RANDOMIZED OPEN LABEL PHASE II TRIAL OF NEOADJUVANT TRASTUZUMAB EMTANSINE (TE) IN COMBINATION WITH LAPATINIB (L) FOLLOW BY ABRAXANE (A) COMPARED WITH TRASTUZUMAB PLUS LAPATINIB FOLLOW BY PACLITAXEL IN HER 2 NEU OVER-EXPRESSED BREAST CANCER PATIENTS

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List of abbreviations

4E-BP1	4E-binding protein
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
CDS	Core data sheet
CoA	Coenzyme A
CPK	Creatine phosphokinase
CRF	Case Report Form
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
DNA	Deoxyribonucleic acid
DS&E	Drug Safety and Epidimology
EOT	End of treatment
EU	European Union
FDA	Food and drug administration
GERD	Gastroesophageal reflux disease
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HMG	3-hydroxy-3-methyl-glutaryl
IB	Investigator brochure
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
$\log_{10}$	Decadic logarithm (common logarithm)
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PgP	P-glycoprotein
PFT	Pulmonary function tests
PI3K	Phosphoinositide 3-kinase
PNET	Pancreatic neuroendocrine tumor
RCC	Renal cell carcinoma
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SEGA	Subependymal giant cell astrocytoma
TS	Tuberous sclerosis
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WOCBP	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	For efficacy evaluations, the baseline assessment will be the last available assessment before or on the date of randomization. For safety evaluations (i.e. laboratory assessments and vital signs), the baseline assessment will be the last available assessment before or on the start date of study treatment. The value obtained at baseline assessments, referred to as "baseline value" will be used as reference for the patient.
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1. Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Several drugs have been developed and are in clinical use to block the HER pathway, most aimed at the receptor level. [T-DM1] Trastuzumab Emtansine Antibody-drug conjugates (ADCs) are monoclonal antibodies to which highly potent cytotoxic agents have been conjugated. They represent a novel approach to conferring selectivity to systemically administered anti-tumor therapeutics. ADCs are designed to focus the delivery of highly potent cytotoxic agents to tumor cells by targeting surface antigens that are tumor-specific and/or overexpressed. This approach potentially creates a more favorable therapeutic window for such agents than can be achieved by their administration as free drugs.

Trastuzumab emtansine (T-DM1) is a HER2-targeted antibody-drug conjugate which contains the humanized anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) via the stable thioether linker MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate). Emtansine refers to the MCC-DM1 complex. An average of 3.5 DM1 molecules are conjugated to each molecule of trastuzumab.

Conjugation of DM1 to trastuzumab confers selectivity of the cytotoxic agent for HER2-overexpressing tumor cells, thereby increasing intracellular delivery of DM1 directly to malignant cells. Upon binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in release of DM1-containing cytotoxic catabolites (primarily lysine-MCC-DM1).

Trastuzumab emtansine has the mechanisms of action of both trastuzumab and DM1

- Trastuzumab emtansine, like trastuzumab, binds to domain IV of the HER2 extracellular domain (ECD), as well as to Fcγ receptors and complement C1q. In addition, trastuzumab emtansine, like trastuzumab, inhibits shedding of the HER2 ECD, inhibits signaling through the phosphatidylinositol 3-kinase (PI3-K) pathway, and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in human breast cancer cells that overexpress HER2.
- DM1, the cytotoxic drug component of trastuzumab emtansine, binds to tubulin. By inhibiting tubulin polymerization, trastuzumab emtansine causes cells to arrest in the G2/M phase of the cell cycle, ultimately leading to apoptotic cell death. Results from in vitro cytotoxicity assays show that DM1 is 20-200 times more potent than taxanes and vinca alkaloids.
- The MCC linker is designed to limit systemic release and increase targeted delivery of DM1, as demonstrated by detection of very low levels of free DM1 in plasma.

Trastuzumab emtansine has demonstrated a consistent toxicity and tolerability profile across all studies conducted to date in breast cancer patients. Thrombocytopenia, increases in serum AST and ALT, infusion/hypersensitivity reaction, and pneumonitis have been identified as risks with trastuzumab emtansine use. Refer to the trastuzumab emtansine Investigator Brochure for additional details about the clinical experience with trastuzumab emtansine. [1]

Lapatinib is an orally active dual HER1/HER2 kinase inhibitor that blocks signal transduction pathways. It markedly reduces tyrosine phosphorylation of HER1 and HER2, as well as activation of ERK1,2 MAPK and PI3K/AKT, affecting downstream effectors of both proliferation and survival. It recently has shown remarkable activity in patients with HER2-overexpressing breast cancers after escape from a monoclonal antibody targeted therapy, nearly doubling progression-free survival compared to chemotherapy alone in these patients. This mix of HER inhibitors is important because when used in combination they could theoretically more completely block the network input layer to make treatment more effective.

