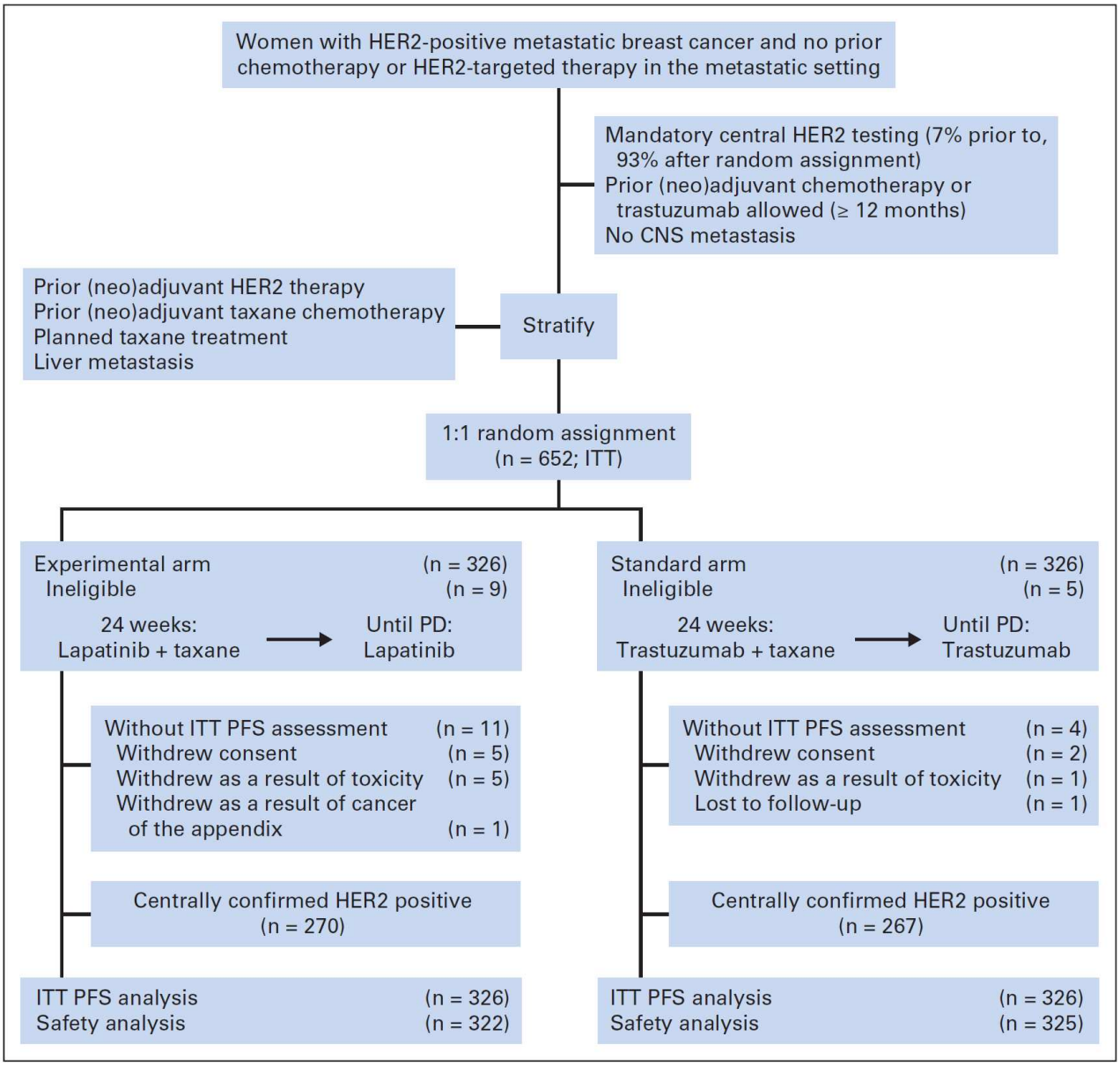

CONSORT diagram of CCTG MA.31 clinical trial (Gelmon KA et al., *J Clin Oncol*. 2015;33 (14):1574-1583)

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NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A RANDOMIZED, OPEN-LABEL, PHASE III STUDY OF TAXANE BASED CHEMOTHERAPY WITH LAPATINIB OR TRASTUZUMAB AS FIRST-LINE THERAPY FOR WOMEN WITH HER2/neu POSITIVE METASTATIC BREAST CANCER

[**COMPLETE:** Comparison of Lapatinib Efficacy vs. Trastuzumab, Each with a Taxane, in First Line Metastatic Breast Cancer]

NCIC CTG Protocol Number: **MA.31**

GlaxoSmithKline Protocol Number: EGF108919

IND Number: 61,362

EudraCT Number: 2007-004568-27

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(For contact information of study personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to GlaxoSmithKline (GSK).

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents.

I will provide copies of the protocol and access to all information furnished by NCIC CTG and GlaxoSmithKline to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of GlaxoSmithKline and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to GlaxoSmithKline and NCIC CTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to NCIC CTG (Canadian centres) or GSK (centres outside Canada). The study may be terminated at any time by NCIC CTG or GlaxoSmithKline with or without cause.

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_____ _____

Investigator
(printed name and signature)

Date

NCIC CTG Protocol Number: MA.31
GlaxoSmithKline Protocol Number: EGF108919
EudraCT Number: 2007-004568-27

CENTRE: _____

TREATMENT SCHEMA

Population
Women with documented evidence of HER2/neu positive breast cancer (by local or central laboratory testing) which is metastatic, and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

Stratification
1. Prior (neo)adjuvant HER2/neu targeted therapy (yes, no)
2. Prior (neo)adjuvant taxane chemotherapy (yes, no)
3. Planned taxane treatment (q weekly paclitaxel versus 3 weekly docetaxel)
4. Liver metastasis (yes, no)

Women with HER2/neu positive metastatic breast cancer	RANDOMIZE	ARM 1 Lapatinib - 1250 mg po daily Taxane based chemotherapy Paclitaxel - 80 mg/m^2 IV q weekly (days 1, 8 and 15 of a 4-week cycle) *or* Docetaxel - 75 mg/m^2 IV q3 weekly (day 1 of a 3-week cycle) *plus* G-CSF - according to institutional standards *Followed by:* Lapatinib - 1500 mg po daily until disease progression (24 weeks) ARM 2 Trastuzumab - IV q weekly (loading dose 4 mg/kg, subsequent doses 2 mg/kg) Paclitaxel - 80 mg/m^2 IV q weekly (days 1, 8 and 15 of a 4-week cycle) *OR* Trastuzumab - IV q 3 weekly (loading dose 8 mg/kg, subsequent doses 6 mg/kg) Docetaxel - 75 mg/m^2 IV q3 weekly (day 1 of a 3-week cycle) (24 weeks) *Followed by:* Trastuzumab- 6 mg/kg IV q 3 weekly until disease progression	Response Evaluation	Disease Progression	Survival Follow-up

Sample size: approximately 600, so as to achieve 536 centrally confirmed HER2/neu positive patients

Endpoints:

Primary

- Progression-Free Survival

Secondary

- Overall Survival
- Time to CNS metastases at the time of first progression
- Incidence rates of CNS metastases at the time of progression
- Overall objective response rate, time to response and duration of response
- Clinical benefit response rate
- Adverse event profile
- Quality of Life (using the EORTC QLQ-C30 and a Trial Specific Checklist)
- Clinical outcomes using biomarker changes in biological samples
- Economic Evaluation: health utilities (using the EQ-5D questionnaire) and healthcare utilization

1.0 OBJECTIVES

1.1 Primary Objective

To compare the progression-free survival of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy, in women with HER2/neu positive breast cancer (by local or central laboratory testing) which is metastatic, and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

1.2 Secondary Objectives

To evaluate and compare the two treatment arms with respect to:

- Overall survival
- Time to CNS metastases at the time of first progression
- Incidence rates of CNS metastases at the time of progression
- Overall objective response rate (complete or partial response), time to response, and duration of response - only patients with at least one measurable lesion at baseline
- Clinical benefit response rate, as determined by the total number of patients who achieve a complete or partial response (patients with at least one measurable lesion at baseline) plus those patients who have stable disease for at least 24 weeks (all patients - with or without measurable disease at baseline)
- Adverse event profile
- Quality of life as measured by the EORTC QLQ-C30 instrument and a Trial Specific Checklist
- Clinical outcomes using biomarker changes in biological samples
- Health economics, including both healthcare utilization and health utilities (Canadian and Australian centres only). Health utilities will be measured by the EQ-5D questionnaire.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Metastatic Breast Cancer

In 2002, an estimated 11 million new cancer cases and 7 million cancer deaths were reported worldwide. Approximately 10% arose in the breast, making it the second most common site of malignant neoplasms after lung and the most common cancer among women. The total number of female breast cancer cases was 1,152,161 with an estimated 411, 932 deaths and a mortality to incidence rate ratio of 0.35. While the incidence rates were nearly three-fold higher in more-developed than less-developed geographic locations (67.8 to 23.8 per 100,000 person years), mortality rates were less than two-fold higher in the former compared to the latter *[Kamanga 2006]*. Despite improvements in early diagnosis and treatment of breast cancer, a significant number of women will relapse and ultimately die of metastatic disease. Recurrent or metastatic breast cancer is an incurable malignancy with a median survival of 20-24 months *[Hortobagyi1998]* and this has not changed significantly over the last decade with fewer than 20% of patients still alive at 5 years after a diagnosis of recurrence.

The goals of treatment for recurrent breast cancer are to improve survival, prolong progression free survival and promote good quality of life. Although initial treatments did not achieve these goals, in the last decade a number of studies have shown an overall survival benefit. Population based studies have suggested that with the introduction of new contemporary agents, women are living longer after a diagnosis of advanced cancer *[Chia 2007]*. Although response rates and shrinkage of tumours have also been used to determine the activity of a new treatment, a more meaningful endpoint for this patient population in a phase III study would be progression free survival since progression is often symptomatic, increases patient anxiety and requires a change of therapy.

2.2 HER2/neu Positive Breast Cancer

Approximately 15 – 20% of human breast cancers overexpress HER2 (also known as c-erbB2 or neu) oncogene. The HER2/neu gene is located on chromosome 17q21 and encodes for a 185-kd transmembrane protein. Compared to other subtypes of breast cancer, these cancers are associated with a greater risk for disease progression and death *[Meric 2002]* as well as resistance to chemotherapeutic and hormonal agents. Upregulation and autocrine activation of the EGFR and HER2/neu receptors appears to confer an increased resistance to hormonal therapy and cytotoxic chemotherapy *[Slamon 2001]* and a poorer prognosis *[Nicholson 2002]*. HER2/neu over-expression is an independent predictor of shorter disease free survival and overall survival in both node positive and node negative early breast cancer. These cancers are often also poorly differentiated, high-grade tumours, with increased rates of cell proliferation and lymph node involvement *[Burstein 2005]*, more advanced disease at presentation and often occur in younger women.

The laboratory assessment of HER2/neu has been examined in a number of studies. Both overexpression and amplification have been associated with defining this group of patients for both prognostic and predictive assessments. A number of laboratory tests are approved to determine HER2/neu status; immunohistochemistry measurement of the protein and/or fluorescent in situ hybridization (FISH) to assess amplification of the gene are the most frequently used. Standardized testing and a uniform description of what constitutes HER2/neu overexpression/amplification for the purposes of treatment has been proposed in a recent ASCO publication *[Wolff 2007]*. As well there has been extensive work on standardizing and centralizing testing of HER2/neu to clearly define homogenous populations and although this has recently come under further discussion, it appears that centralized testing of tumours in high-volume accredited laboratories with standardized procedures does define a clear population in the majority of cases. In view of this, confirmatory centralized HER2/neu testing is planned for all randomized patients on this study. Based on previous experience from clinical trial data and the increasing awareness and use of standardized testing and reporting, it is estimated that approximately 600 patients will be randomized on the basis of local laboratory HER2/neu testing to yield the target number (536) of centrally confirmed HER2/neu positive cases *[Perez 2006a, Press 2005, Paik 2002]*.

2.3 Taxanes in Breast Cancer

Initial studies of paclitaxel in breast cancer in the early 1990s *[Holmes 1991]* established this agent as an active drug in breast cancer. Further studies were done looking at schedule, dose, infusion duration and combination therapy. Although a number of schedules are active, recent data has suggested that a weekly one hour infusion of paclitaxel is active, well tolerated and appropriate for the advanced setting. A variety of regimens have been proposed including continuous, weekly for 5 out of 6 weeks, weekly for 3 out of 4 weeks and doses (80 – 110 mg/m^2). All appear similar in efficacy and the major differences appear to relate to long term tolerance and neurotoxicity. Docetaxel was also first described in the early 1990s and has good efficacy in breast cancer both as a single agent and in combination with other cytotoxics and biological agents. Although a variety of schedules have been studied, it appears that the three weekly one hour infusion is the most effective *[Sparano 2007]*. Doses of 75 – 100 mg/m^2 are well tolerated with neutropenia, alopecia, rashes, nail changes, neurotoxicity and edema being the most frequent toxicities. Although both taxanes are used in the adjuvant setting there is no clear data limiting their use in the advanced setting also, nor is there clear data on assessing resistance. Newer taxanes such as nab-paclitaxel are also being assessed and used in the advanced setting, but at this time this agent is not approved worldwide and its use outside of the US is limited.

In a subset of women with node-positive breast cancer from the adjuvant trial conducted by the Cancer and Leukemia Group B (CALGB 9344), a retrospective analysis was performed to determine whether HER2/neu was predictive of clinical outcome *[Hayes 2007*]. Results showed that HER2/neu positive status (in addition to tau gene expression) may be a predictive factor for the activity of microtubule inhibiting agents suggesting that taxanes may be of particular value in this patient population. These results indicate that the mechanism of action of the chemotherapy agent may be an important factor in the sensitivity of the HER2/neu-positive tumour cells to the HER2/neu combination blockade and may stimulate further use of taxanes in this setting.

2.4 Trastuzumab in Breast Cancer

Trastuzumab is a recombinant humanized monoclonal antibody which binds to the extra-cellular domain of the HER2/neu receptor. In the two phase II studies of trastuzumab alone in women with metastatic breast cancer, heavily pretreated in the majority, the response rates were 11-15%, with a 3% complete response rate *[Cobleigh 1999]* and results from a phase III study of trastuzumab in combination with either an anthracycline combination or taxane as first line treatment in metastatic breast cancer *[Slamon 2001]* showed that the addition of trastuzumab increased the overall response rate from 36% to 62%. With a median follow-up of 30 months, the combination of trastuzumab and chemotherapy had a superior survival rate (median 25 months) compared to chemotherapy alone (21 months) - the relative risk of death was 0.80 (95% CI = 0.64 - 1.00), p-value=0.046. The survival advantage was greatest in the Adriamycin/Cyclophosphamide plus Trastuzumab (AC+T) arm (median 26.8 months) versus the Adriamycin/Cyclophosphamide (AC) alone arm (21.4 months). Benefit was seen in the Paclitaxel plus Trastuzumab (P+T) arm (median 22.1 months) compared to Paclitaxel (P) alone (18.4 months) even though this was not statistically significant. A significant drawback however with the use of trastuzumab has been the unexpected side effect of cardiac toxicity. With trastuzumab alone there was an observed 4% rate of reduced cardiac ejection fraction, with two-thirds of cases being symptomatic. In combination with an anthracycline (AC+T) there was a 19% rate of class III/IV cardiac dysfunction. With the P+T combination the rate of cardiac toxicity was 4%.

Subsequent studies showed similar efficacy of trastuzumab in combination with docetaxel *[Marty 2005]*. Pre-clinical data supports strong synergy, with either a combination of taxanes and trastuzumab or with a triple drug regimen with paclitaxel or docetaxel, combined with a platinum and trastuzumab *[Robert 2006, Forbes 2006]*. A clear survival benefit is not clearly shown with the addition of the platinum.

Table 1: Results of Phase III Studies of Trastuzumab-Based Therapy as First-Line Treatment of HER2/neu-Positive Metastatic Breast Cancer

	Slamon et al.2001		M77001		Robert et al. 2006		BCIRG 007	
	Tras + Chemo* (N=235)	Chemo* (N=234)	Tras + Doc (N=92)	Doc (N=94)	Tras + Pac +Cb (N=98)	Tras + Pac (N=98)	Tras + Doc + Cb (N=132)	Tras + Doc (N=131)
Time to Progression of Disease								
Median, mos.	7.4	4.6	11.7	6.1	10.7**	7.1**	10.35	11.07
HR (95% CI) p value	0.51 (0.41 to 0.63) p<0.001		not reported log-rank p=0.0001		0.66 (050 to 0.73) p=0.03		not reported log-rank p=0.57	
Overall Survival								
Median, mos	25.1	20.3	31.2	22.7	35.7	32.2	41.66	not reached
HR (95% CI) p value	0.80 (0.64 to 1.00) p=0.046		not reported log-rank p=0.0325		0.90 (0.88 to 0.92) p=0.076		not reported log-rank p=0.2	

* chemotherapy included either anthracycline plus cyclophosphamide for patients who never before received an anthracycline OR paclitaxel for patients who received prior adjuvant anthracycline;
** results for progression-free survival.

Abbreviations: Cb = carboplatin; CI = confidence interval; Doc = docetaxel; HR = hazard ratio; N = number of patients; Pac = paclitaxel; Tras = trastuzumab.
Data source: Forbes 2006, Slamon 2001, Marty 2005, Robert 2006

Trastuzumab also has been investigated with other chemotherapy combinations, including gemcitabine, vinorelbine, liposomal anthracyclines and capecitabine, in a number of mainly Phase II studies and has demonstrated activity as first-line treatment of metastatic breast cancer and as treatment after failure of prior chemotherapy *[Fountzilas 2004, O'Shaughnessy 2004, Burstein 2003, Papaldo 2006, Chia 2006, Bartsch 2007]*. Trastuzumab is also being investigated with paclitaxel protein-bound particles for injectable suspension (Abraxane® or nab paclitaxel).

Trastuzumab has been shown to be effective in prolonging survival in women with HER2/neu amplified breast cancer when it is used in the adjuvant setting in five studies. These studies (NCCTG, NSABP, HERA, BCIRG, FinHER) enrolled over 10,000 women with HER2/neu overexpressing breast cancer worldwide, and despite different combinations and schedules (concurrent vs sequential) consistently showed a marked improvement in recurrence rate and an improvement in survival *[Piccart 2005, Romond 2005, Joenssu 2006, Smith 2007, Slamon 2005, Slamon 2006]*.

2.5 Lapatinib

Lapatinib is an orally active, reversible, small molecule tyrosine kinase inhibitor that potently inhibits both EGFR and HER2/neu tyrosine kinase activity *[Spector 2005]*. Lapatinib differs in enzyme inhibition kinetics from other small molecule tyrosine kinase inhibitors such as gefitinib and erlotinib in that the latter are all rapidly reversible ($t_{1/2}$ < 10 mins) whereas lapatinib has a very slow off-rate for both EGFR and HER2/neu (t1/2 > 2 hours) *[Wood 2004]*. *In vitro* studies indicate specificity of lapatinib activity towards the EGFR and HER2/neu targets with resulting tumour growth inhibition.

Most AEs reported in the lapatinib monotherapy studies in humans were mild to moderate in intensity with the most frequently reported AEs being diarrhea, rash, nausea, fatigue, and anorexia. In studies of lapatinib in combination with chemotherapeutic agents and hormonal agents, the AEs were similar to those seen with each individual agent although the frequency and intensity were greater for certain lapatinib and chemotherapy combinations. Cardiac function has been monitored in lapatinib phase I, II and III trials. Using the following definition of a drug-related serious cardiac event:

- Grade 3 or 4 left ventricular systolic dysfunction based on the CTCAE version 3.0 criteria or
- LVEF decrease of $\geq$ 20 relative to the baseline value and below the institutional lower limit of normal an incidence of 1.3% was noted (1.6% if including patients who received blinded therapy). An approximate incidence of 0.1% was seen for symptomatic LVEF decreases.

Lapatinib is metabolized in the liver. Hepatotoxicity has been seen with both single agent lapatinib and in combination with chemotherapeutic agents. The AEs that are usually observed are elevations in liver transaminases, but occasionally severe hepatotoxicity has been reported. Abnormal liver function tests usually return to normal once the lapatinib has been stopped but may return on rechallenge with the agent. Rarely deaths have occurred. The current estimate of severe hepatocellular toxicity is 0.4% based on the current experience with 8702 patients who have received the agent. Mild elevations in liver function tests occur more frequently. Elevated liver enzymes are seen with other tyrosine kinase inhibitors.

FDA approval of lapatinib in the USA and CHMP approval in Europe was based on phase III Study EGF100151 in 399 patients with pretreated breast cancer refractory to trastuzumab. Patients were randomized to combination lapatinib and capecitabine compared to capecitabine alone. An increased time to progression (TTP) was seen with the combination therapy compared to capecitabine alone (HR=0.57, p<0.001) *[US Package Insert August 2007]*. In addition to systemic antitumour effects, data suggest that lapatinib may have antitumour activity in the central nervous system. Two hundred and thirty seven patients with HER2/neu positive breast cancer and brain metastases with progressive disease or relapse on trastuzumab were treated with lapatinib 750 mg twice daily. Preliminary data demonstrated that 8 patients (7.7%) met volumetric criteria for partial response with a median absolute volume reduction of CNS disease of 3.6 cm^3 (range 0.4 to 29.7 cm^3) *[Lin 2007a]*.

2.6 Limitations of Current Treatment Options and Rationale for Current Study

Trastuzumab has been associated with cardiac dysfunction. In patients with metastatic breast cancer treated with trastuzumab, 3% to 27% reported clinically significant cardiac dysfunction depending on the concurrent treatment *[Seidman 2002, Ewer 2007]*. In the subset of patients in the first-line metastatic breast cancer trial conducted by Slamon and colleagues, the rate of cardiac dysfunction was higher among patients who received trastuzumab plus paclitaxel compared with those treated with paclitaxel alone (13% versus 1%) *[Slamon 2001]*. The corresponding rate of cardiac dysfunction of New York Heart Association class III or IV was 2% versus 1%. In the BCIRG 007 study, the rate of cardiotoxicity (all grades of cardiac left ventricular dysfunction) was similar between treatment arms with 9.1% and 8.3% of patients with cardiac dysfunction on the trastuzumab plus docetaxel with and without carboplatin, respectively *[Forbes 2006]*. Treatment with the HER2/neu inhibitor, trastuzumab, is associated with an increased incidence of reversible cardiomyopathy in some subjects. However, it is not known whether this effect is specific to trastuzumab, or a 'class effect' associated with HER2/neu inhibition *[Cook-Bruns 2006]*. Therefore, as a precautionary measure throughout all other HER2/neu targeted therapy studies including lapatinib studies, left ventricular ejection fraction (LVEF) is monitored. To date, data collected across the entire lapatinib program (phase I through phase III clinical studies) indicate that lapatinib-associated LVEF decreases occur at a low incidence and are rarely symptomatic *[Perez 2006b]*.

Although survival has improved, ultimately patients with recurrent HER2/neu positive breast cancer relapse or progress on trastuzumab. Of particular concern is relapse in the central nervous system which appears to occur in approximately 30% of patients on trastuzumab for metastatic cancer and is often associated with significant morbidity and mortality *[Clayton 2004, Lin 2007b]*. Overexpression/ amplification of HER2/neu appears to be an important risk factor for the development of brain metastases *[Kallioniemi 1991]*, but may also be associated with successful systemic treatment and prolonged survival. The increased incidence of brain metastases in patients receiving trastuzumab therapy is generally not thought to be the result of decreased HER2/neu expression in the CNS, but rather, to the inability of trastuzumab to penetrate the blood brain barrier (BBB). More recently, the incidence of isolated brain metastases as first events was reported to be higher in the trastuzumab groups as compared to control groups in the adjuvant setting *[Romond 2005]*. Trastuzumab is a large molecule and monoclonal antibody and does not penetrate the blood brain barrier. Therefore, small molecule tyrosine-kinase inhibitors (TKI) that target HER2/neu overexpressing tumours may represent a promising strategy to decrease the incidence of this grave occurrence. Current clinical data with lapatinib show early indications of a treatment effect on brain metastases in patients with breast cancer *[Stein 2005, Lin 2006, Geyer 2006, Lin 2007a]*.

As well, although the results of the adjuvant studies have been significant there are patients relapsing after adjuvant trastuzumab and there is no data at this time regarding the efficacy of re-treatment with the same targeted agent. Studies to assess this and new therapies for recurrent or advanced HER2/neu amplified cancers are needed. Many therapeutic strategies have, therefore, been employed to block the ErbB signaling pathways as a means to improve the therapeutic efficacy of hormonal and chemotherapy regimens. Lapatinib inhibits both EGFR and HER2/neu, and may provide improved therapeutic benefit as compared with inhibitors that target either receptor alone.

