment with EGFR inhibitors and has been observed to diminish in severity after 4 weeks of treatment in many patients. In some patients, this rash appeared to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with several agents. In patients with severe rash, treatment may need to be discontinued or the dose reduced. Anecdotal reports of improvement have occurred with any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course).

Diarrhea: Diarrhea has been seen with lapatinib and with other EGFR inhibitors. In general EGFR inhibitor-induced diarrhea has been transient, usually not of sufficient severity to hinder administration of the agents, and responsive to loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg q 2–4 hr until diarrhea free for 12 hr.

Lapatinib Diarrhea Management Guidelines:

Uncomplicated grade 1-2 diarrhea:
Stop all lactose containing products;
Drink 8-10 large glasses of clear liquids a day;
Eat frequent small meals;
Grade 2 diarrhea hold cytotoxic chemotherapy;
Grade 2 diarrhea consider dose reduction of lapatinib (discuss with medical monitor);
Administer standard dose of loperamide:
Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool.
We suggest continuation of loperamide until diarrhea free for 12 hours.

For grade 3 or 4 diarrhea or grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, grade 3 or 4 neutropenia, frank bleeding, dehydration):
Use intravenous fluids as appropriate, consider hospital admission;
Use prophylactic antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia;
Hold both cytotoxic chemotherapy and lapatinib and discuss with medical monitor.

These broad general management principles are recommended to proactively try and avoid more serious complications by active management of the diarrhea syndrome. Guidelines such as these should never replace sound clinical judgment. Our experience thus far suggests that when lapatinib is used as monotherapy we mostly are dealing with uncomplicated grade 1 or 2 diarrheas. These general management principles do not discuss comprehensive management of more serious or protracted diarrhea syndromes.

Nausea: Routine premedication for nausea is not necessary, but symptomatic patients should be treated with standard antinausea/antiemetic therapy as necessary.

If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

APPENDIX D

Lapatinib Diary Take 1000 mg (4 tablets) either 1 hour (or more) before meals or 1 hour (or more) after meals. Lapatinib should not be taken with grapefruit or grapefruit juice. Please remember to return your pill bottle (with any remaining pills) and log sheet when you are due to start a new bottle.

Lapatinib	Date:	AM Time:	PM Time:
Day # 1:			
Day # 2:			
Day # 3:			
Day # 4:			
Day # 5:			
Day # 6:			
Day # 7:			
Day # 8:			
Day # 9:			
Day # 10:			
Day # 11:			
Day # 12:			
Day # 13:			
Day # 14:			
Day # 15:			
Day # 16:			
Day # 17:			
Day # 18:			
Day # 19:			
Day # 20:			
Day # 21:			
Day # 22:			
Day # 23:			
Day # 24:			
Day # 25:			
Day # 26:			
Day # 27:			
Day # 28:			

Date Returned: _____ #Pills returned: _____

Patients' signature: _____ RN Signature: _____

APPENDIX E: Prohibited Concomitant Medications with Lapatinib

Drug Class	Agent	Wash-out[1]
CYP3A4 Inducers		
Antibiotics	All rifamycin class agents (ie: rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamazepine, barbiturates (ie: phenobarbital)	14 days
Antiretrovirals	efavirenz, nevirapine	14 days
Glucocorticoids	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)[2]	14 days
Other	St. John's Wort, modafinil	14 days
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	7 days
Antiretrovirals, Protease Inhibitors	declaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinovir	7 days
Calcium channel blockers	verapamil, diltiazem	7 days
Antidepressants	nefazodone, fluvoxamine	7 days
GI agents	cimetidine, aprepitant	7 days
Other	grapefruit, grapefruit juice,	7 days
	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, maalox, tums, rennies	1 hour before and after dosing
Herbal supplements[3]	Ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	14 days

1. At the time of screening, if a patient 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 lapatinib and throughout the study period in order for the patient to be eligible to participate in the study.
2. Glucocorticoid daily doses (oral) of < 1.5 mg dexamethasone (or equivalent) are allowed. Oral or IV steroids given prior to paclitaxel administration as part of this study are allowed.
3. This list is not all-inclusive; thus, for herbal supplements not listed, please contact GSK Medical Monitor or Clinical Scientist.

APPENDIX F: National Cancer Institute Prolonged QTc Clinical Terminology Criteria for Adverse Events

QTc Prolongation Grade	Definition
I	QTc > 450-470 ms
II	QTc > 470-500 ms or > 60 ms above baseline
III	QTc > 500 ms
IV	QTc > 500 ms; life-threatening signs or symptoms (ie: arrhythmia, CHF, hypotension, shock, syncope), torsades de pointes
V	Death

Abbreviations: QTc = corrected QT
ms = millisecond
CHF = congestive heart failure

APPENDIX G: National Cancer Institute Terminology Criteria for Grading Diarrhea Adverse Events

Adverse Event Grade	Olarmea
1	Increase of <4 stools/day over baseline rruld tncrease tn ostomy output compared to baseltne
2	Increase of 4-6 stools/day over baseftne_moderate tnaease tn ostomy output compared to baseline
3	Increase of ?!7 stools/day over baseltne_incontilence_hospitafJZabon tndtcaled. severe increase in ostomy output compared to baseline, limiting self care activities of daily IMng (AOL)
4	Life Ihreatening consequences, urgent mtervention incicated
5	Death

1. Nabonal Cancer Insbhr.e Common Termmaogy Critena 'nr Adverse Events (CTCAE) Versm4)

1 ocompticared diarrhea 15 consldded nuld-to-moderate and defined as CTCAE Grade 1 or 2 wtth no comphcahng signs or symptoms.