Another potential limitation of antibody directed HER2/neu therapy is the occurrence in tumours of p95ErbB2, a truncated variant of HER2/neu that results from the removal of the extracellular receptor domain and therefore lacks the relevant binding site. Small molecule tyrosine kinase inhibitors may, however, prove to be effective against p95ErbB2 positive breast cancers *[Xia 2004]*. Small molecule ErbB TKIs compete for the ATP binding site and inhibit the receptor's activity. In principle, small molecule TKs should inhibit the activity of EGFR in the presence of elevated levels of ligand and should also inhibit the activity of ErbB receptors with truncated extracellular domains.

In summary, relapsed HER2/neu positive breast cancer is associated with a poor prognosis. Treatment with combination taxane trastuzumab therapy is limited by development of resistance to HER2/neu blockade, and the potential for cardiotoxicity. In addition, trastuzumab has no penetration of the central nervous system, a common site of relapse in this group of patients. For these reasons, lapatinib may be a more useful agent in the treatment of HER2/neu positive metastatic breast cancer with similar or improved efficacy to trastuzumab and a better safety profile. This randomized phase III trial has been designed as a non-inferiority study to address these questions.

2.7 Correlative Studies

A major need in the treatment of advanced breast cancer is the ability to understand which patients benefit from which therapy, assess mechanisms of resistance and provide a rationale for treatment with a specific regimen. In the setting of advanced breast cancer this becomes even more crucial as limitations of treatment options, time and economic realities come to bear on the patient. Within the setting of a head to head trial of two anti HER2/neu therapies there is the opportunity to try to define the optimal use of both of these therapies.

2.7.1 *Molecular Biomarkers*

All patients entered into this study will have HER2/neu testing performed by a local or the central (Centre for Translational and Applied Genomics (CTAG) at the British Columbia Cancer Agency (BCCA), Vancouver, BC, Canada) laboratory, prior to randomization. Patients who fulfill the criteria for HER2/neu positivity as outlined in section 5.1.3 will be eligible for randomization, if the other eligibility criteria as outlined in section 5 are also met. Centralized HER2/neu testing using both immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) will also be performed following randomization, for those patients randomized to the trial through local laboratory results. A diagnostic tumour tissue block of formalin fixed paraffin embedded tissue (FFPE) with sufficient invasive tumour present must be submitted to the central laboratory for the HER2/neu investigation. HER2/neu positivity defines the population of interest for this trial and the targeted agents, trastuzumab and lapatinib being investigated.

Other standard molecular biomarkers will be evaluated using this same diagnostic tumour block. After the HER2/neu testing is complete, using whole sections, a tissue microarray (TMA) will be constructed. Standard molecular markers including ER, PgR, EGFR, Ki67, and CK5/6 will be evaluated from the TMA.

Additional markers to evaluate resistance/sensitivity patterns for both trastuzumab and lapatinib will be of interest in this trial. Previous work using breast cancer cell lines have suggested that resistance to trastuzumab may involve abnormalities in PTEN, IGFR and EGFR/other receptor-signaling pathway components including other phosphoproteins. These and other markers will be assessed. This work will be done by the use of IHC.

Specific candidate gene mutation screening to test whether somatic mutations segregate with treatment response will be of interest. Commonly mutated genes include *TP53* and *PI3KCA*. Other genes of interest include Her1-4 and PTEN with other possible candidates emerging. This work will be done on DNA extracted from either FFPE tissue or whole blood.

Another area of interest is the development of genomic marker sets that may define treatment response groups and/or patients likely to develop particular adverse effects of treatment. Current approaches to this would involve genome wide copy number/ LOH analysis, expression profiling including micro RNAs, in combination with Q-PCR assessment of the currently emerging prognostic panels. This work would involve the coring of the FFPE tumour block and subsequent nucleic acid extraction.

Other markers which may be helpful in predicting treatment response and outcomes include circulating tumour cells, sheddases, osteopontin and HER2/neu dimerization markers using tissue, serum and plasma. These may be assessed at baseline and at the time of progression.

A specific sub-study looking at molecular changes in breast cancer where metastasis develops will be an optional part in this trial. For consenting patients, a biopsy from a metastatic lesion will be required at the time of randomization, and a subsequent biopsy at progression. Centre participation to this sub-study is optional (see section 13.3.4).

For consenting patients, serum for potential proteomic studies will also be collected at baseline and at the time of disease progression.

2.7.2 *Pharmacogenetics*

In the past few years, the pharmacogenetics of small molecular kinase inhibitors has led to a number of intriguing findings regarding predictors of outcome and toxicity in various cancers. Little is known about the pharmacogenetics of lapatinib which targets EGFR and HER2/neu. There is however data supporting the potential role of genetic polymorphisms in the response and toxicity in patients treated with traditional EGFR TKIs. Data also exists indicating the importance of polymorphisms in the drug detoxification pathways of other drugs that use the same metabolizing enzymes as lapatinib does. There might be important polymorphisms associated with HER2/neu. Given the lack of data with lapatinib thus far, there is the potential to extend findings with other EGFR TKI studies in other cancers (e.g. lung cancer) to the current setting, as a means of exploring potential pharmacogenetic factors affecting lapatinib outcomes. Comparison to the trastuzumab treatment arm will allow the determination of whether any associations found are related only to kinase inhibitors or more generally to patient prognosis, by looking at treatment interactions with expression levels of investigated polymorphisms. Since taxanes and lapatinib share a number of detoxification pathways (CYPs), this evaluation will also be relevant to taxane pharmacogenetics. A whole blood sample will be collected for genotyping at baseline prior to the start of any drug administration.

2.8 Quality of Life

Quality of life (QOL) is relevant to metastatic cancer patients as it measures, from the patient perspective, the possible benefit from an intervention, in addition to prolongation of survival.

The primary QOL hypothesis in this trial is that lapatinib and trastuzumab are associated with similar effects in overall QOL. It is especially important to confirm that one treatment is no more deleterious than the other from a QOL perspective in a non-inferiority trial such as this one. Further justification for measuring QOL in this study is as follows:

- Previous studies have shown that measuring QOL provides additional information compared to measuring adverse events alone *[Huschka 2007, Paul 1991]*.

- Measuring QOL is especially important when comparing treatments with a unique adverse event profile. Trastuzumab is a well tolerated drug with a known association with infusion-related reactions in about 40% of patients and clinical heart failure in a small minority of patients. Adverse events associated with lapatinib include diarrhea (42%), rash (31%), nausea (13%) and fatigue (10%) *[Burris 2005, Geyer 2006, May 2006]*. For rash in particular, there is an acne-like rash associated with tyrosine kinase inhibitors that typically appears between days 10-14 and peaks by weeks 3 to 5 of treatment *[Agero 2006]*. The impact of this rash has been studied in both cancer and non-cancer patient populations. With respect to non cancer populations, an acneiform rash appears to impact on emotions, its impact is greater in females compared to males and appears to decrease over time with continued treatment *[Jones-Caballero 2007]*. In contrast, a clinical trial of the tyrosine kinase inhibitor erlotinib versus placebo in metastatic lung cancer patients (65% males) *[Shepherd 2005]* showed improvement in emotional functioning as measured by the EORTC QLQ-C30 in patients on erlotinib versus patients on placebo (rash 76% vs. 17%) *[Bezjak 2006]*. Since the present study involves a female population who may also have chemotherapy-induced changes in their physical appearance, the additional effects brought on by lapatinib may impact their QOL (e.g. social functioning).

- The route of delivery of protocol therapy may be important. In this trial, lapatinib will be given orally and trastuzumab intravenously. This may affect patient preference. Previous studies involving patients with colorectal cancer and in which two regimens with similar efficacy but different routes of administration were compared (5-FU + leucovorin, intravenous versus capecitabine, oral) showed conflicting results. Pfeiffer et al. conducted a randomized cross-over trial comparing these two regimens. After 12 weeks, patients were asked about their preference: 61% preferred the intravenous regimen and 39% the oral regimen *[Pfeiffer 2006]*. Another study of a similar design showed the opposite, with the majority of patients preferring the oral chemotherapy *[Twelves 2006]*. In this trial, patient preference will not be assessed directly since there is no cross-over. However, we will inquire about the burden of route of administration and of coming to the hospital.

QOL assessments will be conducted at baseline, every 12 weeks until week 96 and then every 24 weeks thereafter, matching the radiological assessments. Questionnaires will also be completed at the time of off treatment if the reason for off treatment is adverse events (since these adverse events may have an impact on QOL) and at the time of disease progression. Two instruments will be used to capture the QOL experience of patients, the EORTC QLQ-C30 and a Trial Specific Checklist.

EORTC QLQ-C30

The EORTC QLQ-C30 will be used to capture the multidimensionality of QOL in metastatic breast cancer. The EORTC QLQ-C30 is a widely used, cancer specific HR QOL questionnaire which is well accepted by patients *[Aaronson 1993, Conroy 2004]*. It contains five functional subscales (physical, role, cognitive, emotional, social), three multi-item symptom subscales (fatigue, pain and nausea), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact) and a global health measure (physical condition and global QOL). The questionnaire uses 4 and 7-point scales. For each subscale, the range of possible scores is between 0 and 100. Convergent and criterion validity has been demonstrated for this questionnaire in metastatic breast cancer *[Bottomlay 2004, McLachlan 1998]* and reliability is adequate *[Aaronson 1993, Hjermstad 1995]*. The EORTC QLQ-C30 has been shown to be responsive to change associated with chemotherapy and with disease progression *[Osoba 1998, Lemieux 2007]*. The questionnaire is available in multiple languages.

Trial Specific Checklist

Because there are no questions in the EORTC QLQ-C30 regarding skin rash and no questionnaires exist to specifically measure skin toxicity in cancer patients, the following two questions will be added to the Trial Specific Checklist, as follows:

- Did you have skin rash?
  (If you answered "Not at all" skip the following question. If you answered "A Little", "Quite a Bit" or "Very Much" go to the next question)
- Were you bothered by skin rash?

Two other items will also be added to test the impact of the route of drug administration:

- Have you been bothered by taking your prescribed study therapy (oral lapatinib or intravenous trastuzumab)?
- Have you been bothered by having intravenous treatment?

Each of these items will be scored individually and transformed on a scale of 0-100, with the highest score being associated with increased burden.

The Trial Specific Checklist items described above were selected following a search of the NCIC CTG QOL data bank and items currently in use in other trials. The resultant Checklist is comprised of items (with some modifications) from other NCIC CTG studies that have previously assessed rash and impact of route of drug administration.

Completion of the Trial Specific Checklist will be mandatory for all patients. Translations will be provided, as necessary.

2.9 Economic Evaluation

In the past few years, the identification of novel molecular markers has led to the introduction of targeted therapies. Trastuzumab has become the prototype of an increasing stream of "smart" drugs. In this study, trastuzumab is being compared to a novel targeted therapy, lapatinib. A formal economic evaluation based on best clinical data available (i.e. randomized clinical trial) would help understand the potential trade offs and overall cost-effectiveness of these agents. The collection of economic data in this setting will be of particular interest given that breast cancer is a common disease and targeted therapies are expensive.

Economic evaluation in this study will be conducted for Canadian and Australian patients only. The perspective of this evaluation will be that of the Canadian and Australian governments as payers in a universal access health care system.

As part of the economic evaluation in this study, patient preferences, or utilities, will be measured using the EQ-5D questionnaire *[Brooks 1996, Drummond 1997, www.euroqol.org]*. The EQ-5D self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining one level from each of the five dimensions. The EQ VAS records the respondent's self-rated health status on a vertical graduated (0-100) visual analogue scale. The EQ-5D is a validated instrument that has been used in population surveys and clinical trial settings. Analysis will be performed as detailed in the statistical section of the protocol (see section 14).

The health economic evaluation will be completed using existing case report forms and source documentation for each Canadian and Australian patient. Health care resource utilization related to the study drug but not protocol driven, such as supportive care medication, laboratory tests, imaging studies, radiotherapy, transfusions, hospitalization, and outpatient care, including physician, emergency room and home care visits, will be documented. To capture the use of resources due to outpatient care, additional resource utilization care report forms will be used. Utility assessments and resource utilization will be measured at baseline and at predetermined intervals on both arms of the study, until disease progression.

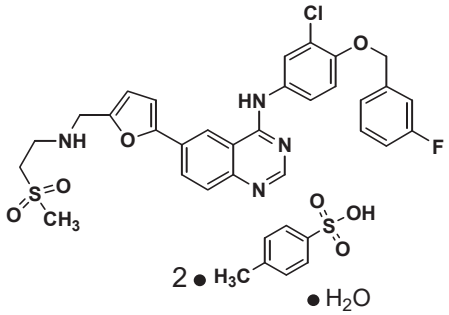
3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Lapatinib

3.1.1 *Name and Chemical Information*

GW572016F denotes the ditosylate monohydrate salt of the free base, GW572016X. Each tablet contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet.

3.1.2 Chemical Structure



Formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$

Appearance: Yellow, solid.

3.1.3 *Mechanism of Action*

Lapatinib is an orally active, reversible, small molecule tyrosine kinase inhibitor that potently inhibits both EGFR and HER2/neu tyrosine kinase activity.

The human EGFR receptor family consists of four transmembrane glycoproteins involved in transmission of signals controlling cell growth and differentiation. EGFR and HER2/neu are closely related members of the Type I family of receptor tyrosine kinases (TK). These growth factor receptors consist of an extracellular ligand binding domain, a single transmembrane domain, an intracellular tyrosine kinase catalytic domain, and a tyrosine rich cytoplasmic tail. Ligand binding induces the formation of receptor hetero- and homodimers with EGFR family members. Dimerization allows the catalytic domain of one receptor monomer to phosphorylate tyrosine residues on the adjacent intracellular domain of the other monomer in the pair. Autophosphorylation of tyrosine residues (p-Tyr) on the cytoplasmic tail creates specific binding sites for SH2 domain containing proteins. The recruitment of SH2 domain containing proteins to the receptor activates signal transduction pathways that initiate cell proliferation *[Ullrich 1990]*. As a result of this signal transduction mechanism, compounds that inhibit the intrinsic tyrosine kinase activity will block the biological activity of the receptor.

Overexpression of EGFR or HER2/neu has been reported in a variety of human tumours *[Davies 1993, Hung 1999]*, and has been associated with poor prognosis and reduced overall survival in patients with cancer *[Slamon 1987, Sainsburry 1985, Salomon 1995]*. Induced overexpression of these receptors in cells *in vitro* produces phenotypes associated with oncogenic transformation such as the ability to grow in soft agar and form tumours in nude mice *[Hudziak 1987, Riedel 1988]*. Thus, a drug that blocks the tyrosine kinase activity of EGFR or HER2/neu should block the transforming activity that results from overexpression of the receptor.

3.1.4 *Experimental Antitumour Activity*

Lapatinib is a potent inhibitor of EGFR and HER2/neu receptor tyrosine phosphorylation in intact cells and is a potent and selective inhibitor of growth in ErbB-driven human transformed cell lines *in vitro* (IC_{90} values $\leq$ 2.66 μM) *[Rushnak 2001]*. It decreases the phosphorylation of EGFR and HER2/neu as well as the downstream signaling molecules, Akt and Erk1,2, resulting in either tumour cell growth arrest or tumour cell apoptosis *[Rusnak 2001, Konechy 2006]*. Lapatinib is also a potent inhibitor of growth in EGFR and HER2/neu overexpressing subcutaneous tumour xenografts in mice, as well as tumours expressing moderate levels of both receptors; phosphorylated EGFR and HER2/neu reduction was correlated with tumour growth inhibition. *In vivo*, tumour suppression or tumour regression was seen *[Rusnak 2001]*. Thus, the available data support EGFR and HER2/neu receptor tyrosine kinase inhibition as the mechanism of action of lapatinib.

3.1.5 *Animal Toxicology*

The principal findings in repeat dose toxicology studies in rats and dogs with lapatinib have been attributed to exaggerated pharmacology and included decrements in body weight, organ weight changes, epithelial effects in multiple target organs and clinical pathology alterations at doses $\geq$ 60 mg/kg/day in rats and $\geq$ 40 mg/kg/day in dogs. The epithelial effects were qualitatively similar to the rash or rash-like symptoms and GI-related events seen in patients receiving lapatinib in combination with capecitabine or as monotherapy. At higher doses, the epithelial effects were not tolerated in pre-clinical species. No cardiac toxicity or interstitial pneumonia, toxicities known to be associated with HER2/neu antibodies and EGFR inhibitors, respectively, occurred in studies of up to 9 months duration. The no-observed adverse effect level (NOAEL) in male and female rats was 60 mg/kg/day and 10 mg/kg/day, respectively, with AUC estimates of 24705 ng.h/mL and 25052 ng.h/mL, respectively. The NOAEL in male and female dogs was 10 mg/kg/day with AUC estimates of 5425 ng.h/mL and 8155 ng.h/mL, respectively. Corresponding systemic exposures at these dose levels were 0.68- and 5-fold the estimated efficacious human exposure for male and female rats, respectively, and were approximately equal to the human exposure in dogs. These ratios are considered acceptable in light of the seriousness of the indication and the established significant clinical benefit. The data from genotoxicity assessments suggest that lapatinib does not present a genotoxic hazard to humans, nor were there any safety or secondary pharmacology findings of concern for clinical use. In addition, there were no reproductive or developmental hazards identified, although post-natal survival was reduced at $\geq$ 60 mg/kg/day in the pre- and post-natal study.

In conclusion, the effects observed in preclinical toxicity studies were either directly or indirectly associated with the pharmacologic action of lapatinib, showed differences in species responsiveness relative to systemic exposure and duration of treatment, and are consistent with the findings seen to date in patients. These nonclinical safety data support the use of lapatinib in the target patient population.

3.1.6 *Phase I Trials*

A total of 385 healthy volunteers have been enrolled in 11 phase I studies; 375 volunteers received lapatinib, nine received placebo, and one did not receive treatment. No deaths or SAEs were reported in the healthy volunteer studies. Most AEs reported in healthy volunteers were considered mild and resolved spontaneously. Overall, the most frequently reported AEs were headache, gastrointestinal-related events (diarrhea, loose stools, dyspepsia, gas, and flatulence), and rash. Lapatinib was well tolerated and there were no consistent lapatinib-related changes in physical examination, hematology, clinical chemistry, ECG, urinalysis, or ophthalmologic examinations.

A total of 723 subjects with cancer have been enrolled in 22 phase I studies and in the phase I component of a phase I/II study; 247 subjects received single-agent lapatinib in six phase I studies and 476 subjects received lapatinib in combination with chemotherapeutic or hormonal anticancer treatments in 15 phase I studies, one phase I rollover study and in the phase I component of a phase I/II study. Most AEs reported in the lapatinib monotherapy studies were mild to moderate in intensity with the most frequently reported AEs being diarrhea, rash, nausea, fatigue, and anorexia. In studies of lapatinib in combination with chemotherapeutic agents and hormonal agents, the AEs were similar to those seen with each individual agent although the frequency and intensity were greater for certain lapatinib and chemotherapy combinations. In phase I lapatinib studies in subjects with cancer, there were no consistent lapatinib-related changes in physical examination, hematology, clinical chemistry, ECG, urinalysis, or ophthalmologic examinations.

The optimal therapeutic regimen doses of combination lapatinib/paclitaxel and lapatinib/docetaxel have been determined *[Lapatinib Investigator Brochure, April 2008]*. In study EGF10009, lapatinib 1500 mg po daily in combination with paclitaxel 80 mg/m^2 IV weekly was found to be feasible and tolerable. The most common adverse events, regardless of relationship to study drug, were diarrhea (92%), vomiting (83%), fatigue (75%), alopecia (67%), anorexia (58%), nausea (58%), rash (58%), constipation (50%), and arthralgia (42%). The majority of these events were of grade 1 or 2 intensity.

For docetaxel, the recommended combination regimen was lapatinib 1250 mg daily in combination with docetaxel 75 mg/m^2 every 3 weeks with growth factor support *[Lo Russo 2008]*. In 52 patients receiving lapatinib (1000 to 1500 mg daily) plus docetaxel (50 to 75 mg/m^2) the most common adverse events, regardless of relationship to study drug, were diarrhea (71%), rash (54%), nausea (31%), vomiting (31%), fatigue (48%), mucosal inflammation (27%), alopecia (25%) and anorexia (38%). Most were grade 1 or 2 intensity. In this study of heavily pretreated subjects with advanced disease, approximately 4% and 10% experienced grade 3 and 4 neutropenia, respectively. For the current study, G-CSF will be required as primary prophylaxis for neutropenia for patients receiving docetaxel and lapatinib.

3.1.7 *Phase II Trials in Breast Cancer*

Study EGF20002, was conducted in 78 female subjects with advanced (Stage IIIb) or metastatic (Stage IV) breast cancer who had progressed while receiving trastuzumab-containing regimens (monotherapy or combined therapy). A positive tumour response (CR or PR) was seen in a total of 4 subjects based on independent review (6 subjects based on investigator review). The duration of response ranged from 50 to 113 days and median time to tumour progression was 15.3 weeks based on independent review.

Study EGF20008 was conducted in female subjects with advanced (Stage IIIb) or metastatic (Stage IV) breast cancer refractory to treatment with anthracycline-, taxane- and capecitabine-containing regimens. Subjects enrolled in Cohort A (N=140) had HER2/neu overexpressing tumours and were refractory to treatment with trastuzumab-containing regimens. Subjects enrolled in Cohort B (N=89) had HER2/neu non-overexpressing tumours and had no prior treatment with trastuzumab. A total of seven subjects in Cohort A had a positive tumour response (CR or PR) based on either independent panel or investigator review. The duration of response ranged from 55 to >250 days (8 to >36 weeks). There were no responders in Cohort B. The median progression-free survival interval was 9.1 weeks in Cohort A and 7.6 weeks in Cohort B based on independent review. The median survival time was 29.4 weeks for subjects in Cohort A and 18.6 weeks for subjects in Cohort B.

Study EGF20009 was conducted in 138 previously untreated patients with HER2/neu positive locally or advanced metastatic breast cancer *[Gomez 2006]*. Patients were randomized to 2 doses of lapatinib (1500 mg daily or 500 mg twice daily). A total of 33 (24%) patients demonstrated a partial response based on independent review. Median time to treatment failure was 17.0 weeks on 500 mg twice daily and 15.7 weeks on 1500 mg daily. Progression-free survival rates at 6 months were 45% and 41%, respectively. Tumour response rate data are comparable to those reported with trastuzumab monotherapy in a similar patient population: 34% in a FISH-positive subgroup *[Vogel 2002]*.

Data suggest that lapatinib may have antitumour activity in the central nervous system *[Lin 2007a]*. In study EGF105084, 237 patients with HER2/neu breast cancer and brain metastases with progressive disease or relapse on trastuzumab were treated with lapatinib 750 mg twice daily. Fifteen patients (6.3%) met volumetric criteria for partial response. The median time to tumour progression in these 15 patients was 1.6months.

3.1.8 *Phase III Trials in Breast Cancer*

Approval of lapatinib was based on phase III study EGF100151in 399 patients with pretreated breast cancer refractory to trastuzumab. Patients were randomized to combination lapatinib and capecitabine compared to capecitabine alone. An increased time to progression (TTP) was seen with the combination therapy compared to capecitabine alone (HR=0.57, p<0.001) *[US Package Insert August 2007]*. No increase in serious adverse events including symptomatic cardiac events was seen with the addition of lapatinib to capecitabine. In addition, there were fewer central nervous system metastases in the combination arm (4 versus 13 events, p=0.0445).

Results from the phase III double blind EGF30001 study of lapatinib plus paclitaxel versus placebo plus paclitaxel in 580 patients with incurable Stage IIIb/IIIc/IV breast cancer at first diagnosis or relapse, untested or negative (0/1+ IHC or FISH neg) for HER2 were recently presented at the 43rd American Society of Clinical Oncology (ASCO) annual meeting *[Di Leo 2007]*. Overall, treatment was well tolerated. No difference in TTP was seen between the treatment arms; median TTP (by independent review) was 33.7 and 26.1 weeks for the combination and monotherapy arms, respectively; hazard ratio = 0.82 (95% CI 0.65 to 1.04); p=0.094. However, in a subset analysis of patients with HER2/neu positive disease on central testing (n=91), TTP was significantly improved with combination therapy compared with monotherapy; median TTP was 8.1 versus 5.8 months; HR=0.57, 0.34 to 0.93; p=0.011.

3.1.9 *Pharmacokinetic Studies*

Data from healthy male and female subjects following a single 250 mg/kg oral dose of ^{14}C-lapatinib have been assessed. In this study, fecal excretion was the predominant route of elimination, accounting for a median of 91.8% (range of 60.3% to 98.4%) of the recovered dose. Urinary excretion was minimal (median of 1.16%; range of 0.49% to 1.61%). Excretion of radioactivity was complete by 168 hours. The median total recovery of radioactivity was 93.1% despite low recoveries from two subjects (61.7% to 71.5%). The metabolism of lapatinib appears to be mediated primarily through CYP3A enzymes. The metabolism pathways of lapatinib consists primarily of oxidation.

The potential for metabolic interactions between lapatinib and co-therapies such as paclitaxel, docetaxel and vinorelbine was evaluated in studies using pooled human liver microsomes. Lapatinib inhibited the metabolism of paclitaxel by CYP3A4 (K_i = 1.1 μM). Lapatinib had only a modest effect (< 2-fold) on the microsomal half-life of docetaxel and vinorelbine. This suggests that lapatinib is likely to interact with paclitaxel but has little potential for interaction with docetaxel or vinorelbine.

GW690006, a phenol metabolite of lapatinib, was glucuronidated by human liver microsomes and recombinant human UDP-glucuronosyltransferases (UGTs) UGT1A1, 1A3, 1A4, 1A8, 1A9 and 1A10, but not by UGT1A6, 1A7, 2B7 or 2B15. The large number of UGT enzymes that can conjugate GW690006 indicate that interactions due to inhibition of UGT by other drugs are unlikely. Further, at concentrations up to 150 μM (87.1 μg/mL), lapatinib did not inhibit UGT activities in human liver microsomes (1A1, 1A3, 1A6, 1A9, 2B4, 2B7 and 2B15), suggesting that lapatinib is unlikely to inhibit the clearance of drugs that are glucuronidated.

A series of *in vitro* and *in vivo* studies demonstrated that lapatinib is mainly metabolized by CYP3A4 and 3A5 and is a substrate for the human Pgp and murine BCRP efflux transporters. Lapatinib, at relevant human concentrations (C_{max} = 4.2 μM; 2.4 μg/mL), inhibits 3A4 and other CYPs and inhibits transporters; human Pgp, murine Bcrp and OATP 1B1.

The greatest potential for drug interactions is with CYP3A inhibitors (ketoconazole) or inducers (carbamazepine) that may alter the pharmacokinetics of lapatinib. Lapatinib may also alter the pharmacokinetics of drugs metabolized by CYP3A or CYP2C8 (e.g. paclitaxel, statins), and may interact with co-medications that are substrates of human Pgp, BCRP or OATP 1B1 (e.g. digoxin or statins). Interactions that are unlikely include enhancing the CNS distribution of lapatinib as most marketed drugs are not potent inhibitors of these efflux transporters *[Hsiao, 2006]*. Interactions with substrates of renal transporters (e.g. methotrexate or antibiotics) are also unlikely. Lapatinib is not likely to induce CYP-mediated clearance of other drugs and no interaction via UGTs or Flavin-Contaning Mono-oxygenases (FMOs) is indicated. The potential for in vitro protein binding displacement of [^{3}H]-docetaxel by lapatinib was investigated by using ultrafiltration in pooled human plasma alone, and in pooled human plasma supplemented with 100 or 250 mg/dL of α1-acidglycoprotein (AAG). No notable protein binding displacement of [^{3}H]-docetaxel by lapatinib was observed.

3.1.10 *Pharmaceutical Data*

Supplied:
Lapatinib will be provided in high-density polyethylene (HDPE) bottles with a child-resistant closure, packaged with 90 tablets per bottle. Each bottle will be labelled with the protocol number, dosing instructions, storage instructions, along with the name and address of the sponsor. The contents of the label will be in accordance with all applicable regulatory requirements. Lapatinib Ditosylate Monohydrate Tablets, 250 mg, are oval, biconvex, orange, film coated tablets that are debossed on one side with FG HLS. The tablets contain 410 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet.

Stability:
Lapatinib tablets have been tested after storage at 30°C/65% RH for up to 18 months and at 40°C / 75% Relative Humidity for up to 6 months. All data complied with specifications after storage at these conditions.

Storage:
Lapatinib should be stored at room temperature (up to 30°C) and protected from light. Unopened bottles are stable until the date indicated on the package label when stored under these conditions.

Route of Administration:
Oral.

Suspension Preparation:
In exceptional circumstances only, lapatinib may be suspended (dispersed) in water for ease of consumption. The suspension preparation is as follows: Place 120 mL (4 oz) of water in a glass container, then add the required lapatinib tablets to the container; add 5 tablets when given concurrently with taxane therapy and 6 tablets when single-agent therapy. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10 minutes or until it is fully dispersed. Stir the container for 5 seconds then administer. Rinse the container with 2 oz of water and repeat the administration process. This completes the administration process (total of 6 oz of liquid is dispensed).

3.2 Trastuzumab

3.2.1 *Background Drug Information*

Trastuzumab is a recombinant humanized anti-$p185^{HER-2}$ monoclonal antibody that binds specifically and with high affinity to the HER2/neu protein extracellular domain. Trastuzumab has been shown to inhibit the proliferation of human tumour cells that overexpress HER2/neu both *in vitro* and *in vivo* and may also have direct tumour cell killing potential against HER2/neu overexpressing tumour cells. In North America and much of Europe, trastuzumab is approved as monotherapy for the treatment of patients with metastatic breast cancer whose tumours overexpress the HER2/neu protein and who have received one or more chemotherapy regimens for metastatic disease, as well as in combination with paclitaxel in patients whose tumours overexpress the HER2/neu protein and who have not received prior chemotherapy for their metastatic disease.

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, or reduced ejection fraction (EF), have been observed in patients treated with trastuzumab. Congestive heart failure (CHF) associated with trastuzumab therapy may be severe and in a few cases has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines or who had received prior anthracycline therapy. Based on this patient and laboratory data, it is recommended that all candidates for treatment with trastuzumab undergo both thorough baseline cardiac assessment and cardiac function monitoring at regular intervals during treatment. Cardiac monitoring is particularly important for patients who have received prior anthracycline based chemotherapy. Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction. The discontinuation of trastuzumab therapy should be strongly considered in patients who develop clinically significant CHF, unless the benefits for an individual patient are deemed to outweigh the risk. In previous clinical experience, most patients with cardiac dysfunction responded to appropriate medical therapy (often including discontinuation of trastuzumab), however the safety of continuation or resumption of trastuzumab in patients who develop cardiotoxicity has not been studied. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring of cardiac function (e.g. every 6 to 8 weeks), and this is recommended. If patients have a continued decrease in LVEF, but remain asymptomatic, therapy discontinuation should be considered if no clinical benefit of trastuzumab therapy has been observed.

In terms of infusion-associated symptoms, a symptom complex most commonly consisting of chills and/or fever has been observed in about 40% of patients during the first infusion of trastuzumab. The symptoms were usually mild to moderate in severity, were effectively treated with acetaminophen, diphenhydramine, or meperidine and infrequently necessitated drug discontinuation. Other infrequently reported signs and/or symptoms associated with the first trastuzumab infusion included nausea, vomiting, pain (in some cases at tumour sites), rigors, headache, dizziness, dyspnea, hypotension, rash, and asthenia. The incidence and recurrence of such symptoms was substantially lower with subsequent trastuzumab infusions. Serious adverse reactions to trastuzumab infusion, including dyspnea, hypotension, wheezing bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, have been reported infrequently, the majority in patients with known pulmonary metastases. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of trastuzumab as indicated. In rare cases, these events were associated with a clinical course culminating in a fatal outcome, and patients with dyspnea at rest due to pulmonary metastases were at increased risk of such a fatal infusion reaction.

Frequently observed adverse events of trastuzumab include anemia, leukopenia, diarrhea and infections (primarily mild upper respiratory infections of minor clinical significance, and central venous catheter infections).

In this trial trastuzumab will be administered intravenously either q weekly or q 3 weekly (see section 8.0 for complete details).

3.3 Paclitaxel

3.3.1 *Background Drug Information*

Paclitaxel is a commercially available anticancer agent used in the management of ovarian and breast cancer. It acts at the cellular level as a promoter of microtubule assembly. Paclitaxel binds preferentially to microtubules, rather than the subunit tubulin dimers, thus stabilizing microtubules and inhibiting the normal dynamic reorganization of the microtubule network. These events culminate in cell death.

Paclitaxel's primary toxic effects include myelosuppression (mostly neutropenia), peripheral neuropathy, arthralgias and myalgias and hypersensitivity reactions. These latter are seldom severe when the drug is infused after appropriate premedication regimens. A series of phase II and subsequent phase III trials have established the efficacy of paclitaxel firstly as a single agent treatment for early and advanced disease and more recently as part of the frontline combination management of this disease.

In this trial paclitaxel will be administered intravenously at 80 mg/m^2 q weekly (see section 8.0 for complete details). Anti-hypersensitivity premedication, in line filtration and the use of appropriate PVC-free tubing and bags are required as per the manufacturer's instructions.

3.4 Docetaxel

3.4.1 *Background Drug Information*

Docetaxel is a semisynthetic analogue of paclitaxel, using a precursor extracted from the needles of the European yew, Taxus baccata. Docetaxel has a mechanism of action which is similar to (or may be identical to) paclitaxel i.e. it enhances microtubule assembly and inhibits the depolymerization of tubulin. As with paclitaxel, this can lead to bundles of microtubules in the cell, which by blocking cells in the M-phase of the cell cycle, results in the inability of the cells to divide. This contrasts with the action of other spindle poisons in clinical use such as colchicine or vinca-alkaloids which inhibit tubulin assembly in microtubules.

Hematologic adverse events observed with docetaxel include neutropenia, anemia and thrombocytopenia. The non-hematologic adverse effects which occurred in more than 20% of patients included alopecia, skin disorders, neurotoxicity, gastrointestinal adverse effects, acute hypersensitivity reaction (AHSR), asthenia, mucous membrane disorders, nail disorders, fluid retention and myalgia.

Fluid retention (mostly edema, pleural effusion and weight gain), acute hypersensitivity reactions (AHSR), and skin reactions (erythema, pruritus, dry skin, macular rash, swelling, burning and desquamation) have presented problems in the clinical development of docetaxel. A number of premedication regimens have been used to attempt to ameliorate these reactions. These have included antihistamines only (anti H1 and/or anti H2), short term corticosteroids (< 2 days +/- anti H1) or long term corticosteroids (> 2 days) given prior to docetaxel.

In this trial docetaxel will be administered intravenously, at a dose of 75 mg/m^2 q 3 weekly (see section 8.0 for complete details).

4.0 TRIAL DESIGN

This is a multi-centre, multinational, randomized, open-label, phase III study comparing combination taxane based chemotherapy plus lapatinib to combination taxane based chemotherapy plus trastuzumab in women with documented evidence of HER2/neu positive breast cancer (by local or central laboratory testing), which is metastatic and with no prior chemotherapy or HER2/neu targeted therapy in the metastatic setting.

4.1 Stratification

Patients will be stratified by:
- Prior (neo)adjuvant HER2/neu targeted therapy (yes, no)
- Prior (neo)adjuvant taxane chemotherapy (yes, no)
- Planned taxane treatment (q weekly paclitaxel versus 3 weekly docetaxel)
- Liver metastasis (yes, no)

4.2 Randomization

Patients will be randomized to one of the following treatments to a planned sample size of approximately 600 patients (so as to achieve 536 centrally confirmed HER2/neu positive patients):
- Taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib
- Taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab.

The choice of taxane will be up to the treating physician and it must be specified at the time of patient randomization. Once a particular taxane is chosen, the patient may not be switched to the other taxane.

Arm	Agent(s)	Dose & Schedule	Route	Duration
1	Taxane based chemotherapy *plus* Lapatinib	Lapatinib: 1250 mg daily	po	24 weeks
		Paclitaxel: 80 mg/m^2 q weekly (days 1, 8 and 15 of a 4-week cycle)	IV	
		OR		
		Docetaxel: 75 mg/m^2 q 3 weekly (day 1 of a 3-week cycle) *plus*	IV	
		G-CSF: dose/route according to institutional standards		
	Lapatinib	1500 mg daily	po	to follow concurrent lapatinib/taxane treatment; treat until progressive disease
2	Taxane based chemotherapy *plus* Trastuzumab	Trastuzumab: q weekly (loading dose 4 mg/kg, subsequent doses 2 mg/kg)	IV	24 weeks
		Paclitaxel: 80 mg/m^2 q weekly (days 1, 8 and 15 of a 4-week cycle)		
		OR		
		Trastuzumab: q 3 weekly (loading dose 8 mg/kg, subsequent doses 6 mg/kg)		
		Docetaxel: 75 mg/m^2 q3 weekly (day 1 of a 3 week cycle)		
	Trastuzumab	Trastuzumab: 6 mg/kg q 3 weekly	IV	to follow concurrent trastuzumab/taxane treatment; treat until progressive disease

5.0 STUDY POPULATION

Women with documented evidence of HER2/neu positive breast cancer (by local or central laboratory testing), which is metastatic and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to requesting randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histologically confirmed adenocarcinoma of the breast.

5.1.2 Metastatic breast cancer (stage IV) at primary diagnosis or at relapse after curative intent therapy.

5.1.3 Local or central* laboratory confirmed HER2/neu overexpressing and/or amplified disease in the invasive component of the primary or metastatic lesion as defined by:

- 3+ over expression by IHC (> 30% of invasive tumour cells);
- 2+ or 3+ (in 30% or less neoplastic cells) overexpression by IHC AND fluorescence or chromogenic *in situ* hybridization (FISH/CISH) test demonstrating HER2/neu gene amplification;
- HER2/neu gene amplification by FISH/CISH (> 6 HER2/neu gene copies per nucleus, or a FISH/CISH ratio (HER2 gene copies to chromosome 17 signals) of $\geq$ 2.2)

Note: Patients with a negative or equivocal overall result (FISH/CISH test ratio of < 2.2, $\leq$ 6.0 HER2/neu gene copies per nucleus and staining scores of 0, 1+, 2+ or 3+ (in 30% or less neoplastic cells) by IHC) are not eligible for participation in the trial.

* *Central laboratory confirmation prior to randomization will occur in instances where local HER2/neu testing is not available or where the result of the local HER2/neu testing is equivocal and confirmatory testing is not available.*

5.1.4 Formalin fixed, paraffin embedded tumour tissue block from the invasive component of the primary or metastatic lesion must be available for central HER2/neu testing to occur either prior to (if no local HER2/neu testing available or if the result of the local HER2/neu testing is equivocal) or after randomization. In addition, the tumour tissue block will be used for central laboratory testing of the mandatory tumour phenotype markers ER, PgR, EGFR, CK5/6 and Ki67, once study accrual is completed. This requires the submission of a paraffin block containing sufficient primary tumour tissue for HER2/neu analysis and the mandatory tumour phenotype markers to the central laboratory (Centre for Translational and Applied Genomics (CTAG) at the British Columbia Cancer Agency (BCCA), Vancouver, BC, Canada). Where required by the enrolling institution, tissue blocks will be returned after sampling. Failure to provide blocks for central HER2/neu testing will exclude patients from randomization. Where local centre regulations prohibit submission of blocks of tumour tissue, or where slides are the only available source of tissue, the approval of the NCIC CTG must be sought on whether such patients may be admissible for randomization to the study.

5.1.5 Patients must have evidence of metastatic disease, but measurable disease is not mandatory. To be considered evaluable for the overall response rate (complete and partial response), patients must have at least one measurable lesion as follows:

- X-ray, physical exam $\geq$ 20 mm
- Conventional CT scan, MRI $\geq$ 20 mm
- Spiral CT scan $\geq$ 10 mm

5.1.6 Prior treatment with chemotherapeutic agents including taxanes in the neoadjuvant or adjuvant setting is permitted provided that at least 12 months has elapsed since the last dose of therapy and all treatment related adverse events are $\leq$ grade 1 at the time of randomization.

5.1.7 Prior treatment with HER2/neu targeted therapy in the neoadjuvant or adjuvant setting is permitted provided that at least 12 months has elapsed since last dose of HER2/neu targeted therapy and all treatment related adverse events are $\leq$ grade 1 at the time of randomization.

5.1.8 Prior treatment with endocrine therapy in the neoadjuvant or adjuvant or metastatic setting is permitted provided that therapy has been discontinued and all treatment related adverse events are $\leq$ grade 1 at the time of randomization.

5.1.9 Prior treatments with radiation therapy in the adjuvant and/or metastatic setting are permitted provided that at least 2 weeks have elapsed since the last fraction of radiation therapy and all treatment related adverse events are $\leq$ grade 1 at the time of randomization.

5.1.10 Prior radiation to a solitary metastatic lesion is permitted provided that progression post radiation has been documented.

5.1.11 Patients must be $\geq$ 18 years of age.

5.1.12 Patients must have life expectancy > 6 months.

5.1.13 ECOG performance status 0, 1 or 2 (see Appendix II).

5.1.14 Patients must have adequate organ and marrow function measured within 14 days prior to randomization as defined below:

Hemoglobin	>	100 g/L (10 g/dL, 6.206 mmol/L)
Absolute granulocyte count (AGC)	>	1.5 x 10^9/L (1,500 cells/mm^3)
Platelet count	>	75 x10^9/L (75,000/mm^3)
Serum creatinine	$\leq$	2.0 x institutional upper limit of normal
Total bilirubin	$\leq$	1.5 x institutional upper limit of normal*
ALT(SGPT) +/- AST(SGOT)	$\leq$	2.5 x institutional upper limit of normal for patients who will be treated with docetaxel therapy
ALT (SGPT) +/- AST (SGOT)	<	5 x institutional upper limit of normal for patients who will be treated with paclitaxel therapy

* < 3 x ULN for patients with Gilbert's disease

5.1.15 Left ventricular ejection fraction $\geq$ 50% as demonstrated by MUGA scan/echocardiogram within 4 weeks prior to randomization.

5.1.16 Imaging investigations must be done within 4 weeks prior to randomization, including:

- chest x-ray or CT chest♦
- CT abdomen♦
- bone scan / PET (if this is the institution's standard procedure for assessing bone metastases), with plain radiographs to confirm disease, as necessary
- other scans as necessary to document all sites of disease

♦ If MRI of chest and/or abdomen is submitted instead, this will also be acceptable

5.1.17 CT/MRI of the brain within 4 weeks prior to randomization (see also 5.2.4).

5.1.18 Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to randomization and must use an acceptable method of contraception for the duration of the study.

5.1.19 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life (QLQ-C30 and Trial Specific Checklist and health utility (EQ-5D - *for patients from Canadian and Australian centres only*) questionnaires in English, French or any other languages for which the questionnaires are available. The baseline assessment must already have been completed. Inability (illiteracy in English, French or other validated languages, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

5.1.20 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided. A sample form is provided. A copy of the initial full board REB approval and approved consent form must be sent to the NCIC CTG central office. The patient must sign the consent form prior to randomization. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTG, GSK and monitoring agencies to review patient records (see Appendix XII for further details).

5.1.21 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.22 In accordance with NCIC CTG policy, protocol treatment is to begin within 5 working days of patient randomization.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 Patients with a history of other malignancies, except: adequately treated DCIS or LCIS, adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours (non-breast) curatively treated with no evidence of disease for $\geq$ 5 years.

5.2.2 Patients who have received prior chemotherapy, immunotherapy, biologic therapy or HER2/neu targeted therapy for recurrent or metastatic breast cancer.

5.2.3 Patients receiving ongoing anticancer treatment or other investigational anti-cancer agents for breast cancer or patients who have used an investigational drug within 30 days or 5 half-lives (if known), whichever is longer, preceding the date of randomization.

5.2.4 Patients with CNS metastases (including leptomeningeal involvement).

5.2.5 Patients with serious cardiac illness or condition including, but not limited to:

- history of documented congestive heart failure (CHF)
- systolic dysfunction (LVEF<50%)
- high risk uncontrolled arrhythmias (ventricular tachycardia, high-grade AV-block, supraventricular arrhythmias which are not adequately rate-controlled)
- unstable angina pectoris requiring anti-anginal medication
- clinically significant valvular heart disease
- evidence of transmural infarction on ECG
- inadequately controlled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg).
- New York Heart Association (NYHA) Class III or IV functional status (see Appendix X)

5.2.6 Pregnant or lactating women.

5.2.7 Patients with serious illness or medical condition which would not permit the patient to be managed according to the protocol including, but not limited to:

- History of significant neurologic or psychiatric disorder which would impair the ability to obtain consent or limit compliance with study requirements.
- Active uncontrolled infection.
- Serious or non-healing wound, ulcer, or bone fracture.

5.2.8 Patients with peripheral neuropathy grade 2 or greater.

5.2.9 Patients with GI tract disease resulting in an inability to take oral medication such as but not limited to malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption (for example resection of stomach or small bowel) or uncontrolled inflammatory GI disease (e.g. Crohn's, ulcerative colitis).

5.2.10 Patients receiving CYP3A4 inhibitors or inducers are not eligible unless it has been $\geq$ 7 and $\geq$ 14 days, respectively since the last dose of medication before the start of protocol treatment (see Appendix IX). For amiodarone in particular, dosing is prohibited for at least 6 months prior to the start of protocol treatment.

5.2.11 Patients with history of allergic or hypersensitivity reactions to any study drug or their excipients or with a history of allergic reactions attributed to compounds with similar chemical composition to any of the study drugs. Previous allergic reactions to taxanes that were adequately treated and that, according to the treating physician, would not prohibit further treatment with taxanes, are allowed.

6.0 PRE-TREATMENT EVALUATION
(Also see Appendix I)

Investigations		Timing
History and Physical Exam including:	• Prior therapy, history, concomitant medications • Height, weight, ECOG Performance Status • NYHA functional status assessment (see Appendix X)	within 14 days prior to randomization
Hematology	• Hemoglobin, WBC, granulocytes, platelet count	
Biochemistry	• Total bilirubin, ALT (SGPT) +/- AST (SGOT), alkaline phosphatase, serum creatinine, BUN/urea	
Radiology*	• Chest x-ray or CT chest** • CT abdomen** • Bone scan / PET *** • CT/MRI of the brain • Other imaging as necessary to document all sites of disease	within 4 weeks prior to randomization
Other Investigations	• Clinical Lesions status****	
	• Serum or urine pregnancy test♦	within 7 days prior to randomization
	• ECG • Echocardiogram/MUGA♦♦	within 4 weeks prior to randomization
	• Local or central laboratory confirmation of HER2/neu positive status♦♦♦	prior to randomization
	• Central laboratory HER2/neu testing♣	post randomization♦♦♦
	• Central laboratory testing for mandatory biomarkers (see section 2.7.1)	post randomization
	• Biopsy from a metastatic lesion for patients participating in the primary metastasis sub-study (consenting patients only, selected centres)	post-randomization and prior to start of treatment
	• Tissue for tumour banking (optional)	left-over material from central lab testing to be retained for banking
	• Serum for biomarkers / proteomics (optional) • Whole blood for pharmacogenetics (optional) • Plasma for biomarkers (optional)	post-randomization and prior to start of treatment

Continued on Next Page (including footnotes) ...

Investigations		Timing
Adverse Events♣♣	• Baseline adverse event evaluation (to document residual adverse events from previous therapy and baseline symptoms)	within 14 days prior to randomization
Quality of Life	• EORTC QLQ-C30 (see Appendix VI) • Trial Specific Checklist (see Appendix VI)	within 7 days prior to randomization
Health Utilities (*Canadian and Australian centres only*)	• EQ-5D questionnaire - see Appendix VII	

* To ensure compatibility, the baseline and subsequent radiological investigations to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner).

** If MRI of the chest and/or abdomen is submitted instead, this will also be acceptable.

*** With plain radiographs to confirm disease as necessary. PET should be used only if it is the institution's standard procedure for assessing bone metastases. If PET is used at baseline, then it should also be used for subsequent bone evaluations.

**** For the purposes of this study evaluation of clinical lesion status is defined as the assessment (including photographic assessment) of superficial lesions such as skin nodules and palpable lymph nodes.

♦ Minimum sensitivity 25 IU/L or equivalent units of HCG.

♦♦ The baseline and subsequent cardiac evaluations must be performed using identical modalities.

♦♦♦ Patients must have laboratory confirmed HER2/neu overexpressing and/or amplified disease (by the criteria described in section 5.1.3) to be considered for randomization. Local laboratory confirmation of HER2/neu positive status will be sufficient for patient randomization. Central laboratory (CTAG in Vancouver, BC, Canada) HER2/neu confirmation will be required prior to randomization only in cases where local HER2/neu testing is not available or where the result of the local laboratory HER2/neu testing is equivocal and confirmatory testing is not available.

♣ A post-randomization confirmation of HER2/neu status will be carried out by the central laboratory, for all patients randomized to the study based on local laboratory results.

♣♣ Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (Appendix V).