Complicated diarrhea ts st-vere and defined as an , CTCAE Grade 3 or 4 diarrhea. or Grade 1 or 2 wllh one or more of the follo\\'1llg stgns or symptoms:

- Moderate ro severe abdorrunnl crampwg
- Naust-a vonutmg .?Grnde2
- Dt"creased performance status
- Fever
- epSlS
- Neutropt-rua
- Frank bleeding (d blood in stool)
- Deh 'drahon

APPENDIX H: Management Guidelines for Subjects Receiving Lapatinib Alone or as Combination Therapy

A) Uncomplicated Diarrhea

I. CTCAE Grade 1

NOTE: Subject should be instructed to: start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and call their physician.

1. Administer loperamide
   a. Initial dose 4mg followed by 2mg after every unformed stool. Re-evaluate after 24 hours, if:
      i. Diarrhea is resolving:
         - Continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
            - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
      ii. Diarrhea is not resolving:
         - Administer loperamide at 2mg every 4 hours for the next 24 hour. Re-evaluate after 24 hours. If diarrhea is resolving, administer loperamide at 2mg after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours. If diarrhea is not resolving continue loperamide treatment at 2mg every 4 hours and re-evaluate every 24 hours.
   b. If Grade 1 diarrhea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (octreotide, budesonide or tincture of opium).
2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
   a. Stop all lactose containing products and eat small meals
   b. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber
      i. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
   c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
   d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
      i. Avoid acidic drinks such as tomato juice and fizzy soft drinks
   e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots) , evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the subject can begin to gradually re-introduce foods from their normal diet.

If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications. Continue with study treatment.

If Grade 1 diarrhea persists for ≥2 weeks, refer to the management guidelines for Persistent Grade 2 Diarrhea.

II. CTCAE Grade 2

NOTE: Subject should be instructed to call physician at first episode of diarrhea and start supportive care immediately

1. Administer loperamide
   a. Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:
      i. Diarrhea is resolving, continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
      ii. Diarrhea is not resolving, consider loperamide dose of 2mg every 2 hours for 24 hours. If Grade 2 diarrhea persists after total of 48 hours of loperamide treatment, start second-line agents (octreotide, budesonide or tincture of opium).
         - Consider performing stool work-up, CBC, electrolytes and other tests as appropriate
2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
   a. Stop all lactose containing products and eat small meals
   b. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber
      i. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
   c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
   d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
      ii. Avoid acidic drinks such as tomato juice and fizzy soft drinks

e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots), evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)

Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the subject can begin to gradually re-introduce foods from their normal diet. Refer to Section IV "Recurrent Diarrhea" for study treatment guidelines.

If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications.

III. **Persistent (≥ 3days/72 hours) Grade 2 Diarrhea**: hold lapatinib and chemotherapy (if applicable) until diarrhea resolves (<Grade 1/return to baseline bowl pattern). If supportive care measures an

1. If supportive care measures and the interruption of study treatment (i.e., lapatinib and if applicable chemotherapy) are ineffective in treating persistent Grade 1 or Grade 2 diarrhea, perform stool work-up, CBC, electrolytes and other tests as appropriate, consider consulting with a gastrointestinal (GI) specialist.

   a. After diarrhea resolves (≤Grade 1), resume treatment with lapatinib and chemotherapy (if applicable).

IV. **Recurrent Diarrhea (more than 1 occurrence of Grade 2 diarrhea):** once the 2nd occurrence of Grade 2 diarrhea resolves to ≤Grade 1, consider reducing the dose of lapatinib by 250mg or 1 tablet, unless the lapatinib dose already had been reduced to 750mg. No further dose reduction is recommended for subjects taking lapatinib at 750mg.

2. Consider a dose reduction for chemotherapy (if applicable)

B) Complicated Diarrhea

3. **CTCAE Grade 3 or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration)**

1. Subject **must** call physician immediately for any complicated severe diarrhea event
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool
3. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhea
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolytes and other tests as appropriate

6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia
7. Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤Grade 1 and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750mg, contact medical monitor for further guidance)
   a. Consider a dose reduction for chemotherapy (if applicable)
8. Supportive care and other interventions should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for subjects most at risk for life threatening complications

II CTCAE Grade 4

1. Subject must call physician immediately for any Grade 4 diarrhea event
2. Discontinue treatment with lapatinib, hold chemotherapy (if applicable)
3. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolyte and other tests as appropriate
6. Recommend consulting with GI specialist
7. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
8. Supportive care and other intervention should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for subjects most at risk for life threatening complications

Algorithm for the management of diarrhea in subjects treated with lapatinib-based therapy