7.0 ENTRY / RANDOMIZATION PROCEDURES

Patients must first undergo HER2/neu testing, by a local or the central (CTAG in Vancouver, BC, Canada) laboratory. Pre-randomization, central laboratory HER2/neu confirmation will be required only in cases where local HER2/neu testing is not available or where the result of the local laboratory HER2/neu testing is equivocal and confirmatory testing is not available. Following confirmation of HER2/neu overexpressing and/or amplified disease and fulfillment of all other eligibility criteria, patients will be randomized to one of the two treatment arms. Patients will be allocated to the treatment arms using minimization *[Tu 2003, Pocock 1975]* to ensure balance in the treatment arms by each stratification factor.

All randomizations will be done by the NCIC CTG by means of the web-based Mango Patient Allocation System. Randomization will involve signing into Mango and completing a Web Eligibility Checklist (WEC) electronically. A paper template (Eligibility Worksheet) of the WEC can also be obtained from the MA.31-specific web page on the NCIC CTG Website. Sites are encouraged to print the Eligibility Worksheet and complete the information on it prior to logging into Mango (so as to make the completion of the Mango screens easier and faster). However completion of this Worksheet is not mandatory and the Worksheet does *not* need to be submitted with the Case Report Forms.

To start the Mango Patient Allocation System, go to the NCIC CTG Website and click on the "Mango" icon near the top of the Website. Alternatively, Mango can be accessed through the following location in your web browser: https://mango.ctg.queensu.ca/mango/mango.php .

The userid and password provided to each user by the NCIC CTG must be used to sign on to the online Mango. The userids are not case sensitive, but the passwords are.

If there is any difficulty in accessing Mango, randomizations may be obtained by calling the NCIC CTG Clinical Trials Assistant at (+1)-613-533-6430 or by faxing a completed paper copy of the Eligibility Worksheet to (+1)-613-533-2941.

7.1 Randomization

To randomize a patient, access the web-based Mango Patient Allocation System and enter all information required, including all information on the WEC. The following will be needed:

- trial code (NCIC CTG MA.31)
- treatment centre and investigator
- patient's initials, hospital number (if permitted by the local REB)
- version of the informed consent that the patient signed (Canadian Centres)
- version of the Tissue Banking and Blood Collection consent that the patient signed (Canadian Centres)
- version of the Primary Metastasis Sub-Study Consent that the patient signed (participating Canadian Centres)
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values (i.e. completed WEC)
- stratification parameters
- height and weight

Randomization will be confirmed by means of a confirmation of randomization email which will automatically be sent to the centre following each successful randomization. In addition to randomization information (time/date of randomization, stratification factors, arm assignment etc.), this email will also include an electronic record of the patient eligibility information previously entered by the site on the Mango WEC. The WEC information provided on the confirmation email should be printed and signed (at the designated space, at the bottom of the print-out) by the investigator. The signed WEC print-out should be submitted together with the Form 1 (see also Appendix IV).

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis.

All patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death. In accordance with the requirement for the intent-to-treat analysis described in section 14.2, ineligible patients will be followed using four forms: Form 5P, Form 5, Form 9 and Form 6 (see Appendix IV).

7.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight.

7.3 Stratification

1. Prior (neo)adjuvant HER2/neu targeted therapy (yes, no)
2. Prior (neo)adjuvant taxane chemotherapy (yes, no)
3. Planned taxane treatment (q weekly paclitaxel vs. q 3weekly docetaxel)
4. Liver metastasis (yes, no)

8.0 TREATMENT PLAN

Although the NCIC Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with NCIC CTG policy, protocol treatment is to begin within 5 working days of patient randomization.

It is expected that centres will use their commercial supply of trastuzumab and taxane-based therapy for this trial. In situations where the cost of these drugs is not covered by third party payment (i.e. insurance), then every effort will be made to reimburse centres for their cost.

8.1 Treatment Plan

All randomized patients will receive taxane based chemotherapy (weekly paclitaxel or 3 weekly docetaxel). The choice of taxane will be up to the treating physician and it must be specified at the time of patient randomization (note: choice of taxane is a stratification factor - see section 7.3). Once a particular taxane is chosen, the patient may not be switched to the other taxane.

In addition to taxane chemotherapy, patients in arm 1 will receive lapatinib and patients in arm 2 will receive trastuzumab. The treatment code for lapatinib/trastuzumab will be open-label.

Patients in arm 1 will receive lapatinib orally at a daily dose of 1250 mg concurrently with intravenous q weekly paclitaxel (days 1, 8 and 15 of a 4-week cycle) or intravenous q 3 weekly docetaxel (day 1 of a 3-week cycle) for a total of 24 weeks (6 cycles if on paclitaxel therapy or 8 cycles if on docetaxel therapy). Primary prophylaxis with G-CSF is required with docetaxel and lapatinib combination therapy. The frequency dose and route of G-CSF administration is at the investigator's discretion. Once concurrent lapatinib / taxane treatment is concluded, patients will continue receiving daily oral lapatinib at a dose of 1500 mg until progressive disease. Note: only the non-pegylated form of filgrastim (i.e. Neupogen) will be reimbursed by GlaxoSmithKline.

Patients in arm 2 will receive trastuzumab intravenously concurrently with taxane based chemotherapy. The type of taxane therapy chosen (paclitaxel or docetaxel) will determine the trastuzumab schedule. Thus, patients will receive intravenous q weekly paclitaxel (days 1, 8 and 15 of a 4-week cycle) together with intravenous q weekly trastuzumab (loading dose 4 mg/kg, subsequent doses 2 mg/kg; on days 1, 8, 15 and 22 of a each paclitaxel 4-week cycle) *or* intravenous q 3 weekly docetaxel (day 1 of a 3-week cycle) together with intravenous q 3 weekly trastuzumab (loading dose 8 mg/kg, subsequent doses 6 mg/kg) for a total of 24 weeks (6 cycles if on paclitaxel therapy or 8 cycles if on docetaxel therapy). Once concurrent trastuzumab/ taxane treatment is concluded, patients will receive 6 mg/kg of single agent trastuzumab intravenously, q 3 weekly until progressive disease.

The treatment plan is summarized in the following table:

<table>
<tr><td colspan="6">Patients will be randomized to one of the following two arms:</td></tr>
<tr><td>Arm</td><td>Agent(s)</td><td>Dose</td><td>Route</td><td>Schedule</td><td>Duration</td></tr>
<tr><td rowspan="4">1</td><td rowspan="4">Taxane based chemotherapy
plus
Lapatinib</td><td>Lapatinib: 1250 mg</td><td>po</td><td>daily</td><td rowspan="4">24 weeks</td></tr>
<tr><td>Paclitaxel: 80 mg/m^2</td><td>IV</td><td>q weekly
(days 1, 8 and 15 of a 4-week cycle)</td></tr>
<tr><td><u>OR</u></td><td></td><td></td></tr>
<tr><td>Docetaxel: 75 mg/m^2
plus</td><td>IV</td><td>q 3 weekly
(day 1 of a 3-week cycle)</td></tr>
<tr><td></td><td>Lapatinib</td><td>1500 mg</td><td>po</td><td>daily</td><td>To follow concurrent lapatinib / taxane treatment; treat until progressive disease</td></tr>
<tr><td rowspan="4">2</td><td rowspan="3">Taxane based chemotherapy
plus
Trastuzumab</td><td>Trastuzumab: loading dose 4 mg/kg, subsequent doses 2 mg/kg
Paclitaxel: 80 mg/m^2</td><td>IV</td><td>q weekly
(Paclitaxel: days 1, 8 and 15 of a 4-week cycle) ; Trastuzumab: days 1, 8,15 and 22 of each paclitaxel 4-week cycle)</td><td rowspan="3">24 weeks</td></tr>
<tr><td colspan="3"><u>OR</u></td></tr>
<tr><td>Trastuzumab: loading dose 8 mg/kg, subsequent doses 6 mg/kg
Docetaxel: 75 mg/m^2</td><td>IV</td><td>q 3 weekly
(Docetaxel: day 1 of a 3-week cycle; Trastuzumab: day 1 of a 3-week cycle;))</td></tr>
<tr><td>Trastuzumab</td><td>6 mg/kg</td><td>IV</td><td>q 3 weekly</td><td>To follow concurrent trastuzumab / taxane treatment; treat until progressive disease</td></tr>
</table>

8.2 Lapatinib

Lapatinib treatment for patients randomized to arm 1 should begin at the same day as taxane-based chemotherapy and within 5 working days of randomization. Lapatinib will be taken together with taxane based chemotherapy, orally, once a day, daily, at a dose of 1250 mg for 24 weeks. After that single-agent lapatinib will continue at a daily oral dose of 1500 mg until disease progression. These statements are summarized in the table below:

Arm	Agent	Dose	Route	Schedule	Duration
1	Lapatinib	1250 mg	po	daily	Concurrently with taxane based chemotherapy * for 24 weeks
1	Lapatinib	1500 mg	po	daily	Single-agent, following concurrent lapatinib/taxane treatment; treat until progressive disease

* If the taxane of choice is docetaxel then primary prophylaxis with G-CSF is required. The frequency dose and route of G-CSF administration is at the investigator's discretion. Note: only the non-pegylated form of filgrastim (i.e. Neupogen) will be reimbursed by GlaxoSmithKline.

8.2.1 *Drug Administration - Lapatinib*

The initial lapatinib supply dispensed to patients on day 1 of cycle 1 of combined taxane/lapatinib treatment will consist of 2 bottles of lapatinib, containing 90 tablets each. During the combined taxane/lapatinib treatment phase, patients will be re-supplied with lapatinib on day 1 of each cycle and each re-supply will consist of 2 bottles (180 tablets) of medication. During the single agent lapatinib phase of treatment, when patients will be seen at the clinic every 12 weeks, each patient will receive a 12 week supply of lapatinib (six bottles of lapatinib of 90 tablets each), at each clinic visit.

Tablets of lapatinib are available in a strength of 250 mg. To achieve the dose required (1250 or 1500 mg) either 5 or 6 tablets, respectively, should be swallowed once daily.

Patients will be instructed to take their dose of lapatinib at approximately the same time each day. Lapatinib should be taken either 1 hour (or more) before a meal, or 1 hour (or more) after a meal.

Lapatinib may also be administered as a suspension in water. For further details please refer to section 3.1.10.

If vomiting occurs shortly after the lapatinib tablets are swallowed, the dose should be replaced only if all of the intact tablets can actually be seen and counted. Otherwise, the next dose should be taken the following day, as per schedule. Missed doses should be skipped.

NOTE: Lapatinib should NOT be taken with grapefruit or grapefruit juice. Grapefruit and grapefruit juice are not permitted for the duration of the study.

8.2.2 *Dose Adjustments - Lapatinib*

Doses may be held or reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V).

With the exception of a dose escalation to 1500 mg from 1250 mg when patients transition from the combined taxane/lapatinib therapy to the single-agent lapatinib phase of treatment, dose escalation of lapatinib is not permitted. Once dose-reduced due to adverse events, patients should not be re-challenged to a higher dose level.

If a decision is made to discontinue the taxane agent prematurely (i.e. prior to the end of the 24 weeks of protocol-mandated combination therapy), then treatment with single-agent lapatinib alone should continue. However, the lapatinib dose should not be escalated to 1500 mg until such time when a total of 24 weeks of treatment are completed.

Note: The lapatinib dose escalation to 1500 mg at the onset of the single-agent phase of treatment should only occur for patients with no protocol-mandated lapatinib dose reductions during the combined taxane/lapatinib therapy portion of the study. So, for example, a patient completing 24 weeks of combined lapatinib/taxane treatment without requiring a lapatinib dose reduction should have her lapatinib dose escalated to 1500 mg. However, for a patient requiring a lapatinib dose reduction (for example to 1000 mg) while on combined lapatinib/taxane therapy, the starting dose of lapatinib in the single-agent phase of treatment should be kept the same (for example 1000 mg).

The major toxic effects of lapatinib which limit dose are nausea, vomiting, diarrhea, rash and fatigue. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

The lapatinib dose will be decreased according to the schedule displayed in the following table:

Dose Level	Starting Dose (mg)	1st Reduction (mg)	2nd Reduction (mg)	3rd Reduction (mg)	4th Reduction (mg)
Combined taxane and lapatinib treatment phase	1250	1000	750	discontinue	NA
Single-agent lapatinib phase	1500*	1250	1000	750	discontinue

* starting dose will be 1500 mg provided there was no previous dose reduction during the combined taxane and lapatinib treatment phase of treatment. If there was a protocol-mandated dose reduction of lapatinib during the combined taxane / lapatinib treatment phase, then the starting dose will be the reduced dose (i.e. 1000 or 750 mg).

A dose of 750 mg represents the lowest dose that a patient can receive either during the combination therapy or the single-agent phase of the study.

8.2.3 *Hematologic Adverse Events - Lapatinib*

Absolute Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Lapatinib Dose Management
$\geq$ 1.0	and	$\geq$ 50	No dose change
< 1.0	and/or	< 50	• Hold lapatinib until hematologic values have recovered (maximum delay 14 days)* • Resume treatment at the same dose level

* If no recovery after 14 days and the hematologic adverse event is thought to be related to lapatinib, then discontinue lapatinib

8.2.4 *Non-hematologic Adverse Events - Lapatinib*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix V).

Skin Adverse Events:
A papulopustular rash is the most commonly observed skin adverse event for lapatinib. Such rash frequently improves with an unchanged, uninterrupted dose of lapatinib therapy. Severe skin AEs (CTC Grade 3 or more) associated with lapatinib are rare (1-3%). In general, patients with poorly tolerated skin toxicities may be successfully managed by providing a brief (up to 14 days) therapy interruption and resuming lapatinib at the same dose. In some cases, the rash may improve without the need for interrupting therapy with lapatinib.

Subjects should be encouraged to avoid exposure to sunlight. Broad spectrum sunscreens (containing titanium dioxide or zinc oxide) with an SPF of at least 15 should be applied.

A variety of agents can be used to manage skin reactions. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines and immunomodulators, as well as moisturizers.

There is no standard treatment, known or established, that is proven effective for drug-related skin rashes or changes due to lapatinib. The need for oral or topical antibiotics and topical steroids is a clinical decision of the investigator and, if indicated, a dermatology consultation. Oral retinoids are not recommended because of theoretical concerns about negatively affecting the lapatinib mechanism of action and topical steroids result in irritation/severe dryness. Oral steroids may be used for a short treatment course (maximum of 14 days) which may help patients to remain on study therapy. Upon consultation with a dermatologist, other treatment options may exist for difficult to treat/unresponsive skin toxicities.

The decision to administer, delay, dose-reduce or discontinue lapatinib due to skin adverse events is as follows:

<table>
<tr><th>Adverse Event</th><th>Grade</th><th>Guideline for management</th><th>Lapatinib dose modification</th></tr>
<tr><td rowspan="4">Skin adverse Events</td><td>1</td><td>No intervention</td><td>None</td></tr>
<tr><td>2</td><td rowspan="2">Any of the following as appropriate: oral or topical antibiotics, topical steroids, oral steroids (short course)</td><td>None *</td></tr>
<tr><td>3</td><td>Hold until recovery to ≤ grade 1**
If this is the first occurrence, resume at the same dose; if this constitutes recurrence, resume at 1 dose level lower</td></tr>
<tr><td>4</td><td>As clinically appropriate</td><td>Discontinue lapatinib</td></tr>
<tr><td colspan="4">* if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1** and then resume at the same dose; if dose has been previously held for grade 2 skin toxicity and grade 2 symptoms recur , hold dose until recovery to ≤ grade 1** and then resume at 1 dose level lower
** maximum hold for 14 days; if no recovery after 14 days, discontinue lapatinib</td></tr>
</table>

Diarrhea:
Experience thus far suggests that when lapatinib is used as monotherapy, most diarrhea is uncomplicated grade 1 or 2. If gastrointestinal adverse events are not appropriately managed, they may be associated with the development of dehydration.

Diarrhea can be debilitating, and on rare occasions, potentially life threatening. The following guidelines were developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea:

- Loperamide, administered as an initial 4-mg dose, followed by 2-mg doses every 4 hours. This dose and regimen are moderately effective.
- Clonidine, non-steroidal anti-inflammatory drugs, and the serotonin antagonist cyproheptadine have been shown to be effective in controlling diarrhea associated with inflammation of the bowel.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 μg twice daily to 500 μg 3 times daily, with a maximum-tolerated dose of 2000 μg 3 times daily in a 5-day regimen.

The decision to administer, delay, dose reduce or discontinue lapatinib due to diarrhea is as follows:

Adverse Event	Grade	Guideline for management	Lapatinib dose modification
Diarrhea	1	Introduce oral hydration; consider introducing loperamide especially in patients who are considered to be high risk (for example, elderly).	None
	2		None *
	3	Follow ASCO guidelines (see above)	Hold until recovery to ≤ grade 1** And then resume at 1 dose level lower
	4	As clinically appropriate	Hold until recovery to ≤ grade 1** And then resume at 1 dose level lower
* if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1** and then resume at the same dose; if dose has been previously held for grade 2 diarrhea and grade 2 symptoms recur , hold dose until recovery to ≤ grade 1** and then resume at 1 dose level lower ** maximum hold for 14 days; if no recovery after 14 days, discontinue lapatinib			

Please also refer to Appendix XII for more detailed guidelines for the management of diarrhea.

Interstitial Pneumonitis:

Adverse Event	Guideline for management	Lapatinib dose modification
Signs and symptoms of Interstitial Pneumonitis	Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated	Hold pending diagnosis
		Permanently discontinue if interstitial pneumonitis diagnosis is confirmed

Cardiac Adverse Events:
The LVEF and NYHA functional status (see Appendix X) assessment results must be available prior to deciding subsequent administration of lapatinib. Specifically, the decision to administer, delay or discontinue lapatinib is as follows:

Adverse Event	Action
NYHA Class I or II event*	Administer, delay or discontinue lapatinib based on the algorithm shown in Appendix XI
severe symptomatic NYHA class III or IV event* or confirmed LVEF dysfunction	Discontinue lapatinib
* see Appendix X	

It is strongly recommended that patients who have symptomatic decreases in LVEF or those who meet the criteria for stopping treatment seek cardiologic consultation for advice on potential treatment for their cardiac dysfunction. Furthermore, in patients who permanently discontinue lapatinib due to cardiac toxicity, cardiac evaluations should be performed as clinically indicated, ideally every 4 weeks for at least 16 weeks or until resolution.

Hepatic Toxicity:

Hepatoxicity has occurred with the use of lapatinib. The changes most commonly seen are elevations in transaminases, but rarely severe hepatocellular damage may occur. Elevated liver enzymes usually return to baseline levels when lapatinib is stopped, but may rise again on re-exposure.

The decision to administer, hold, or discontinue lapatinib is as follows:

A. For Patients with no evidence of liver metastasis at study entry:

Bilirubin		ALT	Lapatinib Dose Modification
≤ 2 x UNL	and	≤ 3 x UNL	None
≤ 2 x UNL	and	>3 to ≤5 x UNL	• If no symptoms* of liver injury: None • If presence of symptomatic liver injury* which, in the opinion of the investigator, is related to lapatinib: Discontinue lapatinib
		>5** to ≤20 x UNL	• If no symptoms* of liver injury: Hold lapatinib and repeat LFTs weekly until recovery to baseline levels*** and then resume lapatinib at 1 dose level lower • If presence of symptomatic liver injury* which, in the opinion of the investigator, is related to lapatinib: Discontinue lapatinib
		> 20 x UNL	Discontinue lapatinib
> 2 x UNL	and	≤ 3 x UNL	Management of patient is at the treating physician's discretion♦
> 2 x UNL	and	>3 x UNL	Discontinue lapatinib

* signs and symptoms may include abdominal pain, fever, jaundice, rash, eosinophilia or a performance status drop of ≥ 1 point from baseline

** for patients with ALT > 5 x UNL, liver imaging is recommended to assess liver status; other investigations to rule out infectious causes of hepatitis to be done at the discretion of the investigator

*** maximum hold for 21 days; if no recovery after 21 days, discontinue lapatinib

♦ Options include: continuation of treatment with lapatinib with no dose modification *OR* continuation of treatment with lapatinib at 1 dose level lower *OR* holding lapatinib, repeating LFTs weekly until recovery to baseline levels and then resuming lapatinib at 1 dose level lower *OR* permanent discontinuation of lapatinib

NOTIFICATION REQUIRED
In those cases where resumption of lapatinib dosing occurs following a dose hold for liver toxicity, as per the table above, the GSK medical monitor (non-Canadian centres) or the NCIC CTG MA.31 Study Coordinator (Canadian Centres) must be notified. Notification must take place within 24 hours of the patient actually restarting lapatinib and may occur by means of an email, phone call or fax. The notification should include the NCIC CTG Patient Serial number (for e.g. CAXX0001) of the patient who received lapatinib after a temporary dose hold.

B. For Patients who have liver metastasis at study entry:

Bilirubin		ALT	Lapatinib Dose Modification
≤ 2 x UNL	and	≤ 3 x UNL	None
≤ 2 x UNL	and	>3 to ≤5 x UNL	• If no symptoms* of liver injury: None • If presence of symptomatic liver injury* which, in the opinion of the investigator, is related to lapatinib: Discontinue lapatinib
		>5 to ≤8 x UNL	• If no symptoms* of liver injury: Management of patient is at the treating physician's discretion♦ • If presence of symptomatic liver injury* which, in the opinion of the investigator, is related to lapatinib: Discontinue lapatinib
		>8 to ≤20 x UNL	• If no symptoms* of liver injury: Hold lapatinib and repeat LFTs weekly until recovery to baseline levels** and then resume lapatinib at 1 dose level lower • If presence of symptomatic liver injury* which in the opinion of the investigator, is related to lapatinib: Discontinue lapatinib
		> 20 x UNL	Discontinue lapatinib
> 2 x UNL	and	≤ 3 x UNL	Management of patient is at the treating physician's discretion♦
> 2 x UNL	and	>3 x UNL	Discontinue lapatinib

* signs and symptoms may include abdominal pain, fever, jaundice, rash, eosinophilia or a performance status drop of ≥ 1 point from baseline

** maximum hold for 21 days; if no recovery after 21 days, discontinue lapatinib

♦ Options include: continuation of treatment with lapatinib with no dose modification *OR* continuation of treatment with lapatinib at 1 dose level lower *OR* holding lapatinib, repeating LFTs weekly until recovery to baseline levels and then resuming lapatinib at 1 dose level lower *OR* permanent discontinuation of lapatinib

NOTIFICATION REQUIRED

In those cases where resumption of lapatinib dosing occurs following a dose hold for liver toxicity, as per the table above, the GSK medical monitor (non-Canadian centres) or the NCIC CTG MA.31 Study Coordinator (Canadian Centres) must be notified. Notification must take place within 24 hours of the patient actually restarting lapatinib and may occur by means of an email, phone call or fax. The notification should include the NCIC CTG Patient Serial number (for e.g. CAXX0001) of the patient who received lapatinib after a temporary dose hold.

Other Non-hematologic Adverse Events (not specifically addressed above):

Grade of Event	Management / Lapatinib Next Dose
≤ grade 2	Symptomatic care – no change in dose. If prolonged duration (≥ 14 days) of grade 2 adverse event despite symptomatic treatment, then hold lapatinib until ≤ grade 1* and resume at same dose. If grade 2 adverse event recurs OR if the patient finds the symptoms unacceptable, hold lapatinib until recovery to ≤ grade 1 and then resume at 1 dose level lower.
grade 3	Hold for up to 14 days* until ≤ grade 1, then resume at 1 dose level lower
grade 4	Off lapatinib therapy
* Patients requiring a delay of > 14 days should discontinue lapatinib	

8.2.5 *Duration of Therapy - Lapatinib*

Unless unmanageable adverse events occur, treatment with lapatinib will be given until disease progression.

8.2.6 *Patient Compliance - Lapatinib*

Compliance with daily lapatinib is very important to the conclusions of this study. Study site pharmacy staff will make tablet counts at each patient visit during treatment. Patients will be instructed to notify study site personnel of missed doses. Dates of missed, held or reduced doses will be recorded on the CRF.

8.3 Trastuzumab

Trastuzumab treatment for patients randomized to arm 2 should begin at the same day* as taxane-based chemotherapy and within 5 working days of randomization. Trastuzumab will be taken concurrently with taxane based chemotherapy for 24 weeks, either on a q weekly (if in combination with paclitaxel) or q 3 weekly (if in combination with docetaxel) schedule. If q weekly, trastuzumab will be given with a loading dose of 4 mg/kg and subsequent doses of 2 mg/kg. If q 3 weekly, trastuzumab will be given with a loading dose of 8 mg/kg and subsequent doses of 6 mg/kg. Once concurrent trastuzumab/ taxane treatment is concluded, patients will receive 6 mg/kg of single agent q 3 weekly trastuzumab until progressive disease. These statements are summarized in the table below:

** Note: For centres that administer a loading dose of trastuzumab followed by a prolonged observation period, the initial taxane dose may be given 24 hours later to accommodate local institutional policy.*

Arm	Agent	Dose	Route	Schedule	Duration
2	Trastuzumab	Loading: 8 mg/kg Subsequent: 6 mg/kg	IV	q 3 weekly	Concurrently with q 3 weekly docetaxel for 24 weeks
		OR			
		Loading: 4 mg/kg Subsequent: 2 mg/kg	IV	q weekly	Concurrently with q weekly paclitaxel for 24 weeks
2	Trastuzumab	6 mg/kg	IV	q 3 weekly	Single-agent, following concurrent trastuzumab/taxane treatment; treat until progressive disease

8.3.1 *Patient Monitoring - Trastuzumab*

Patients should be monitored as directed in the Product Monograph and/or Institutional Standard of Care.

8.3.2 *Dose Adjustments- Trastuzumab*

Doses will be held or discontinued for adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V).

The major toxic effects of trastuzumab which limit dose are hypersensitivity reactions and cardiotoxicity. The guidelines which follow outline dose adjustments for several of these toxic effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the most conservative course of action (i.e. discontinuation rather than dose-hold).

If a decision is made to discontinue the taxane agent prematurely (i.e. prior to the end of the 24 weeks of protocol-mandated combination therapy), then treatment with single-agent trastuzumab alone should continue. However, for patients receiving paclitaxel as the taxane of choice, trastuzumab should not be switched from a weekly to a 3-weekly schedule until such time when a total of 24 weeks of treatment are completed.

8.3.3 *Hematologic Adverse Events- Trastuzumab*

Trastuzumab dose should not be held for hematological adverse events.

8.3.4 *Non-hematologic Adverse Events- Trastuzumab*

Adverse Events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix V).

Hypersensitivity Reactions:
Patients with extensive pulmonary disease e.g. lymphangitis, multiple metastases, recurrent pleural effusions, and those with pre-existing respiratory compromise may be at increased risk from serious hypersensitivity reactions.

The decision to administer or discontinue trastuzumab due to hypersensitivity reactions is as follows:

Hypersensitivity Reaction	Action
Life threatening reaction (e.g. tachypnea, bronchospasm, hypotension, hypoxia)	Discontinue trastuzumab
Severe or moderate reaction	• Slow or stop the trastuzumab infusion • Provide supportive care with oxygen, beta agonists, antihistamines or corticosteroids • Patient may be retreated with trastuzumab • Premedication with corticosteroids, antihistamines and antipyretics may be used before subsequent trastuzumab infusions
Moderate or mild reaction	• Treat with antipyretics and antihistamines • Re-treat with trastuzumab next dose

Cardiac Adverse Events:
The LVEF and NYHA functional status (see Appendix X) assessment results must be available prior to deciding subsequent administration of trastuzumab. Specifically, the decision to administer, delay or discontinue trastuzumab is as follows:

Adverse Event	Action
NYHA Class I or II event*	Administer, delay or discontinue trastuzumab based on the algorithm shown in Appendix XI
severe symptomatic NYHA class III or IV event* or confirmed LVEF dysfunction	Discontinue trastuzumab
* see Appendix X	

It is strongly recommended that patients who have symptomatic decreases in LVEF or those who meet the criteria for stopping treatment seek cardiologic consultation for advice on potential treatment for their cardiac dysfunction. Furthermore, in patients who permanently discontinue trastuzumab due to cardiac toxicity, cardiac evaluations should be performed as clinically indicated, ideally every 4 weeks for at least 16 weeks or until resolution.

Other Non-hematologic Adverse Events (not specifically addressed above):

Grade of Event	Management/Next Dose of Trastuzumab
≤ grade 2	Symptomatic care. Continue trastuzumab
grade 3	Hold trastuzumab until recovery to ≤ grade 2*.
grade 4	Discontinue trastuzumab
* maximum hold for 14 days; if no recovery after 14 days, discontinue trastuzumab	

8.3.5 *Duration of Therapy- Trastuzumab*

Unless unmanageable adverse events occur, treatment with trastuzumab will be given until disease progression.

8.3.6 *Patient Compliance - Trastuzumab*

Compliance with trastuzumab treatment is very important to the conclusions of this study. Dates of delayed doses will be recorded on the CRF.

8.4 Paclitaxel

Paclitaxel treatment should begin at the same day as lapatinib / trastuzumab and within 5 working days of randomization according to the schedule below:

Arm	Agent	Dose	Route	Schedule	Duration
1 & 2	paclitaxel	80 mg/m^2	IV	q weekly (days 1, 8 and 15 of a 4-week cycle)	24 weeks (6 cycles)

8.4.1 *Premedication - Paclitaxel*

Anti-hypersensitivity premedication is required for paclitaxel, as per the manufacturer's instructions.

8.4.2 *Patient Monitoring - Paclitaxel*

Patients should be monitored as directed in the Product Monograph and/or Institutional Standard of Care.

8.4.3 *Dose Adjustments - Paclitaxel*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V).

If a decision is made to permanently discontinue lapatinib / trastuzumab prior to the end of the 24 weeks of protocol-mandated combination therapy, then treatment with single-agent paclitaxel alone should continue until 24 weeks of treatment are completed. At that time the patient will go off protocol treatment.

The major adverse events of paclitaxel likely to be encountered in this study include neurotoxicity, myalgia/ arthralgia, and myelosuppression. Hypersensitivity reactions (mild) to paclitaxel are common but seldom severe with standard pre-medication regimens. The guidelines which follow outline dose adjustments for several of these adverse events.

If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

There will be no re-escalation of dose after reduction for adverse events. Patients may undergo a maximum of 2 dose reductions for adverse events. If a third dose reduction is required, then paclitaxel must be permanently discontinued.

Paclitaxel dose levels are as follows:

Dose level:	Starting Dose	1st Reduction	2nd Reduction	3rd Reduction
Paclitaxel	80 mg/m^2	reduce by 20%	reduce by a further 20%	discontinue

8.4.4 *Hematologic Adverse Events - Paclitaxel*

Treatment Day Counts:			
Absolute Neutrophils (x109/L)		Platelets (x109/L)	Paclitaxel Dose Management
$\geq$ 1.0	and	$\geq$ 75	No dose change
< 1.0	and/or	< 75	• Hold until recovery of absolute neutrophils to $\geq$ 1.5 x 10^9/L and platelets to $\geq$ 100 x 10^9/L • If counts recover within 7 days, resume paclitaxel at the same dose • If count recovery takes longer than 7 days*, resume paclitaxel at 1 dose level lower
* if not recovered within 3 weeks, discontinue paclitaxel permanently			

8.4.5 *Non-hematologic Adverse Events - Paclitaxel*

Adverse Events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix V).

	Management / Next Dose of Paclitaxel
Gastrointestinal:	
• ≥ grade 2: mucositis	Hold until recovery to ≤ grade 1*. Then resume at 1 dose level lower **
• grade 4: vomiting despite antiemetic premedication	Permanently discontinue
Nephrotoxicity (Creatinine):	
• increase of serum creatinine < 2 x UNL	No change
• increase of serum creatinine ≥ 2 x UNL	Hold until recovery to ≤ grade 1*. Then resume at the same dose level
Neuropathy: sensory or motor	
• grade 2	Hold until recovery to ≤ grade 1*. Then resume at 1 dose level lower
• ≥ grade 3	Permanently discontinue
Pain - Muscle / Joint:	
• grades 0-2	No change, symptomatic management
• grade 3	Hold until recovery to ≤ grade 2*. Then resume at 1 dose level lower
• grade 4	Permanently discontinue
Bilirubin:	
Bilirubin ≥ 2 x UNL	Hold until recovery to ≤ grade 1*. Then resume at the same dose level
Hypersensitivity Reactions (grade as Allergic Reaction / Hypersensitivity, CTCAE v 3.0):	
• grades 0-2 (e.g. flushing, skin rash, asymptomatic bronchospasm)	No change, symptomatic management
• grade 3 (e.g. symptomatic bronchospasm with or without urticaria; parenteral medications indicated, allergy related edema or angioedema; hypotension)	– Stop infusion. Treat as per local protocol. – Once recovered, may restart infusion slowly to complete infusion – Next cycle: may re-challenge giving the drug as per protocol
• grade 4 (life threatening anaphylaxis)	Permanently discontinue
Other Non-Hematological Adverse Events (not specifically addressed above):	
• grade ≤ 2	Continue paclitaxel
• grade 3 (except alopecia)	Hold until recovery to ≤ grade 2*. Then resume at 1 dose level lower 1
• grade 4	Off paclitaxel therapy
* if not recovered within 2 weeks, discontinue paclitaxel permanently. ** may receive a dose reduction or permanently discontinue. This decision will depend upon the type of non-hematologic toxicity seen and which course of action is medically most sound in the judgement of the physician investigator.	

8.4.6 *Duration of Therapy - Paclitaxel*

Unless unmanageable adverse events or disease progression occur, treatment with paclitaxel will be given for 24 weeks (6 cycles).

8.4.7 *Patient Compliance - Paclitaxel*

Compliance with paclitaxel treatment is important to the conclusions of this study. Dates of delayed or reduced doses will be recorded on the CRF.

8.5 Docetaxel

Docetaxel treatment should begin at the same day as lapatinib / trastuzumab and within 5 working days of randomization according to the table below:

Arm	Agent	Dose	Route	Schedule	Duration
1 & 2	Docetaxel	75 mg/m^2	IV	q3 weekly (day 1 of a 3-week cycle)	24 weeks (8 cycles)

NOTE: Prophylactic G-CSF use is mandatory for the administration docetaxel concomitantly with lapatinib. The frequency dose and route of G-CSF administration is at the investigator's discretion. Only the non-pegylated form of filgrastim (i.e. Neupogen) will be reimbursed by GlaxoSmithKline.

8.5.1 *Premedication - Docetaxel*

Prophylactic premedication with dexamethasone will be administered according to institutional guidelines in order to prevent the onset of acute hypersensitivity reaction (AHSR) and to reduce and/or delay the occurrence of delayed skin toxicity and/or edema and fluid retention related to docetaxel.

Standard antiemetics are permitted according to institutional guidelines.

8.5.2 *Patient Monitoring - Docetaxel*

Patients should be monitored as directed in the Product Monograph and/or Institutional Standard of Care. Hypersensitivity reactions should be managed as outline in section 8.5.6 of this protocol.

8.5.3 *Dose Adjustments - Docetaxel*

Doses will be reduced and/ or delayed for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V).

If a decision is made to permanently discontinue lapatinib / trastuzumab prior to the end of the 24 weeks of protocol-mandated combination therapy, then treatment with single-agent docetaxel alone should continue until 24 weeks of treatment are completed. At that time the patient will go off protocol treatment

The major toxic effect of docetaxel which limit dose is neutropenia. Other toxic effects which may be seen include anaphylactoid type reactions and cutaneous reactions, digestive tract toxicities (nausea, vomiting, oral mucositis, diarrhea), reversible paresthesias, alopecia, asthenia and mild local venous reactions (phlebitis) at site of injection and fluid retention/edema. The guidelines which follow outline dose adjustments for several of these toxic effects.

If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

There will be no re-escalation of dose after reduction for toxicity. Patients may undergo a maximum of 2 dose reductions for adverse events. If there has not been recovery after a 2-week delay of treatment or a third dose reduction is required, then docetaxel must be permanently discontinued.

Docetaxel dose levels are as follows:

Dose level:	Starting Dose	1st Reduction	2nd Reduction	3rd Reduction
Docetaxel	75 mg/m^2	60 mg/m^2	45 mg/m^2	discontinue

8.5.4 *Hematologic Adverse Events - Docetaxel*

Treatment Day Counts:			
Absolute Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Dose Management
$\geq$ 1.5	and	$\geq$ 100	Treat on time, no dose adjustment
< 1.5	and/or	< 100	Delay by one week intervals* Reduce dose by one dose level**
For febrile neutropenia (ANC <1.0 $x10^9$/L and fever >38.5^{o}C) during the previous cycle.			Reduce dose by one dose level**
* If no recovery after 2 weeks, discontinue drug. ** Dose modification applies to all subsequent cycles. Note: Primary prophylaxis with G-CSF is required to be administered with docetaxel and lapatinib combination therapy. Otherwise, G-CSF and other hematopoietic growth factors may not be used as a substitute for a scheduled dose reduction unless this is the centre's standard practice; however, they may be used in the management of acute toxicity such as febrile neutropenia when clinically indicated at the discretion of the investigator.			

8.5.5 *Non-hematologic Adverse Events - Docetaxel*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix V).

Hepatic Toxicity:
Patients who develop abnormal liver function tests, will have the following dose reductions:

ALT / AST and/or Alkaline Phosphatase	Dose Management
$\leq$ 2.5 ULN ($\leq$ gr 1)	No change
> 2.5 to $\leq$ 5.0 x ULN (gr 2)	Reduce by one dose level**
> 5.0 ULN (> gr 2)	Delay by one week intervals* until $\leq$ g 1 then treat as medically appropriate.
* If no recovery after 2 weeks, discontinue drug. ** Dose modification applies to all subsequent cycles.	

Other Toxicities:

Description of Adverse Event		Management /Docetaxel Dosage
Dermatology/Skin		
Alopecia	Any Grade	No change
Cardiac Arrhythmia/ Cardiac General		
Any Cardiovascular toxicity	Grades 0-2	No change
	Grade 3 or 4	Permanently discontinue
Gastrointestinal		
Nausea and/or Vomiting	Grades 1-3	Treat symptomatically, no change in dose
	Grade 4 vomiting despite anti-emetic medication	Permanently discontinue
Neurology		
Neuropathy: sensory or motor	Grade 1	No change
	Grade 2 or 3	Delay * until resolved to ≤ grade 1 Reduce one dose level in subsequent doses
	Grade 4	Permanently discontinue
All other Docetaxel-Related Adverse Events (excluding hypersensitivity reactions)		
All other docetaxel-Related Adverse Events	Grade 0-2	Treat symptomatically, no change in dose
	Grade 3	Delay* until resolved to ≤ grade 1 Reduce one dose level in subsequent doses
	Grade 4	Permanently discontinue
* A maximum of 2 weeks delay is permitted. If delay exceeding 2 weeks is required by docetaxel-related adverse events, the patient must permanently discontinue docetaxel		

8.5.6 *Hypersensitivity Reactions - Docetaxel*

Acute hypersensitivity reactions to docetaxel should be managed according to the centre's standard of care. *No dose reductions will be made.* Any life-threatening anaphylactic reactions should be treated as necessary and no further therapy with docetaxel will be given.

In case of late-occurring hypersensitivity symptoms (e.g. appearance within 1 week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g. oral antihistamine). Additional oral or parenteral premedication with antihistamine may also be given for the next cycle of treatment, depending on the intensity of the reaction observed. No dose reductions will be made in any case.

Management of Subsequent Cycles: Patients with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

8.5.7 *Duration of Therapy - Docetaxel*

Unless unmanageable adverse events or disease progression occur, treatment with docetaxel will be given for 24 weeks (8 cycles).

8.5.8 *Patient Compliance - Docetaxel*

Compliance with docetaxel treatment is important to the conclusions of this study. Dates of delayed or reduced doses will be recorded on the CRF.

8.6 Concomitant Therapy

The case report forms (CRFs) will capture the use of all drugs, over-the-counter medications, or alternative therapies including herbal supplements, taken by the patient from 2 weeks prior to randomization and until 4 weeks after the end of protocol treatment.

8.6.1 *Permitted*

- Use of supportive therapy for protocol treatment induced toxicities is permitted
- Patients should receive full supportive care (including bisphosphonates) and palliative care (e.g. pain control) as clinically indicated during the trial, including transfusion of blood products, and treatment with antibiotics, antiemetics, antidiarrheals and analgesics when appropriate, *with the exception of* (1) palliative radiotherapy (see 8.6.2 below) and (2) the agents listed in Appendix IX.
- Primary prophylaxis with G-CSF is required to be administered with docetaxel and lapatinib combination therapy. Otherwise, G-CSF, GM-CSF and other hematopoietic growth factors may not be used as a substitute for a scheduled dose reduction for standard chemotherapy regimens unless this is the centre's standard practice; however, they may be used in the management of acute toxicity such as febrile neutropenia when clinically indicated at the discretion of the investigator. Erythropoietin may be used if clinically indicated and as per institutional standards. Use of growth factors must be documented on the case report forms.

8.6.2 *Not Permitted*

- Anti-cancer treatment other than protocol therapy.

Cytochrome P450 inhibitors or Inducers:

- Lapatinib is primarily metabolized by liver enzymes, particularly CYP3A4. Co-administration of potent inhibitors or inducers of this enzyme can result in significant changes in exposure to lapatinib. For this reason, use of CYP3A4 inhibitors and inducers is not permitted before or during the study:
  - Inhibitors – prohibited 7 days before dosing (6 months for amiodarone) and during protocol treatment
  - Inducers – prohibited 14 days before dosing and during protocol treatment

  A comprehensive list of CYP3A4 inhibitors and inducers is provided in Appendix IX. The Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes. If any of the not permitted concomitant medications listed in Appendix IX become necessary for patient management, please contact the NCIC CTG to discuss appropriate washout periods and possible drug interactions.

Glucocorticosteroids (oral):

- Oral glucocorticosteroid use is not allowed during lapatinib treatment unless absolutely necessary (e.g. for treatment of adverse events or protocol-required premedications) or short-term (up to 2 weeks) because many such steroids effectively lower lapatinib exposure through CYP3A4 interactions. See Appendix IX for a list of prohibited oral glucocorticosteroid medications.

Palliative Radiotherapy:

- Palliative radiotherapy must not be administered after randomization. Patients who receive palliative radiotherapy will be declared off protocol therapy.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

9.1 Evaluation During Protocol Treatment

Note: During combined taxane and lapatinib/trastuzumab treatment, cycle length is as follows: if the taxane of choice is paclitaxel each cycle is 4 weeks; if the taxane of choice is docetaxel each cycle is 3 weeks. All timing quoted in weeks in the table below is counted from the first day of protocol treatment.

Investigations		Timing
Physical Exam including:	• physical exam • weight, ECOG Performance Status • concomitant medications • NYHA functional status assessment (see Appendix X)***	*combined taxane and lapatinib / trastuzumab treatment:* day 1 of each cycle *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter
Hematology	• hemoglobin, WBC, granulocytes, platelet count	*combined taxane and lapatinib / trastuzumab treatment:* weekly or 3-weekly on days of taxane chemotherapy administration* *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter
Biochemistry	• total bilirubin, ALT (SGPT) +/- AST (SGOT), alkaline phosphatase, serum creatinine, BUN/urea	
Radiology[1,2]	• chest x-ray or CT chest♦ • CT abdomen♦	*combined taxane and lapatinib / trastuzumab treatment:* at the end of weeks 12 and 24 *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter
	• bone scan / PET♦♦♦	as necessary to confirm CR or PR♦♦ or as clinically indicated or if patient has bone-only evaluable disease (in which case they should be performed at the same time as the chest x-ray / chest CT and CT abdomen scans).
	• CT/MRI of the brain	if clinically indicated (presence of symptoms); mandated at the time of disease progression, regardless of the site of progression.
	• other scans/imaging as necessary to document all sites of disease	*combined taxane and lapatinib / trastuzumab treatment:* at the end of weeks 12 and 24 *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter
Other Investigations	clinical lesion status**	*combined taxane and lapatinib / trastuzumab treatment:* at the end of weeks 12 and 24 *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter
	echocardiogram/MUGA	every 12 weeks
	• serum for biomarkers / proteomics (optional) • plasma for biomarkers (optional)	at the time of disease progression
	biopsy from a metastatic lesion (consenting patients only, selected centres)	

Continued (including footnotes) on next page …

Investigations		Timing
Adverse Events	recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (Appendix V)	*combined taxane and lapatinib / trastuzumab treatment:* day 1 of each cycle *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter
Quality of Life	• EORTC QLQ-C30 (see Appendix VI) • Trial Specific Checklist (see Appendix VI)	*combined taxane and lapatinib / trastuzumab treatment:* at the end of weeks 12 and 24 *single agent lapatinib / trastuzumab treatment:* every 12 weeks until 96 weeks; then every 24 weeks thereafter *also:* at the time patient comes off treatment, if off-treatment reason is either progression or toxicity
Health Utilities *(Canadian and Australian centres only)*	• EQ-5D questionnaire - see Appendix VII	

1 To ensure compatibility, radiological investigations to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner).

2 Patients with a CR or PR should have scans repeated after 4 weeks to confirm response.

* Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed , every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol. Hematology and Biochemistry do not need to be repeated prior to cycle 1 if the baseline evaluations were done within 14 days prior to day 1 of cycle 1.

** For the purposes of this study evaluation of clinical lesion status is defined as the assessment (including photographic assessment) of superficial lesions such as skin nodules and palpable lymph nodes.

*** For patients with cardiac disease only

♦ If MRI of the chest and/or abdomen is submitted instead, this will also be acceptable.

♦♦ Note: For the purposes of PR or CR confirmation, bone scans need to be repeated only for patients who had a positive bone scan at baseline.

♦♦♦ Use PET only if it is the institution's standard procedure for assessing bone metastases.

9.2 Evaluation After Protocol Treatment

After protocol treatment has been stopped, follow up is required at 4 weeks from the date of off protocol therapy (Form 5P) and then at 12 week intervals, counting from the start of protocol treatment, until death. A Form 5 should be used to capture follow-up information prior to progression and a Form 5S should be used after progression.

Investigations		Timing
Physical Exam including:	• physical exam	at each visit
	• weight, ECOG Performance Status	at each visit until disease progression
	• concomitant medications • NYHA functional status assessment (see Appendix X)***	at the 4 weeks visit only
Hematology	• hemoglobin, WBC, granulocytes, platelet count	at the 4 weeks visit only
Biochemistry	• total bilirubin, ALT (SGPT) +/- AST (SGOT), alkaline phosphatase, serum creatinine, BUN/urea	
Radiology[1,2]	• chest x-ray or CT chest♦ • CT abdomen♦	*Until Disease Progression*: every 12 weeks until 96 weeks; then every 24 weeks thereafter**
	• bone scan / PET♦♦♦	*Until Disease Progression*: As necessary to confirm CR or PR♦♦ or as clinically indicated
	• CT/MRI of the brain	*Until Disease Progression*: if clinically indicated (presence of symptoms); mandatory at the time of disease progression, regardless of the site of progression.
	• other scans/imaging as necessary to document all sites of disease	*Until Disease Progression*: every 12 weeks until 96 weeks; then every 24 weeks thereafter**
Other Investigations	clinical lesion status*	*Until Disease Progression*: every 12 weeks until 96 weeks; then every 24 weeks thereafter**
	echocardiogram/MUGA ECG	at the 4 weeks visit♣; at subsequent follow-up visits if clinically indicated
	• serum for biomarkers / proteomics (optional) • plasma for biomarkers (optional)	at the time of disease progression
	biopsy from a metastatic lesion (consenting patients only, selected centres)	
Adverse Events	recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (Appendix V)	each visit[3]
Quality of Life	• EORTC QLQ-C30 (see Appendix VI) • Trial Specific Checklist (see Appendix VI)	*Until Disease Progression:* every 12 weeks until 96 weeks; then every 24 weeks thereafter** *also*: at the time of progression
Health Utilities *(Canadian and Australian centres only)*	• EQ-5D questionnaire - see Appendix VII	

footnotes on next page …

1 To ensure compatibility, radiological investigations to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner) as baseline.

2 Patients with a CR or PR should have scans repeated after 4 weeks to confirm response.

3 Only Adverse Events deemed related to protocol therapy (lapatinib, trastuzumab or taxane chemotherapy).

* For the purposes of this study evaluation of clinical lesion status is defined as the assessment (including photographic assessment) of superficial lesions such as skin nodules and palpable lymph nodes.

** All timing quoted in weeks is counted from the first day of protocol treatment.

*** For patients with cardiac disease only

♦ If MRI of the chest and/or abdomen is submitted instead, this will also be acceptable.

♦♦ Note: For the purposes of PR or CR confirmation, bone scans need to be repeated only for patients who had a positive bone scan at baseline.

♦♦♦ Use PET only if it is the institution's standard procedure for assessing bone metastases.

♣ If an echocardiogram / MUGA was done at the time the patient came off treatment and it was normal , then it does not need to be repeated at the 4 week visit.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 *Progression Free Survival*: Progression free survival is defined as the time interval between the date of randomization and the date of disease progression or death from any cause, whichever comes first. If neither event has been observed, then the patient will be censored at the date of the last adequate disease assessment. Disease progression is defined as objective (radiological / clinical) progression (see sections 10.2.5 and 10.2.6 for definitions of radiological progression and section 10.5.1 for definition of clinical lesions).

10.1.2 *Overall Survival*: Overall survival is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive.

10.1.3 *CNS Metastasis*: CNS metastasis is defined as proof of CNS metastatic involvement by objective means i.e. one or both of the following:
- radiologic evidence (CT or MRI of the brain)
- evidence of malignant cells as proven by biopsy or cytology

10.1.4 *Evaluable for Response*: All patients who have had their disease re-evaluated at least once since baseline will be considered evaluable for response regardless of the amount of treatment received. Patients who are evaluable for response will have their response classified according to the definitions set out in section 10.2 below.

10.1.5 *Overall Objective Response Rate*: The overall objective response rate applies only to patients with measurable disease (see section 10.2.1 for definition) at baseline. It is defined as the rate of complete and partial responses (see section 10.2.5 for definitions).

10.1.6 *Clinical Benefit Response Rate*: The clinical benefit response rate applies to all patients. It is defined as the total number of patients who achieve a complete or partial response (patients with at least one measurable lesion at baseline) plus those patients who have stable disease for at least 24 weeks (all patients - with or without measurable disease at baseline). The response criteria applicable to patients with measurable disease at baseline (Response Evaluation Criteria in Solid Tumours - RECIST) are defined in section 10.2.5. The response criteria applicable to patients without measurable disease at baseline are defined in section10.2.6.

10.1.7 *Evaluable for Quality of Life Assessment*: All patients who have completed the quality of life questionnaire are evaluable for quality of life assessment.

10.1.8 *Evaluable for Adverse Events*: All patients will be evaluable for adverse event evaluation from the time of their first dose of protocol therapy. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (see Appendix V). Safety data will be analysed according to each patient's actual treatment received. Thus, if a patient is randomized to receive lapatinib/taxane, but mistakenly receives trastuzumab/taxane, her safety data will be summarized in the trastuzumab/taxane arm.

10.2 Response and Evaluation Endpoints

Response and progression for patients with at least one measurable lesion at baseline will be evaluated in this study using the international guidelines proposed by the RECIST committee *[Therasse 2000]*. Changes in the largest diameter (unidimensional measurement) of the tumour lesions are used in the RECIST guidelines.

10.2.1 *Measurable Disease*. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm with conventional techniques (physical examination, CT, x-ray, MRI) or as $\geq$ 10 mm with spiral CT scan. All tumour measurements must be recorded in millimetres.

10.2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable.

10.2.3 *Target Lesions*. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease. If there are > 10 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions (see 10.2.4).

10.2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 10 listed as target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present”, “absent” or "unequivocal progression".

10.2.5 *RESPONSE - Patients With At Least One Measurable Lesion*
Patients with at least one measurable lesion, will be assessed for both the Overall Objective Response Rate and the Clinical Benefit Response Rate endpoints. Prior to inclusion in the rate calculations, each patient will have their BEST OVERALL OBJECTIVE RESPONSE on study classified as outlined below:

Complete Response (CR): disappearance of all clinical and radiological evidence of tumour (both target and non-target).

Partial Response (PR): at least a 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum LD and no evidence of progression in non-target lesions.

Stable Disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD and no evidence of progression in non-target lesions.

Progressive Disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as reference the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute progressive disease. Unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response for this category also requires
CR	CR	No	CR	≥ 4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥ 4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* Unequivocal progression in non-target lesions may be accepted as disease progression.

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

10.2.6 *RESPONSE - Patients With Non-Measurable Disease Only*

Patients with only non-measurable disease, will be assessed for the Clinical Benefit Response Rate endpoint (i.e. will *not* be considered for the Overall Objective Response Rate endpoint). Prior to inclusion in the rate calculation, each patient will have their BEST OVERALL RESPONSE on study classified as outlined below:

Stable Disease (SD): steady state of disease. No new lesions and not sufficient progression of non-target lesions to qualify for PD.

Progressive Disease (PD): the appearance of new lesions and/or unequivocal progression of non-target lesions.

Non-Measurable Lesions*	New Lesions	Overall Response	Best Overall Response for this category also requires
Complete disappearance	No	SD	documented at least once ≥ 4 wks. from baseline
Non-PD	No	SD	
PD**	No	PD	no prior SD
Any	Yes	PD	

* Note that these lesions should be recorded under the "Non-Target" lesions table on the CRFs

** Unequivocal progression in non-measurable lesions will be accepted as disease progression.

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

10.3 Response Duration

For patients with measurable disease and who show a confirmed CR or PR, response duration will be measured from the time the measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented or death from any cause, taking as reference the smallest measurements recorded since the treatment started.

10.4 Stable Disease Duration

For patients with at least one measurable lesion, and stable disease as their best overall response, stable disease duration will be measured from the time of start of therapy until the criteria for progression as described in 10.2.5 are met, taking as reference the smallest measurements recorded since the treatment started.

10.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

10.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by colour medical photography including a ruler to estimate the size of the lesion is required.

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

10.5.3 *CT, MRI*. CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

10.5.4 *Ultrasound*. When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

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

10.5.6 *Tumour Markers*. Tumour markers will not be used to assess response in this study.

10.5.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

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

11.0 SERIOUS ADVERSE EVENT REPORTING

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 3.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the NCIC CTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to NCIC CTG.

11.1 Definition of a Reportable Serious Adverse Event

All serious adverse events regardless of whether they are unexpected or related to investigational product, and *also* serious events assessed as related to study participation (i.e. protocol-mandated procedures (e.g. tissue biopsies)), must be reported in an expedited manner (see Section 11.2 for reporting instructions). Note: study participation does not apply to investigational product.

A serious adverse event (SAE) is any adverse event that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support for the purposes of decreasing hematological toxicity (e.g. GCSF), elective surgery and admissions for palliative or terminal care)
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

In addition, because cardiovascular events have previously been seen in patients taking compounds that inhibit HER2/neu when used in combination with or following anthracyclines and also because interstitial pneumonitis has been reported in patients taking compounds that inhibit EGFR, as a precaution, the following will be reported in an expedited manner in this study:

- Severe symptomatic congestive heart failure (CHF) defined as NYHA Class III (not capable of climbing one flight of stairs) or Class IV (having symptoms at rest) AND an absolute decrease in LVEF of more than 10 percentage points from baseline AND to an LVEF value below 50%.
- Any signs or symptoms of pneumonitis that are $\geq$ Grade 3 (by the NCI Common Terminology Criteria for Adverse Events Version 3.0- see Appendix V).
- ALT > 3 times the institutional upper limit of normal AND bilirubin > 2 times the institutional upper limit of normal.
- Any lapatinib dose discontinuation due to hepatotoxicity (see section 8.2.4).

Please Note: An event which is part of the natural course of the disease under study (e.g. hospitalization for signs/symptoms of the disease or disease progression or death due to disease progression) does not need to be reported as an SAE even though serious criteria are met. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between protocol treatment or protocol design/procedures and the disease progression, then this must be reported as an SAE.

11.2 Serious Adverse Event Reporting Instructions

The NCIC CTG Serious Adverse Event Report CRF will be used to capture SAE information. All serious adverse events, INCLUDING those reported in an expedited fashion must also be recorded on the Case Record Forms (CRFs).

All reportable SAEs (as defined in section 11.1), occurring from the time a patient consents to participate and up until and including 28 days from the last dose of the investigational product must be reported in an expedited manner as described below. Exception: SAEs related to study-participation should be reported regardless of when they occur.

If the investigator becomes aware of any SAEs, including death, at any time after a patient has stopped protocol treatment (i.e. after the 28-day post-last-dose period), and he/she considers the event reasonably related to the investigational product, the investigator should report the SAE in an expedited fashion as noted below.

SAEs must be reported as follows:

Canadian Centres:

Within 24 hours: Fax preliminary Serious Adverse Form to:

MA.31 Physician Coordinator or Dora Nomikos or Yvonne Murray
NCIC Clinical Trials Group
Fax: 613-533-2941

Within 10 days: Mail Serious Adverse Event form to the NCIC CTG (signed by the investigator and updated as much as possible).

Non-Canadian Centres:

Report as per local GlaxoSmithKline (GSK) protocol contact instructions.

11.3 Reporting Secondary Malignancies or Myeloid Dysplasia

Secondary malignancies or myeloid dysplasia that do not meet the criteria in section 11.1 must be reported in writing on a Serious Adverse Event Form within 15 working days of when diagnosis is known to the investigator.

11.4 NCIC CTG Responsibility for Reporting Serious Adverse Events to Health Canada (Office of Clinical Trials)

The NCIC CTG will provide expedited reports of SAEs from this study to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting in Canada, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

11.5 NCIC CTG Reporting Responsibility to GlaxoSmithKline

NCIC CTG will notify GSK within 24 hours of receipt of all reportable serious adverse events (as defined in section 11.1) from Canadian centres.

The NCIC CTG will provide GSK with all available information for SAEs from Canadian centres that have been previously deemed reportable to regulatory authorities by NCIC CTG, no later than 72 hours prior to the time these events are due to regulators, so that GSK can prepare IND Safety Reports for the regulatory submission (see also 11.6).

11.6 GlaxoSmithKline Reporting Responsibilities

GSK will notify the NCIC CTG within 24 hours of receipt of all reportable serious adverse events (as defined in section 11.1) from non-Canadian centres. Regional GSK Protocol Contacts will be responsible for reporting SAEs occurring in non-Canadian centres to GSK Safety.

GSK will be responsible for providing the NCIC CTG with the most up-to-date safety reports for events from this study that need to be reported to regulators, no later than 1 working day before they are due to regulators, so that NCIC-CTG can report them to Health Canada (according to section 11.4) within Health Canada's timelines.

GSK will notify NCIC CTG of all Safety Updates (SUs - serious adverse events from other clinical studies with lapatinib which have been deemed reportable to regulators), already reported to regulatory authorities (including Health Canada) by GSK, so that NCIC CTG (following internal assessment) can report them to the MA.31 Canadian Investigators.

11.7 Reporting Safety Reports to Local Research Ethics Boards

Canadian Centres:

NCIC CTG will notify all *Canadian* Investigators of all Safety Reports (SAEs from this trial which have been deemed reportable to regulators) and Safety Updates (SUs- from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Drug Brochure. The date of REB Submission for SAEs and SUs will need to be entered into the NCIC CTG trial MA.31 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:

- this letter must be either printed on institutional letterhead or contain the centre identification/ REB name
- the date of REB submission must be provided
- this form must be signed by one of the approved participants (according to the participants list) for this trial

The submission of these events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned.

Non-Canadian Centres:

GSK will notify all Non-Canadian Investigators of all Safety Reports [this includes INDSRs from this trial, SUs from other clinical trials and Periodic Safety Reports from Investigators (PSRIs)], as appropriate according to local regulations.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy
- Unacceptable toxicity as defined in Section 8.0
- Tumour progression as defined in Section 10.0. Patients ***may*** be permitted to remain on protocol therapy beyond formal objective progression at the medical discretion of the investigator ***and*** after consultation with the NCIC CTG. However:
  - A Form 9 (Relapse/Progressive Disease Report, see Appendix IV) should be completed to document the occurrence of objective progression
  - The CT/MRI of the brain, mandated by the protocol at the time of disease progression, should be performed (see section 9.1)
  - All other investigations (quality of life and health utility questionnaires, serum, plasma and biopsy collection) mandated by the protocol at the time of disease progression (see section 9.1) should be done

  If a patient is allowed to continue on protocol treatment beyond formal objective progression, disease assessment (radiology investigations and physical exam/medical photography, if appropriate) should occur four weeks later, at which time the patient should be taken off protocol treatment if objective progression as per the RECIST criteria is confirmed.
- Symptomatic progression
- Request by the patient
- Pregnancy
- Physician decision to discontinue treatment for any reason

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Duration of Protocol Treatment

Protocol therapy will continue until objective disease progression is documented.

12.3 Therapy After Protocol Treatment is Stopped

After protocol treatment is stopped, therapy is at the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

Refer to section 9.2 and Appendices I and IV for details of follow up and required investigations.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Disease Assessment Review

No central disease assessment review will be performed.

13.2 Central Pathology Review

Patients may be randomized to the study based on local laboratory HER2/neu results. However, central pathology verification of HER2/neu status will also be done on all patients. This will be carried out at the CTAG laboratory at the British Columbia Cancer Agency, Vancouver, BC, Canada.

13.3 Collection of Tumour Tissue

13.3.1 *Central HER2/neu Testing*

The collection of blocks for central HER2/neu testing is a critical part of this trial (see section 5.1.4). Failure to provide blocks for central HER2/neu testing will exclude patients from randomization. Where local centre regulations prohibit submission of blocks of tumour tissue, or where slides are the only available source of tissue, the approval of the NCIC CTG must be sought on whether such patients may be admissible for randomization to the study.

Blocks from existing tumour specimens will be used, thus no further biopsy is required for central HER2/neu testing. Unused tissue block material will be further used for protocol-mandated biomarker studies - see section 13.3.2. Optional tissue banking will be carried out for all consenting patients using any tissue remaining after the protocol-mandated tests have been completed - see section 13.3.7. Upon completion of HER2/neu and other protocol-specified mandatory marker testing (see also section 13.3.2) unused tissue will be returned by courier to the submitting hospital, if required.

Detailed instructions for the submission and shipping of tissue blocks for central laboratory testing will be provided in a separate trial-specific Correlative Sciences Manual.

Central testing will be conducted and reported according to the CAP/ASCO guidelines current as of July 2007.

13.3.2 *Protocol-Mandated Correlative Studies*

The primary tumour phenotype of the entire study cohort will be assessed by conducting immunohistochemistry assessment of ER, PgR, EGFR, CK5/6 and Ki67. Measurement of these markers is mandatory, to ensure that uniformity is achieved with respect to the molecular classification of the tumours, in relation to clinical outcomes. This will be undertaken by constructing a tissue microarray (TMA) from the blocks submitted to the central laboratory (CTAG, Vancouver).

13.3.3 *Correlative Genomic Studies from Submitted Tissue Blocks (Optional)*

The correlative science group will undertake more extensive tumour phenotyping studies that involve testing nucleic acids from the primary tumour (DNA, RNA, microRNAs) using re-sequencing and array based methodologies for genome-scale correlative science as well as further interrogation of the TMAs by immunohistochemistry and in-situ hybridization. These nucleic acids can be extracted from the submitted tissue block providing sufficient tumour material is present and require no additional biopsy or intervention, providing that patient consent is obtained for the optional correlative studies. These studies are regarded as hypothesis-generating and represent a vital opportunity to derive predictive marker sets and pathway analysis in the context of a randomized trial. Collection of normal DNA from blood or other tissue is also desirable as the canonical reference for somatic genomic studies. These studies will be hypothesis generating analyses from the study.

13.3.4 *Primary Metastasis Sub-study (Optional)*

The correlative science group wish to survey genomic aberrations and tumour expression profiles from primary tumour material in a direct comparison with metastatic tumour, to address whether genomic signatures of relapse can be identified and to assess whether signatures of therapeutic resistance/responsiveness can be identified in the primary or metastatic tumour. This will require the submission of primary tumour material as in 13.3.3 from tissue blocks, but additionally the collection of tumour metastatic tissue pre-treatment. The latter will require an additional biopsy from the patient and is optional. For enrolling centres, the protocol for acquisition, storage and dispatch of the tumour tissue to the central laboratory will be provided in a separate Correlative Studies Manual. Tumour tissue will be processed for extraction of tumour nucleic acids (DNA, RNA, microRNAs) by the CTAG laboratory and a bank of tissue and nucleic acids established.

13.3.5 *Biomarkers / Proteomics (Optional)*

A serum and a plasma sample from all consenting patients will be collected prior to the start of treatment and stored for future potential protein studies which may contribute to the understanding of the disease or the response/toxicity associated with treatment. A subsequent serum and a plasma sample will be obtained at the time of disease progression. Details of the samples required and mailing instructions will be provided in a trial specific Correlative Studies Manual.

13.3.6 *Pharmacogenetics (Optional)*

A whole blood sample will be collected at baseline on all consenting patients for pharmacogenetic studies as described in section 2.7.2. Evaluation of genetic polymorphisms will be very important in furthering our understanding of response and toxicity to the therapeutic agents used in this protocol. Details of the samples required and mailing instructions will be provided in a trial specific Correlative Studies Manual.

13.3.7 *Collection of Tumour Tissue for Tumour Banking (Optional)*

Mandatory submission of tumour tissue for HER2/neu testing and additional biomarker testing (ER, PgR, EGFR, Ki67, CK5/6) has been described above. Patients will be asked to separately consent to the banking of the remaining of the paraffin-embedded block of tumour tissue, which will be initially kept at the CTAG laboratory in British Columbia, where the mandatory testing is being conducted and subsequently at the NCIC CTG tissue/tumour bank at Queen's University in Kingston, Ontario. The collection of tissue material for optional banking is not mandatory for participation in the study, but the participation of all centres is strongly encouraged.

As part of the mandatory studies to be done in this trial, a tissue microarray will be constructed. Every effort will be made to preserve the tissue block submitted. Residual paraffin embedded material will be carefully banked as part of the NCIC CTG tissue/tumour bank at Queen's University in Kingston, Ontario. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

This tissue may be used by researchers now or in the future to better understand the nature of breast cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will only be identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out unless the patient has specifically given consent.

All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is a randomized, phase III, open-label study to compare the efficacy of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy (LTax/L) to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy (TTax/T), in women with documented evidence of HER2/neu positive breast cancer (by local or central laboratory testing), which is metastatic and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting. Stratification is by prior (neo)adjuvant HER2/neu targeted therapy (yes, no), prior (neo)adjuvant taxane chemotherapy (yes, no), planned taxane treatment (weekly paclitaxel versus 3 weekly docetaxel), and liver metastasis (yes, no). Patients will be allocated to the treatment arms using minimization *[Tu 2003, Pocock 1975]* to ensure balance in the treatment arms by each stratification factor.

Biomarker Analysis:
All patients will be required to submit a tumour block; this will ensure complete data for central laboratory confirmation of HER2/neu positivity. HER2/neu positivity, as determined by local or central laboratory assessment, is a requirement for justification of participation in this trial due to hypothesized efficacy to both L and T. We will assess EGFR and ER and PgR. EGFR is hypothesized to affect response to L, although not T; the lack of established cut-point for positivity precludes use of EGFR as a stratification factor. Central laboratory testing of ER, PgR and EGFR will permit more uniform assessment of these markers that are known to suffer from inter-laboratory variation. EGFR, ER, and PgR will be included as continuous factors in the exploratory Cox investigations described below as different levels of positivity may affect efficacy.

14.2 Primary Endpoints and Analysis

Primary Endpoint:
Progression free survival will be the primary statistical endpoint. The primary analysis will be a test for non-inferiority in PFS between the treatment arms of LTax/L and TTax/T, where PFS is defined as time from randomization to objective disease progression or death from any cause. If there is evidence of non-inferiority at the final analysis, a test of superiority of LTax/L compared to TTax/T will be performed.

Lack of tumour assessments post-randomization will lead to censoring at the date of randomization. Progression documented between scheduled visits will be assigned to the date of the scan or clinical lesion evaluation indicating progression. No evidence of progression will lead to the assignment of censored at the date of last visit with adequate assessment. Death before first PD assessment, including death between adequate assessment visits, will lead to the assignment of progression, at date of death. Death or progression after more than one missed visit will lead to the assignment of censored at date of last visit with adequate assessment.

Assessment of Primary Event:
Radiological evaluations for tumour measurements, including CT/MRI head, will be required at baseline. CT/MRI evaluation of the head will be required at baseline, at CNS symptomatology, and at any progression. Other radiological evaluations will be at end of Week 12, then every 12 weeks until Week 96, then every 24 weeks, thereafter. Supporting documentation for radiologic / clinical evaluations will be sent to the NCIC CTG for central review, as per standard NCIC CTG process.

Secondary Objectives:
The secondary objectives are to evaluate and compare the two treatment arms with respect to overall survival, time to CNS metastases at the time of first progression, incidence rates of CNS metastases at first progression, overall response rate (complete or partial response), time to response, and duration of response and clinical benefit response rate (CR, or PR, or stable disease at end of week 24). As well, we will examine adverse event profile including cardiac adverse event profile; quality of life as measured by the EORTC QLQ-C30 instrument, and a Trial Specific Checklist; clinical outcomes using relevant biomarker changes in biological samples; and health economics, including both healthcare utilization and health utilities (Canadian and Australian centres only), the latter measured by the EQ-5D Questionnaire.

Populations for Analytic Investigations:
The intent-to-treat (ITT) population will comprise all randomized patients, will be based on the allocated treatment regardless of whether the patient received the assigned treatment, and will be based on the at-randomization values of the stratification factors.

Additional efficacy analyses will involve only those with centrally confirmed HER2/neu positive tumours and per protocol (PP) populations. The PP population will include all eligible patients who received at least 1 cycle of assigned therapy, will utilize baseline values of the stratification factors, and will be based on assigned treatment (expected < 1% change from ITT population).

Analyses:
Analyses will be performed on ITT (primary), centrally confirmed HER2/neu positive patients, and PP data. Time to event endpoints (PFS and OS) for the ITT and PP analyses will be described with a Kaplan-Meier plot, and comparisons between treatment arms will use the stratified log-rank test, adjusted for the stratification factors. These procedures will also be employed for centrally confirmed HER2/neu positive patients, should the balance of patients by stratification factors be maintained for the treatment arms; otherwise, PFS and OS will be described by a Cox survivor plot, which adjusts for effects of stratification factors, with comparisons between treatment arms being the adjusted Cox hazard ratio. Unadjusted analyses will also be performed. As exploratory analyses, Cox proportional hazards model will be used to adjust the observed treatment effect for the influence of baseline study factors, and to identify factors significantly associated with the outcomes listed above, with forward step-wise regressions using the likelihood ratio test criterion.

Sensitivity Analyses:

There will be six types of Sensitivity Analyses performed on the ITT population:

1. Sensitivity Analysis where progression documented between scheduled visits will have progression date assigned to the date of the next scheduled visit.
2. Sensitivity Analysis where Primary Analysis indicator for censored and progressed is reversed *[DiRienzo 2001]*.
3. Sensitivity Analysis where patients who start new anticancer therapy prior to documented progression are considered to be censored on the date of last visit with adequate assessment prior to the start of new anticancer therapy. If a patient has not progressed, died, or received alternative therapy, PFS will be censored at the date of last visit with adequate assessment.

4. Sensitivity Analysis where patients who, prior to documentation of disease progression or death, have treatment discontinuations for undocumented progression, toxicity, or the start of new anticancer therapy are considered to be censored on the date of last visit with adequate assessment. If a patient has not progressed, died, or received alternative therapy, PFS will be censored at the date of last visit with adequate assessment.
5. Sensitivity Analysis where patients who, prior to documentation of disease progression or death, have treatment discontinuations for undocumented progression, toxicity, or the start of new anticancer therapy will be considered to have had an event on the date of last visit with adequate assessment. If a patient has not progressed, died, or received alternative therapy, PFS will be censored at the date of last visit with adequate assessment.
6. If there is evidence of non-inferiority of LTax/L to TTax/T at the final analysis, and there is not evidence of superiority, the effect observed in the TTax/T arm will be compared to that in the historic TTax regimen.

Secondary Analyses:
Secondary endpoints of this study include the incidence of CNS metastases, and time to CNS metastases, at first progression. The latter is defined as the time from randomization until disease progression where CNS metastasis is documented at the time of breast cancer progression. Cumulative incidence curves will describe experience by treatment arms, and comparisons between treatment arms will use two-sided stratified log rank tests. Disease progression without CNS progression will be considered as a competing risk. The incidence of CNS metastases at first progression will be the ratio of the number of subjects with CNS metastases at progression over the total number of subjects.

Quality of Life Analysis:
The EORTC QLQ-C30 and the Trial Specific Checklist will be mandatory. Scoring of questionnaires will be conducted by the central office of NCIC CTG according to the scoring manual of the EORTC QLQ-C30. The Trial Specific Checklist items will be scored individually.

The EORTC QLQ-30 Global Score will be used for our primary assessment of quality of life. The published EORTC QLQ-C30 data of Efficace, et al *[Efficace 2004]* for a similar metastatic patient population indicated a baseline SD of 24 for the Global Score. A minimally clinically important difference obtained from patients is a 10 point difference over time *[Osoba 1998]*. The 10 point mean difference can also be justified by being between 0.3 and 0.5 SD, with the Global Score SD of 24 *[Norman 2003]*. With this trial's sample size of approximately 600 patients (so as to achieve 536 patients with centrally confirmed HER2/neu disease) we will have over 80% power to detect a 10 point mean difference between treatment arms of the Global Score of the EORTC QLQ-C30 at the 12 week assessment, in a two-sided 5% alpha test. A lack of significance would indicate no evidence of difference in Global Score between trial therapies at the above statistical test specifications.

Economic Analysis:
A prospective health economic evaluation will be performed comparing treatment and resource use related to study drugs but not protocol driven. The analysis will be conducted over the study period ending at time of disease progression. Data will be gathered and assessed using descriptive statistics. Health economic outcomes to be studied include the following: 1) incremental costs between study arms, 2) incremental life-year (LY) gained between study arms, 3) incremental quality adjusted life-year (QALY) gained between study arms, 4) incremental cost/LY ratio, and 5) incremental cost/QALY ratio. The perspective of this analysis will be that of the Canadian and Australian governments as payers in a universal access health care system. It is anticipated that most, if not all, important analysis elements will be available as prospectively collected.

14.3 Sample Size and Duration of Study

Three phase III trials were used to estimate the historic-base effect for TTax. The effect should be similar to historic due to the following reasons: based on the timing of the release of adjuvant trastuzumab trial data and relatively low rate of relapse seen to date, it is anticipated that a substantial proportion of patients enrolled to the proposed study will not have received prior trastuzumab therapy in the (neo)adjuvant setting; for patients who relapse at least 1 year after completion of trastuzumab, there is a reasonable expectation that the tumour will retain sensitivity to HER2/neu blockade and will experience a similar response to historic with a combination taxane and trastuzumab therapy followed by single-agent trastuzumab in the proposed study. We also hypothesize that regardless of the taxane used, the tumour response will be similar to that reported with taxol. The study has been stratified by taxane in the event this is not true. The three year PFS for patients is estimated to be 10.4% based on averaging exponential hazards observed for patients assigned to the TTax arms of published phase III studies [paclitaxel + T *(Slamon, Robert)*; docetaxel + T *(Forbes)*].

This study will examine whether the LTax/L treatment regimen is non-inferior to the TTax/T regimen i.e. H_0: Hazard Ratio (HR)=1.25, for LTax/L as compared to TTax/T; H1: HR=0.9. Although the primary analysis is ITT on all randomized patients, we want to ensure adequate power to test this hypothesis in the centrally confirmed HER2/neu positive patient population. With 390 events, in the centrally confirmed HER2/neu positive patient population, the study will have 90% power and one-sided alpha of 2.5% for this test of non-inferiority.

The basis (H1: HR=0.9) for non-inferiority is that ad hoc analyses from a randomized phase III trial of capecitabine plus or minus L have indicated a reduction in the incidence of CNS as the first site of relapse *[Geyer 2006]*. This leads to the postulation in the non-inferiority setting, that L may be slightly superior to T.

To obtain a more conservative estimate for the non-inferiority margin, we used the upper bound of the 95% confidence limit for chemotherapy $\pm$ T (0.63) instead of Tax $\pm$ T (0.53; (*Slamon 2001)*). If in this trial, the 95% confidence interval for the hazard ratio for TTax/T regimen compared with LTax/L regimen can be shown to be entirely above the square root of 0.63 (=0.8), this will demonstrate avoidance of loss of 50% of the established TTax effect. This criterion is identical to the confidence interval for the hazard ratio for LTax/L compared with TTax/T being entirely below the reciprocal of 0.8 (1/0.8 = 1.25). Thus, the test of H0: Hazard Ratio (HR) = 1.25 vs H1: HR=0.9 is equivalent to demonstrating avoidance of loss of 50% of the established TTax effect. The non-inferiority margin of 1.25 is also the upper limit for loss of efficacy that would be clinically acceptable using data from a randomized trial of standard chemotherapy (anthracycline and cyclophosphamide or Tax) $\pm$ T.

The comparison of LTax/L relative to TTax/T will be to evaluate non-inferiority by comparing the upper bound of the 95% confidence interval for the hazard ratio (LTax/L vs TTax/T) to a rigorously defined margin (1.25), i.e. 1-sided alpha for HR to exceed 1.25 is 2.5%. If the upper bound of the confidence interval is equal to, or falls below, the pre-specified margin at the final analysis, there is evidence of non-inferiority and a test of superiority of LTax/L compared to TTax/T will be performed.

As a stepwise procedure is adopted, whereby the test for superiority will be performed if the lapatinib-containing therapy is deemed to be non-inferior, no adjustments to alpha will be made for the superiority comparison. For the superiority test, with 390 events, the study will have approximately 80% power with a 2-sided alpha of 5.0% to provide evidence to support the null hypothesis H0: HR=1.0 or to reject in favor of the alternative hypothesis H1: HR=0.75.

A non-inferiority trial requires similar conclusions from both full analysis data, based on the intention to treat (ITT) principle, and the per protocol (PP) analysis data (The European Agency for the Evaluations of Medicinal Products Evaluation of Medicines for Human Use CPMP/EWP/482/99 London, 27 July 2000). As the study is powered at 90% for the test of non-inferiority in the centrally confirmed HER2/neu positive population and we anticipate < 1% of subjects to be excluded from the per protocol population, there will be adequate power to test for non-inferiority in the PP population.

We will accrue a sample size of 536 patients who are HER2/neu positive by central laboratory testing. Accrual will continue until there are 536 such patients; we would accrue 600 patients based on local positive test indication if there are 64 (12% of 536) discrepant HER2/neu test results with the central laboratory. Accrual should take place in 2 years, with further follow-up of 1 year for PFS, for a three-year study period for the primary endpoint. Based on previous accrual to NCIC CTG MA.19, which was an international study involving metastatic breast cancer patients, we consider this accrual rate to be achievable.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.

The safety population will consist of patients who receive at least one dose of study medication and will be based on actual treatment received if this differs from randomized treatment assignment.

The incidence of toxicities will be summarized by type of adverse event and severity. A Fisher's exact test will be used to compare toxicities between the treatment groups. Toxicity data will be reviewed by the Group's DSMC on a six-monthly basis.

14.5 Interim Analysis

An interim analysis will be performed on the ITT population after about 50% of the events (approximately 195 events) have been observed in the centrally confirmed HER2/neu positive population. The test at the interim analysis will be a two-sided test of superiority. The two-sided p-value for the interim and final superiority analyses using Lan and DeMet O'Brien-Fleming-type boundaries will be 0.00305 and 0.04695, respectively, so that the nominal alpha level of 0.05 will be maintained in the final analysis. The trial would be stopped at the interim analysis if there is evidence of superiority, or of harm, for LTax/L. The results of the interim analysis will be presented to the Data Safety Monitoring Committee.

The basis for test specifications for both non-inferiority and superiority is the confidence limits around the hazard ratio; therefore, the alpha for the non-inferiority test at the final analysis will be adjusted to account for the interim PFS analysis (i.e. 1-sided alpha for the non-inferiority test=0.02347) to maintain the nominal alpha level of 0.025 in the final analysis.

14.6 Post-Marketing Analyses

Appendix XIII outlines the plans for the FDA requested post marketing OS analyses. The planned analyses will take place following completion of the final analysis for PFS , and will have no impact on the conduct or analyses for PFS.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the NCIC Clinical Trials Group and GlaxoSmithKline, may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.
- In the event of a separate paper dealing with the correlative studies outcomes, the first author will generally be the Correlative Sciences Coordinator on the trial committee.
- In the event of a separate paper dealing with the Health Economics outcomes, the first author will generally be the Health Economics Coordinator on the trial committee.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the NCIC Clinical Trials Group with support from the Canadian Cancer Society and from GlaxoSmithKline. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the study chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by GlaxoSmithKline, the NCIC CTG physician, senior biostatistician, study coordinator, and approval of the study chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Institution Eligibility for Participation

Selected member centres in good standing of the NCIC CTG are eligible to participate in this study. Any centre joining the NCIC CTG is required to sign a Participating Centre Study Agreement and have Standard Operating Procedures regarding the conduct of clinical trials.

The NCIC CTG will submit via fax to Health Canada for each participating Canadian centre prior to local activation a completed Health Canada Clinical Trial Site Information Form.

16.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the NCIC CTG:

- A current curriculum vitae, updated and submitted within two years at the time of randomization.

For all *Canadian* investigators (principal investigators and co-investigators) the following documentation must be on file with the NCIC CTG:

- Documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate).
- Completion of the required NCIC CTG GCP modules

For the principal investigator of *Canadian* centres only:

- A Health Canada Qualified Investigator Undertaking Form must be completed and signed by the principal investigator of the study at participating Canadian centres and received by the NCIC CTG central office before that centre can be locally activated.

16.3 REB (Research Ethics Board) Approval for Protocols

16.3.1 *CANADIAN Centres*:

Each Canadian participating centre will have on file with the NCIC CTG central office, as part of its membership/ agreement documents, a description of its ethics review process and composition of its REB.

REB Composition

Membership of an REB approving this protocol must be consistent with Canadian regulatory requirements, summarized as follows:

- at least 5 members;
- majority of members are Canadian citizens or permanent residents;
- includes 2 members whose primary expertise and experience are in a scientific discipline with broad experience in the methods and areas of research to be approved (1 of these is from a medical discipline);
- includes 1 member knowledgeable in ethics;

- includes 1 member knowledgeable in Canadian laws relevant to the biomedical research to be approved;
- includes 1 member whose primary experience and expertise are in a non-scientific discipline;
- includes 1 member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the NCIC CTG or the centre where the clinical trial is to be conducted.

A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation to the following may be included in the signed local ethics approval document:

- The membership of the Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations;
- The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice; and
- The Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified investigator named at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

This documentation must be received by the NCIC CTG central office before the centre can be locally activated.

Initial Approval
Canadian member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB.

Annual Re-Approvals
Annual re-approvals must continue until NCIC CTG informs you that they are no longer required.

Amendments/Administrative Updates
All amendments or administrative updates to the protocol must undergo review by local REBs. Amendments/administrative updates will be circulated to all participating sites in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified.

Amendments will be reviewed and approved by Health Canada prior to central implementation of the amendment, and by REBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects. Amendments may be distributed with Health Canada REB attestation forms; if so, this form must be completed. For each amendment NCIC CTG will collect documentation of REB approval, and a completed REB attestation form, including the date the amendment is implemented (if applicable).

REB Refusals
If an REB refuses to approve this protocol (or an amendment/administrative update to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

Serious Adverse Events, Safety Updates and Investigator Brochure Updates
During the course of the study serious adverse events, safety updates or investigator brochure updates may be sent to you for reporting to your REB. The date of REB submission for these documents will need to be entered into the NCIC CTG trial MA.31 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

16.3.2 *NON-CANADIAN Centres*:

Prior to initiation of a non-Canadian site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a U.S. IND.

The study will be conducted in accordance with all applicable regulatory requirements, including a U.S. IND.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both. Written informed consent must be obtained from each subject prior to participation in the study.

16.4 Informed Consent

Informed Consent Document
The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

It is essential that the consent form contain a clear statement which gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the NCIC CTG, GSK and other agencies as necessary. The consent form must include all ICH-GCP consent elements. In addition, the consent form should include all elements required by NCIC CTG policy, and centres receiving funding from NCEHR, SSHRC and/or CIHR should include elements from the Tri Council Policy Statement (TCPS).

Informed consent forms that do not contain all ICH-GCP required elements will require an amendment and will lead to the delay of local activation. A complete list of the elements required by regulations, guidelines and NCIC CTG policy can be found by accessing the NCIC CTG website at http://www.ctg.queensu.ca/private/ethics/consent_RE_Checklist.html.

Consent Process/Patient Eligibility
Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

16.5 Retention of Patient Records and Study Files

16.5.1 *CANADIAN Centres*

ICH Good Clinical Practice guidelines apply to NCIC CTG studies. It is the responsibility of NCIC CTG to inform Canadian investigators/institutions as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

NCIC CTG will notify all the trial Canadian investigators/institutions and all the regulatory authorities if clinical development of an investigational product discontinues or when trial related records no longer need to be retained.

16.5.2 *NON-CANADIAN Centres*

Following closure of the study, Non-Canadian investigators or heads of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform Non-Canadian investigators of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

Non-Canadian investigators must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

16.6 Centre Performance Monitoring (applicable to *Canadian* centres only)

This study is eligible for inclusion in the Centre Performance Index (CPI). Forms are to be submitted according to the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

16.7.1 *CANADIAN Centres*:

In addition to the routine review of case report forms and supporting documents sent to the NCIC CTG central office, site monitoring will be conducted at participating Canadian centres during the course of the study as part of the overall quality assurance program. The monitors will require access to patient medical records to verify the data, as well as essential document binders, standard operating procedures (including electronic information) and ethics documentation.

In addition to monitoring, audits of the site records may be conducted and regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

16.7.2 *NON-CANADIAN Centres*:

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact Non-Canadian sites prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study in Non-Canadian centres to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all relevant documents

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are listed in Appendix IV.

16.9 Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities for Non-Canadian centres, with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

NCIC CTG or GSK, upon mutual consultation, reserve the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If NCIC CTG and/or GSK determines that such action is required, they will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, NCIC CTG / GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, NCIC CTG and GSK will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. NCIC CTG / GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

16.10 Provision of Study Results and Information to Investigators for *Non-Canadian* Centres

For Non-Canadian sites, where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. NCIC CTG will make the content of the standard NCIC CTG Spring Meeting Book tables (comprised of summary tables on accrual, eligibility, patient characteristics, adverse and serious adverse events, reasons off-protocol treatment and causes of death) available to the investigator signatory, upon request. Requests for additional information as a result of local regulatory requirements must be approved by NCIC CTG and will be dealt with on an individual basis.

Upon completion of the clinical study report, GSK will provide Non-Canadian site investigators with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

16.11 Data Safety Monitoring Committee (DSMC)

A DSMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study.

17.0 REFERENCES

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APPENDIX I – PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-Study	During Treatment				At the time of PD	Post-Treatment			
		Combined taxane and lapatinib / trastuzumab treatment phase			Single agent treatment phase Every 12 wks		4 wk visit only	Each Visit	Each Visit until PD	Every 12 wks until PD
		Day 1 of each cycle✪	On days of taxane treatment	End of wks 12 and 24						
History and Physical Exam										
Medical History	✓							✓		
Physical examination	✓	✓			✓**			✓		
Height	✓									
Weight, ECOG Performance Status	✓	✓			✓**				✓	
Concomitant Medications	✓	✓			✓**		✓			
NYHA functional status assessment (see Appendix X)****	✓	✓			✓**		✓			
Hematology										
Hemoglobin, WBC, granulocytes, platelet count	✓		✓♣♣		✓**		✓			
Biochemistry										
Total bilirubin, ALT (SGPT) +/- AST (SGOT), alkaline phosphatase, serum creatinine, BUN /urea	✓		✓♣♣		✓**		✓			
Radiology[1]										
Chest x-ray or CT chest♦♦; CT abdomen♦♦	✓			✓	✓**					✓**
Bone scan / PET[2]	✓									
CT/MRI of the brain[3]	✓					✓				
Other imaging as necessary to document all sites of disease	✓			✓	✓**					✓**
Other Investigations										
Clinical Lesion Status[4]	✓			✓	✓**					✓**
Pregnancy test (serum or urine)	✓									
ECG	✓						✓♣			
Echocardiogram/MUGA	✓			✓	✓		✓♣			
Local or central laboratory confirmation of HER2/neu positive status✪✪	✓									
Central laboratory HER2/neu testing	✓♦									
Central laboratory testing for mandatory biomarkers (see section 2.7.1)	✓♦									

Continued on Next Page (including footnotes) …

Required Investigations	Pre-Study	During Treatment: Combined taxane and lapatinib / trastuzumab treatment phase: Day 1 of each cycle○	During Treatment: Combined taxane and lapatinib / trastuzumab treatment phase: On days of taxane treatment	During Treatment: Combined taxane and lapatinib / trastuzumab treatment phase: End of wks 12 and 24	During Treatment: Single agent treatment phase Every 12 wks	At the time of PD	Post-Treatment: 4 wk visit only	Post-Treatment: Each Visit	Post-Treatment: Each Visit until PD	Post-Treatment: Every 12 wks until PD
Other Investigations *continued*										
Biopsy from a metastatic lesion (primary metastasis sub-study – consenting patients, optional centre participation)	✓*					✓				
Tumour Banking (optional)	✓♦									
Serum for biomarkers / proteomics (optional)	✓*					✓				
Whole Blood for pharmacogenetics (optional)	✓*									
Plasma for biomarkers (optional)	✓*					✓				
Adverse Events										
Recorded and graded according to NCI CTCAE Version 3.0	✓	✓			✓**			✓[5]		
Quality of Life										
EORTC QLQ-C30, Trial Specific Checklist	✓			✓	✓***	✓				✓**
Health Utilities *(Canadian and Australian centres only)*										
EQ-5D questionnaire	✓			✓	✓***	✓				✓**

✪ During combined taxane and lapatinib/trastuzumab treatment, cycle length is as follows: if the taxane of choice is paclitaxel each cycle is 4 weeks; if the taxane of choice is docetaxel each cycle is 3 weeks.

✪✪ Patients must have laboratory confirmed HER2/neu overexpressing and/or amplified disease (by the criteria described in section 5.1.3) to be considered for randomization. Local laboratory confirmation of HER2/neu positive status will be sufficient for patient randomization. Central laboratory (CTAG) HER2/neu confirmation will be required prior to randomization only in cases where local HER2/neu testing is not available or where the result of the local laboratory HER2/neu testing is equivocal.

♦ Tumour specimen to be collected at the time of randomization. Actual testing to be done post-randomization.

♦♦ If MRI of the chest and/or abdomen is submitted instead, this will also be acceptable

* To be done after randomization and prior to the start of treatment.

** Every 12 weeks until 96 weeks; then every 24 weeks thereafter.

*** Every 12 weeks until 96 weeks; then every 24 weeks thereafter; also at the time patient comes off treatment if off treatment reason is toxicity or PD.

**** For patients with cardiac disease only.

♣ Also perform at subsequent follow-up visits if clinically indicated. If an echocardiogram / MUGA was done at the time the patient came off treatment and it was normal , then it does not need to be repeated at the 4 week visit.

♣♣ Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol. Hematology and Biochemistry do not need to be repeated prior to cycle 1 if the baseline evaluations were done within 14 days prior to day 1 of cycle 1.

1 To ensure compatibility, the baseline and subsequent radiological investigations to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner). Patients with a CR or PR should have their scans repeated after 4 weeks to confirm response.

2 At baseline a bone scan or PET (if this is the institution's standard procedure for assessing bone metastases), with plain radiographs to confirm disease as necessary, is mandatory. Thereafter, bone scans / PETs do not need to be repeated routinely except to confirm CR or PR (only for patients who had a positive bone scan at baseline) or as clinically indicated, or if the patient has bone only evaluable disease.

3 CNS imaging to be performed at baseline. Thereafter to be done if clinically indicated (presence of symptoms) and at the time of disease progression, regardless of the site of progression.

4 Evaluation of clinical lesion status is defined as the assessment (including photographic assessment) of superficial lesions such as skin nodules and palpable lymph nodes.

5 Only Adverse Events deemed related to protocol agents (lapatinib, trastuzumab or taxane chemotherapy).

APPENDIX II – PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III – DRUG DISTRIBUTION, SUPPLY AND CONTROL

Note: It is expected that centres will use their commercial supply of trastuzumab and taxane-based therapy for this trial. In situations where the cost of these drugs is not covered by third party payment (i.e. insurance), then every effort will be made to reimburse centres for their cost.

Sites should use their own local supply of G-CSF for prophylactic use in patients receiving the docetaxel/lapatinib combination. Reimbursement will occur for up to a maximum of the cost of non-pegylated filgrastim upon receipt by GlaxoSmithKline of the corresponding invoice/receipt.

General and Drug Accountability

Investigational product (lapatinib) should be stored in a secure area according to local regulations and under the storage conditions stipulated on the investigational product label. The contents of the label will be in accordance with all applicable regulatory requirements. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.
- Retain samples sent to third party for bioavailability/bioequivalence, if applicable.

NCIC CTG will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements. Accountability will be maintained and bottles will be treated as unit dose containers (i.e., bottles and or tablets will not be shared between patients).

The health care professional will determine the number of bottles, and the appropriate bottle dosage strength, to dispense to the patient. The health care professional will instruct the patient that all dispensed bottles must be returned at each follow-up visit, at which time a tablet count will be conducted to assure patient dosing compliance.

Destruction and Return of Investigational Product

- Patients must return all unused study medication and empty containers to the investigator or pharmacist. Returned study medication and empty containers should be kept at the centre until a monitor has visited the center and completed drug accountability on the patient returns.
- At the end of the study, it must be possible to reconcile delivery records with records of usage/returned stock by completion of the study drug accountability form. Any discrepancies must be accounted for.
- For Canadian sites, all unused or returned study medication, after accountability and reconciliation are concluded, should be destroyed locally. In non-Canadian sites and after completion of the study, all unused study medication will be inventoried and packaged for return shipment by the site, or where applicable, study medication will be destroyed locally at the site and not returned to GSK. Destruction of study medication must not take place without accountability and reconciliation been performed first by a monitor.

Distribution

Drug will be distributed by GlaxoSmithKline or designee to each participating centre. Start up supplies will be dispatched upon receipt at NCIC CTG of all required regulatory documentation including copies of REB approval and the REB-approved consent form. Full details regarding drug reordering will be supplied at study initiation.

APPENDIX IV – DOCUMENTATION FOR STUDY

Follow-up is required for all patients from the time of randomization. Ineligible patients will be followed using Forms 5P, 5, 9 and 6.

Form	To be Completed	Due in the NCIC CTG Central Office (Canadian Centres*)	Supporting Documentation Required
Signed Web Eligibility Checklist (WEC) print-out	To be printed from the Confirmation of Randomization email**	Within 6 weeks of randomization	*Canadian Centres:* Copies of all signed consent forms♦♦, relevant pathology/ cytology reports, operative and radiology reports, ECG report, ECHO/MUGA report and pregnancy test results, if applicable *Non-Canadian Centres:* Copies of signature and checkbox pages for correlative studies (tissue, blood and sub-study) consent forms, relevant pathology/ cytology reports, operative and radiology reports, and ECHO/MUGA report
Form 1 Initial Evaluation	Within 2 weeks of randomization		
Form 3A & Form 3B Systemic Therapy/ Adverse Event Report	Form 3A - Combined Treatment *During the combined treatment phase:* at the end of each cycle of combined treatment Form 3B - Monotherapy *Single-agent treatment phase:* every 12 weeks until 96 weeks; then every 24 weeks thereafter***	Within 2 weeks of completion of the treatment period	Relevant radiology reports to document all sites of disease
Form 5P Post-Treatment Follow-up Report	ALL patients: 4 weeks after off protocol treatment	Within 8 weeks of follow up visit	
Form 5 Follow-up Report	Prior to progression: every 12 weeks until progression	Within 8 weeks of follow up visit	Relevant radiology reports to document all sites of disease
Form 5S Short Follow-up Report	After progression: every 12 weeks	Within 8 weeks of follow up visit.	
Form 6 Final Report	When patient dies	Within 8 weeks of patient's death	Autopsy report, if done.
Form 9 Relapse/Progressive Disease Report	Upon objective disease progression	Within 8 weeks of progression	CT/MRI of Brain Report
Serious Adverse Event Report Form[1]	At the time of event	Serious Adverse Event Report Form to be FAXED within 24 hours[1].	

Continued (including footnotes) on next page …

Form	To be Completed	Due in the NCIC CTG Central Office (Canadian Centres*)	Supporting Documentation Required
Quality of Life: QLQ-C30 and Trial Specific Checklist	*At Baseline* *During the combined treatment phase:* at the end of weeks 12 and 24	With the relevant form (Form 1, Form 3, Form 5 or Form 9)	None
Health Utilities: EQ-5D questionnaire *Canadian and Australian Centres only*	*Single agent treatment phase:* every 12 weeks until 96 weeks; then every 24 weeks thereafter *Also:* at the time patient comes off treatment, if off-treatment reason is either progression or toxicity and at the time of PD		
Resource Utilization Assessment Form *Canadian and Australian Centres only*	Prior to progression: every time a Form 3 or Form 5♦ gets completed Also: at the time of progression	With the relevant form (Form 3, Form 5 or Form 9)	

1 See Section 11.0 Serious Adverse Event Reporting for details.

* Different timelines will apply to Non-Canadian centres depending on monitoring schedule - details to be provided at study initiation

** The WEC will be completed electronically in Mango as part of the randomization process. A confirmation of randomization email will automatically be sent to the centre following each successful randomization. In addition to randomization information (time/date of randomization, stratification factors, arm assignment etc.), this email will also include an electronic record of the patient eligibility information previously entered by the site on the Mango WEC. The WEC information provided on the confirmation email should be printed and signed (at the designated space, at the bottom of the print-out) by the investigator. The signed WEC print-out should be submitted together with the Form 1.

*** All timing quoted in weeks, is counted from the first day of protocol treatment.

♦ A Resource Utilization Assessment Form should also be submitted together with the Form 5P, but ONLY if the patient has come off treatment for reasons other than progression, i.e. if the 4-week post-treatment visit occurs prior to PD.

♦♦ For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the checkbox page(s)/signature page(s) of the optional consent (if applicable), provided that the version date of the consent form is indicated.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 3.0 (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) for adverse events and serious adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page: http://ctep.cancer.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Note: Patients from Canadian and Australian centres should complete the quality of life assessment before the health utilities assessment.

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The centre CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that she prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

   The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule (see section 6, 9.1 and 9.2).

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

   The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

   There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

   A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

      Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if she is willing to complete one:

      If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if she is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the centre clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **MA.31**
GSK Protocol Number: EGF108919

This **page** to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _____ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization ☐ At the time of disease progression ☐ At the time of off treatment, if off due to toxicity

☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Week 60 ☐ Week 72 ☐ Week 84 ☐ Week 96
☐ Week 120 ☐ Week 144 ☐ Week 168 ☐ Week _____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:	Pharm Co:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

(NCIC CTG Trial MA.31; GSK Protocol Number EGF108919)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

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

During the past week:	Not At All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very Poor						Excellent

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

1	2	3	4	5	6	7
Very Poor						Excellent

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

During the past week:	Not At All	A Little	Quite a Bit	Very Much
31. Did you have a skin rash? *(If you answered "Not At All" skip question 32. If you answered "A Little", "Quite a Bit" or "Very Much" go to question 32)*	1	2	3	4
32. Were you bothered by skin rash?	1	2	3	4
33. Have you been bothered by taking your prescribed study therapy (oral lapatinib or intravenous trastuzumab)?	1	2	3	4
34. Have you been bothered by having intravenous treatment?	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VII - HEALTH UTILITIES ASSESSMENT

Introduction

Note: Health Utilities Assessment applies to Canadian and Australian centres only. Patients from these centres should complete the quality of life assessment before the health utilities assessment.

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, progression free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

   Health utilities data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, symptoms, side-effects, *et cetera*.

The centre Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that she prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule (see sections 6, 9.1 and 9.2).

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if she is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if she is willing to complete a questionnaire over the phone. If the patient agrees, read out questions 1-5 and range of possibilities, and record the answers. The visual analogue scale should not be completed in this case. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Health Utilities Component

The only time that we will not require a patient to complete the health utilities questionnaires is if she is not literate in either English or French. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Health Utilities Questionnaire

If a patient speaks and reads English or French, but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

8. Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D Questionnaire in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

EQ-5D Questionnaire – **ENGLISH**

NCIC CTG Trial: **MA.31**
GSK Protocol Number: EGF108919

This **page** to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _____ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization ☐ At the time of disease progression ☐ At the time of off treatment, if off due to toxicity

☐ Week 12 ☐ Week 24 ☐ Week 36 ☐ Week 48 ☐ Week 60 ☐ Week 72 ☐ Week 84 ☐ Week 96
☐ Week 120 ☐ Week 144 ☐ Week 168 ☐ Week _____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:	Pharm Co:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____	_____

EQ-5D Questionnaire

NCIC CTG: MA.31
GSK Protocol Number: EGF108919

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

1. **Mobility**
   a. I have no problems in walking about ☐
   b. I have some problems in walking about ☐
   c. I am confined to bed ☐

2. **Self-Care**
   a. I have no problems with self-care ☐
   b. I have some problems washing or dressing myself ☐
   c. I am unable to wash or dress myself ☐

3. **Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
   a. I have no problems with performing my usual activities ☐
   b. I have some problems with performing my usual activities ☐
   c. I am unable to perform my usual activities ☐

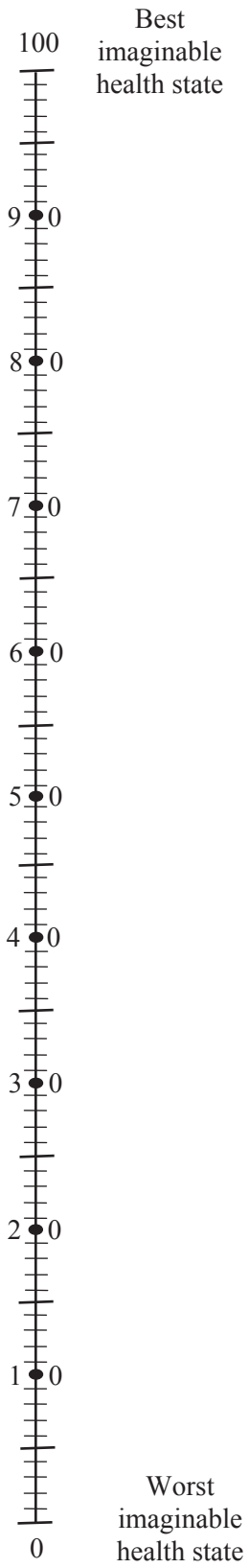
4. **Pain/Discomfort**
   a. I have no pain or discomfort ☐
   b. I have moderate pain or discomfort ☐
   c. I have extreme pain or discomfort ☐

5. **Anxiety/Depression**
   a. I am not anxious or depressed ☐
   b. I am moderately anxious or depressed ☐
   c. I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VIII - 6TH EDITION OF THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 6th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org/initiatives.html). These staging criteria should be used for new trials.

APPENDIX IX - PROHIBITED MEDICATIONS

Drug class	Agent	**Wash-out** (period of time that the medication should be discontinued prior to administration of the first dose of protocol treatment)*
Inducers of CYP3A4		
Antibiotics	All rifamycin class agents (rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (phenobarbital)	14 days
Antiretrovirals	Efavirenz, nevirapine, tipranivir, etravirine	14 days
Glucocorticoids (oral) (premedication before the administration of taxanes is allowed)	Chronic use of cortisone (> 50mg), hydrocortisone (> 40 mg), prednisone or prednisolone (> 10 mg), methylprednisolone or triamcinolone (> 8 mg), betamethasone or dexamethasone (> 1.5 mg). Glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed. Short term steroid use (up to 2 weeks) is allowed**.** Premedication for taxane treatment is permitted.	14 days
Other	St. John's Wort, modafinil	14 days
Inhibitors of CYP3A4		
Antibiotic	clarithromycin, erythromycin, troleandomycin, flucloxacillin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (> 150 mg daily), voriconazole	7 days
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir, atazanavir	7 days
Calcium channel blockers	verapamil, diltiazem	7 days
Antidepressants	nefazodone, fluvoxamine	7 days
GI Agents	Cimetidine**, aprepitant	7 days
Other	grapefruit, grapefruit juice, star fruit, papaw amiodarone	7 days 6 months
Miscellaneous		
Antacids	Magnesium and aluminium hydroxide, simethicone, calcium carbonate, magnesium carbonate	1 hour before and after dosing
Herbal or dietary supplements and traditional Chinese medicines	Ginkgo biloba, kava, grape seed, valerian, ginseng, *Echinacea*, evening primrose oil.	14 days

* All patients must have observed the specified washout period for all prohibited drugs prior to randomization. However if the patient is randomized to Arm 2 (trastuzumab arm) then it is acceptable for the Investigator to restart the medications

** Note: cimetidine may be used as taxane pre-medication if this is the local institutional practice

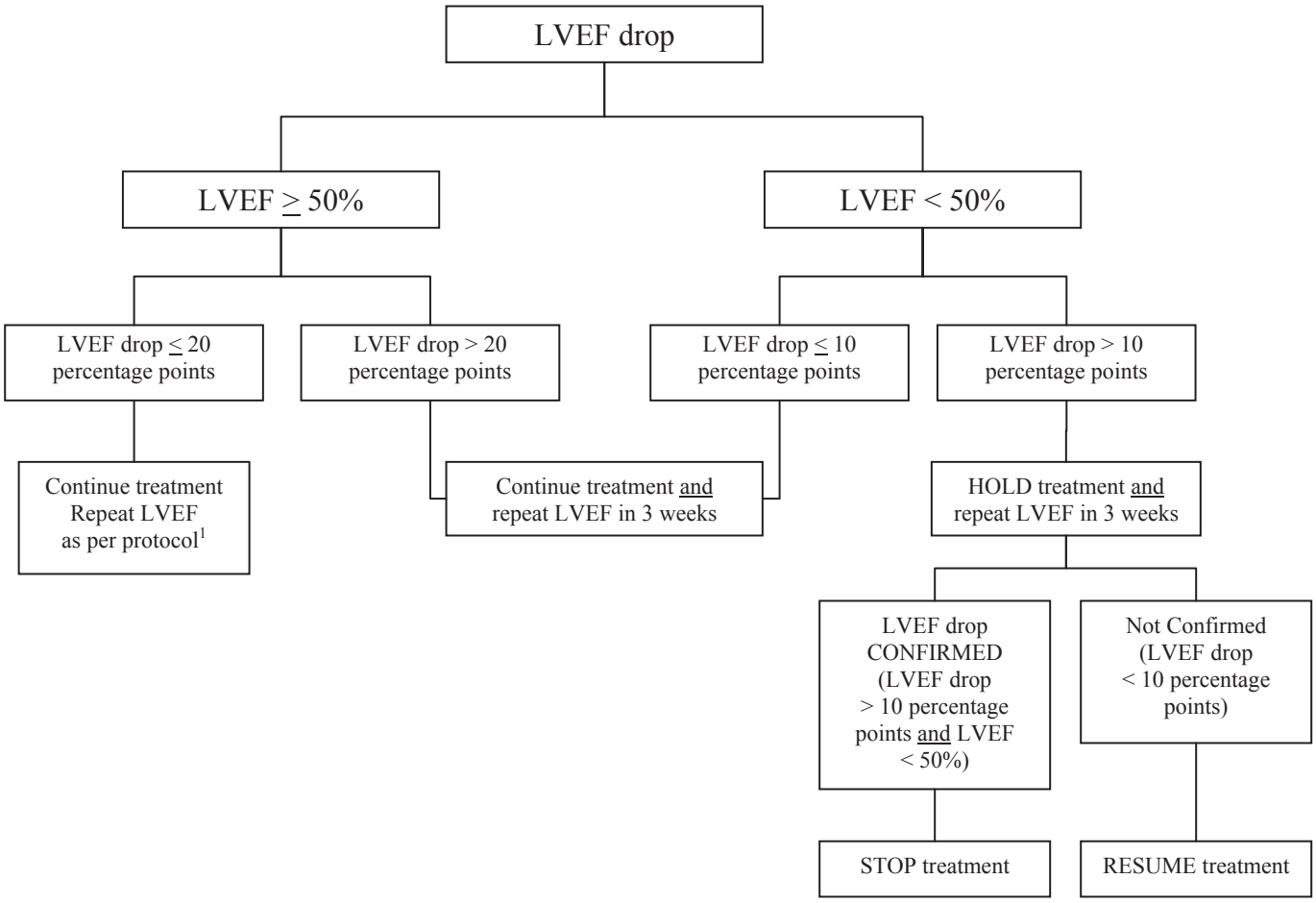
APPENDIX X - NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity				
Class	Cardiac Symptoms	Limitations	Need for Additional Rest *	Physical Ability to Work **
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.
Reference: Bruce, RA: Mod Concepts Cardiovasc Dis 25:321, 1956. (Modified from New York Heart Association, 1953)

APPENDIX XI - LVEF ASSESSMENT ALGORITHM

Algorithm for continuation and discontinuation of lapatinib or trastuzumab based on interval LVEF assessments in patients with NYHA class I or II (no symptoms) congestive heart failure.



[1] Cardiac evaluation by echocardiogram / MUGA should recommence at the time points described in section 9.

APPENDIX XII - GUIDELINES FOR MANAGEMENT OF DIARRHEA

Experience thus far suggests that when lapatinib is used as monotherapy most diarrhea is uncomplicated NCI CTCAE Grade 1 or 2. In rare cases, diarrhea can be debilitating, and potentially life threatening with dehydration, renal insufficiency, and 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]*. Early identification and intervention is critical for the optimal management of diarrhea. A patient's baseline bowel patterns should be established so that changes in patterns can be identified while on treatment. An assessment of frequency, consistency, duration and knowledge of other symptoms such as fever, cramping pain, nausea, vomiting, dizziness and thirst should be taken at baseline and patients at high risk of diarrhea can be identified. Patients should be educated on signs and symptoms of diarrhea with instructions to report to any changes in bowel patterns to the physician. At the time of starting lapatinib, all patients should be given a prescription for loperamide or analogue and be advised to keep the prescription/medication with them at all times.

Definitions

NCI CTCAE v 3.0 guidelines define diarrhea compared to baseline (Table 1)

Table 1: NCI Common Terminology Criteria for Grading Diarrhea[1]

Toxicity Grade	**Diarrhea** (includes diarrhea of small bowel or colonic origin and/or ostomy diarrhea)
1	Increase of < 4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; IV fluids > 24 h; moderate increase in ostomy output compared to baseline; not interfering with daily living
3	Increase of > 7 stools/day over baseline; incontinence; IV fluids; severe increase in ostomy output compared to baseline; interfering with daily living activities
4	Life threatening consequences (i.e. hemodynamic collapse)
5	Death

[1] National Cancer Institute Cancer Therapy Common terminology criteria for adverse events v 3.0 (CTCAE).

Uncomplicated diarrhea is considered mild to moderate and defined as CTCAE Grade 1-2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with one or more of the following signs or symptoms: cramping, nausea/vomiting (Grade $\geq$2), decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration. GI syndrome is a constellation of symptoms including diarrhea, nausea, vomiting, anorexia and abdominal cramping and is associated with severe dehydration, neutropenia, fever, and electrolyte imbalances. These patients are at risk for life threatening complications.

Diarrhea

If a subject experiences CTCAE Grade 1 or 2 diarrhea, introduce supportive care in the form of oral hydration and consider introducing loperamide especially in patients who are considered to be high risk (i.e. elderly).

- Loperamide, administered as an initial 4 mg dose, followed by 2 mg doses every 4 hours. This dose and regimen are moderately effective.
- Clonidine, non-steroidal anti-inflammatory drugs, and the serotonin antagonist cyproheptadine have been shown to be effective in controlling diarrhea associated with inflammation of the bowel.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 μg twice daily to 500 μg 3 times daily, with a maximum-tolerated dose of 2000 μg 3 times daily in a 5-day regimen.

If a subject experiences Grade 3 or 4 diarrhea, hold lapatinib until the subject recovers to Grade 1 or less and treat with anti-diarrhea medications (listed above) and appropriate supportive care.

Management Guidelines

Uncomplicated diarrhea of CTC Grade 1 or 2

- Dietary modifications; Stop all lactose containing products and eat small meals
- Hydratation: drink 8-10 large glasses of clear liquids a day (i.e. Gatorade or broth)
- For Grade 2 diarrhea, may hold cytotoxic chemotherapy until recovery to Grade ≤ 1 if patient finds symptoms unacceptable (refer to protocol for full details on lapatinib dose modification)
- Administer standard dose of loperamide :
  - Initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool.
  - Continuation of loperamide is suggested until diarrhea-free for 12 hours.
- If mild to moderate diarrhea persist for more than 24 hours, administer loperamide 2 mg q 2 hours, and oral antibiotics
- If mild to moderate diarrhea persist after 48 hours total treatment with loperamide, start second-line agents (otreotide, budesonide or tincture of opium)

For complicated diarrhea of CTCAE 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) requires aggressive management:

- Patient must call physician immediately for any complicated severe diarrhea event
- If loperamide has not been initiated, initiate loperamide immediately. Initial dose 4 mg followed by 2 mg every 2 hours or after every unformed stool
- For dehydration use intravenous fluids as appropriate, if severe dehydration administer octreotide
- Administer antibiotics as needed (e.g. fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia
- Discontinue lapatinib until symptoms resolve and consider reintroducing at a reduced dose (refer to protocol for full details on lapatinib dose modification)
- Intervention should be continued until diarrhea free for 24 hours

- Intervention may require hospitalization for patients most at risk for life threatening complications

References:

Benson A, Jaffer AA, Catalano RB, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea. J Clin OncolJCO 2004, 22; 2918-2926.

Saltz LB. Understanding and Managing Chemotherapy-Induced Diarrhea. J Support Oncol. 2003; 1:35-46.

Charma R, Tobin P, Cllarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhea. Lancet, 2005, 6; 93-102

APPENDIX XIII - OVERALL SURVIVAL ANALYSIS FOLLOWING FINAL ANALYSIS FOR PROGRESSION FREE SURVIVAL

The purpose of this Appendix is to describe a protocol for additional Overall Survival (OS) analyses beyond those specified for the MA.31 trial in Section 14; the purpose of these additional OS analyses, outside the context of the final analysis for PFS on the MA.31 study is for separate reporting by GSK to the FDA to meet post marketing requirements. These OS analyses have no impact on the analysis plans for PFS on the study. The data for these analyses will be managed and analyzed by NCIC CTG by the mechanisms utilized for the ongoing MA31 study; a statistical report and copy of the database will be provided to GSK for the purpose of meeting the FDA post-marketing requirements.

Objectives and Design

NCIC CTG MA.31 is a randomized, phase III, open-label study to compare the efficacy of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy (LTax/L) to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy (TTax/T), in women with documented evidence of HER2/neu positive breast cancer (by local or central laboratory testing), which is metastatic and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting. Stratification is by prior (neo)adjuvant HER2/neu targeted therapy (yes, no), prior (neo)adjuvant taxane chemotherapy (yes, no), planned taxane treatment (weekly paclitaxel versus 3 weekly docetaxel), and liver metastasis (yes, no). Patients are allocated to the treatment arms using minimization *[Tu 2003, Pocock 1975]* to ensure balance in the treatment arms by each stratification factor.

Endpoints of MA.31 trial:

Progression free survival (PFS) is the primary statistical endpoint, where PFS is defined as time from randomization to objective disease progression or death from any cause.

Overall Survival (OS) is a secondary endpoint of the MA.31 trial (Section 14.2), which will be assessed following the final primary analysis for PFS. Overall survival (OS) is defined as the time from randomization until death due to any cause. For subjects who do not die, time of death will be censored at the date of last contact. The focus of this Appendix is OS analysis in the intent to treat population. Kaplan-Meier method and a two-sided stratified log-rank test statistic, adjusted for the stratification factors, will be used to compare the treatment arms.

The Pike estimator *[Berry, 1991]* of the treatment HR based on the log-rank test along with 95.1% CIs (using adjusted alpha) will be provided. In addition, for each treatment group, the Kaplan-Meier estimates for the median overall survival time, the first and third quartiles will be presented, along with approximate 95% CIs.

Exploratory analyses with the Cox proportional hazards model will be used to adjust the observed treatment effect for the influence of baseline study factors, and to identify factors significantly associated with the outcomes listed above.

The MA.31 baseline factors referred to are:

1. Age at allocation (classified here as <65 vs. >=65)
2. Race (white vs. other)
3. ECOG performance status (0 vs. ≥1)
4. Prior (neo) adjuvant anti HER2/Neu targeted therapy (yes vs. no)
5. Prior (neo)adjuvant Taxane chemotherapy (yes vs. no)
6. Planned Taxane treatment (weekly paclitaxel vs. 3 weekly docetaxel)
7. Liver metastasis (yes vs. no)
8. Disease Status (metastatic breast cancer at primary diagnosis vs. metastatic breast cancer relapse after curative intent therapy).

Additionally, other patient and disease history factors are well documented and have been historically associated with survival so are prognostic for the management of MBC patients [Henderson, 1998]. Therefore, the Cox regressions here will also include the following covariates:

9. Hormonal status of ER/PR (ER + and/or PR+ vs. ER- and PR-)
10. Number of metastatic sites (<3 vs. ≥3).

Cox Regression analysis will be used to examine first univariate effects, and then to evaluate all main effects (i.e. baseline characteristics specified above) plus treatment in the model. A figure displaying the adjusted survival curves considering the main effect terms by Cox regression will be generated. This analysis will be done using the ITT population.

Additional exploratory analyses for OS will also be performed as described below.

- Cox Regression analyses, based on main effects, will also be evaluated using a stepwise procedure (entry/removal significance level of 0.05) in which the treatment remains in the model**.** Figures displaying the adjusted survival curves considering the main effect terms identified by Cox regression will be generated as appropriate.
- Stratified log-rank test for OS for the centrally tested HER2+ population should the balance of patients for stratification factors be maintained. Otherwise, for OS, the comparison between treatments arms will be the adjusted Cox hazard ratio with graphical description by a Cox survivor plot, as well as an unadjusted log-rank test.
- Cox Regression analyses for the centrally HER2+ population, based on main effects, will also be evaluated using a stepwise procedure (entry/removal significance level of 0.05) in which the treatment remains in the model always**.** Figures displaying the adjusted survival curves considering the main effect terms identified by Cox regression will be generated as appropriate.

The number and percentage of deaths will be summarized, along with the primary cause of death, as reported on the Record of death CRF page. A listing of this information plus the date of death will also be provided.

Sample Size Justification for Overall Survival

This additional analysis is powered to detect a 33% improvement in overall survival of LTax/L over TTax/T in centrally tested HER2+ patients. A total of 414 deaths will be required in order to detect this improvement. Planned sample size for this study is 600 locally tested HER2+ patients in order to yield 536 centrally confirmed HER2+ patients. The following assumptions were made in order to estimate the sample size:

- An interim analysis for the OS endpoint at the time of, and immediately following, final analysis of PFS which will be when approximately 390 PFS events have been observed.
- Exponential distribution for overall survival
- Two-sided Type I error of 0.05, i.e. a 2.5% risk of erroneously claiming superiority of lapatinib+taxane over trastuzumab+taxane in the presence of no true underlying difference
- Power of 80%
- 1:1 randomization scheme stratified by prior anti-HER2 or prior taxane therapy, planned taxane treatment on study, and liver metastases, but sample size calculations ignore stratification
- Average accrual rate of 12 patients per month
- H_o: HR=1versus H_a: HR=0.75, corresponding to a 33% increase in median OS in patients who receive lapatinib+taxane compared to patients who receive trastuzumab+taxane

Interim Analysis

There is one formal interim statistical analysis of overall survival data planned during the course of the study. This interim analysis of OS will be performed when the final analysis of PFS is performed. This will occur when approximately 390 PFS events have been observed and enrollment to the study has been completed. Study will be stopped early for a “dramatic benefit” or “harm” in OS. "Dramatic Benefit" would correspond to a large improvement in OS of the lapatinib+taxane compared with trastuzumab+taxane. "Harm" would correspond to declaring the lapatinib+taxane to be worse than the trastuzumab+taxane for OS.

As the amount of information (i.e. fraction of required events) available at the scheduled interim analyses for OS may differ from what has been planned, a flexible alpha spending function, defined below, will be used. The nominal significance values at the interim and final analyses will be adjusted accordingly to preserve an overall 5% two sided significance level for OS. Interpolated Lan and DeMets [Lan, 1983] alpha- and beta-spending stopping boundaries will be used.

The EAST software package will be used to calculate the appropriate bounds at the time of the analyses, given the fraction of information available.
For example if approximately 38% of OS events are observed (390 PFS events have occurred). the nominal significance levels corresponding to the error spending functions as well as planned stopping boundaries and decision rules in terms of hazard ratios for the analysis time points of overall survival, are as follows:

- α=0.001, stop for efficacy if HR<0.59 or stop for harm if HR>1.69;
- 100% of expected OS events: α=0.049, claim superiority of the experimental arm if HR<0.82 or claim harm if HR>1.21

The results of the final analysis for PFS and other secondary endpoints which include cardiac safety evaluations, as well as the results of the interim analysis for OS will be known to GSK time of the first interim analysis for overall survival.

REFERENCES

Berry G., Kitchin R.M., and Mock P.A. A comparison of two simple hazard ratio estimators based on logrank test. Statistics in Medicine 10(5): 749-755 1991.

Cox DR. Regression Models and Life Tables (with Discussion). Journal of the Royal Statistical Society, Series B 34:187—220, 1972.

Henderson, C. and Patek, A.J. The relationship between prognostic and predictive factors in the management of breast cancer. Breast Cancer Research and Treatment, 1998; 52:261-288

LIST OF CONTACTS

	Contact	Tel. #	Fax #
STUDY SUPPLIES Forms, Protocols	Available on NCIC CTG Website: http://www.ctg.queensu.ca under: Clinical Trials	613-533-6430	613-533-2941
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Dora Nomikos *or* Yvonne Murray Study Coordinators *or* Gina Howard Clinical Trials Assistant NCIC CTG Email: dnomikos@ctg.queensu.ca ymurray@ctg.queenus.ca ghoward@ctg.queensu.ca		
	or: Dr. Wendy Parulekar *or* Dr. Lois Shepherd Physician Coordinators NCIC CTG Email: wparulekar@ctg.queensu.ca lshepherd@ctg.queensu.ca		
STUDY CHAIR	Dr. Karen Gelmon Study Chair Email: kgelmon@bccancer.bc.ca	614-877-6000	614-877-0585
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Wendy Parulekar / Dr. Lois Shepherd Physician Coordinators NCIC CTG or: Dora Nomikos / Yvonne Murray Study Coordinators NCIC CTG		
DRUG ORDERING See Appendix III.	Details to be provided at the time of centre activation		