Given the highly specific and potent tyrosine kinase inhibition of lapatinib, it is postulated that breast cancer cells resistant to trastuzumab due to enhanced signaling through alternative pathways (i.e., HER2/HER3 heterodimerization) or decreased antibody binding to HER2 receptors would still retain sensitivity to lapatinib. In breast cancer, HER2/HER3 dimerization promotes the strongest mitogenic signaling, primarily through the PI3K/AKT pathway, which is critical in maintaining cell proliferation and survival.[2,3] Constitutive activation of the PI3K/AKT pathway through upregulation of HER3 and direct binding to PI3K in both ligand-dependent and ligand-independent mechanisms have been implicated in resistance to targeted therapies.[4,5] In HER2 overexpressing

cells and tumors that are ligand-independent, enhanced downstream signaling is inhibited by trastuzumab whereas ligand-dependent signaling can be blocked by the addition of pertuzumab to disrupt HER2 homo- and heterodimers.[6,7] Tyrosine kinase inhibitors such as lapatinib have shown potent activity against HER2-overexpressing breast cancer cells/tumor xenografts by inhibiting phosphorylation and activation of HER2/HER2, EGFR/HER2, and HER2/HER3 homo- and hetero-dimers and downstream signaling effectors (RAF, ERK, AKT) regardless of trastuzumab resistance or ligand association.[8-11] In addition, we have strong correlative, statistically significant, data that activation of the PI3K pathway was associated with resistance to trastuzumab, consistent with published data.[12,13] With lapatinib, the opposite was observed where activation of this pathway lead to increased sensitivity, with 87% (13/15) of patients achieving pCR while only 13% (2/15) had residual disease (p=0.04). Thus, activation of the PI3K pathway was associated with response to this lapatinib-containing regimen.

Abraxane Paclitaxel, nanoparticle albumin-bound (nab), its active ingredient paclitaxel, is an antimicrotubule agent that promotes the assembly and stabilization of microtubules, thus inhibiting normal dynamic reorganization of the microtubule network. Paclitaxel induces abnormal bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. It is thought that albumin-bound paclitaxel (nab-paclitaxel) facilitates the transport of paclitaxel across the endothelial cell via an albumin-receptor mediated pathway. Nab-paclitaxel is cell cycle phase-nonspecific. [14]

Nab-paclitaxel is a unique albumin formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble nanoparticle state. While nab-paclitaxel has been shown to be one of the most active agents in metastatic breast cancer, it has not been approved as part of combination therapy in the neoadjuvant setting. A prior neo-adjuvant study showed that newly diagnosed HER2 Neu over-expressed stage I to III breast cancer received lapatinib 1000 mg po/d and nab-paclitaxel 260 mg/m2 IV every three weeks for a total of four cycles. Postoperative therapy was at the discretion of the investigator. The primary endpoint of the study was the clinical response rate (CRR) as determined by clinical examination and imaging studies. Response data in 29 patients showed a CRR of 82%, with 4 (13.8%) patients demonstrating a complete response and 20 (69%) showing a partial response. Five (17.2%) patients had stable disease. Five (18.5%) patients achieved pathologic complete response (pCR). The most common toxicities were rash, neuropathy, fatigue, and myalgias. Most toxicities were grade 1 & 2 although one patient developed grade 3 rash and five patients developed grade 3 diarrhea. There were no cases of cardiac toxicity. [15] Toxicities such as diarrhea and rash were medically managed, and patients did not receive prophylactic medications for rash or diarrhea. Nab-Paclitaxel had shown favorable efficacy and toxicity profiles compared to other taxanes in the treatment of metastatic breast cancer. A pilot study using nab-paclitaxel-containing adjuvant regimen in patients with node-positive or high-risk node-negative early-stage breast cancer was well tolerated, and full doses of all agents were administered in >90% of cycles. All the patients received four cycles, at 21-day intervals, of nab-paclitaxel (100 mg/m(2) IV days 1, 8, and 15) and cyclophosphamide (600 mg/m(2) IV day 1). HER2-positive patients also received trastuzumab 8 mg/kg IV on cycle 1 day 1, followed by 6 mg/kg every 21 days for a total of 52 weeks. The purpose of this trial was to evaluate feasibility and toxicity of this nab-paclitaxel-containing adjuvant regimen. 62 patients were treated between 2/08 and 11/08. The majority of the patients (87%) were HER2-negative. This adjuvant regimen Grade 3/4 neutropenia occurred in 53% of the patients; however, only one episode of febrile neutropenia occurred in a total of 249 cycles administered. Other grade 3/4 adverse events occurred in less than 5% of patients. After short follow-up, all the patients remain alive and disease-free. The combination of nab-paclitaxel and cyclophosphamide, with or without trastuzumab, was feasible and well tolerated in patients with early stage breast cancer. [16]

2. Significance and Rationale

The significance of this proposal is to establish the superior efficacy and predictive molecular-genetic biomarkers of the combination of the antibody-drug conjugate trastuzumab-emtansine with lapatinib followed by the addition of chemotherapy (Abraxane) in patients with HER2 overexpressing breast cancers in the neoadjuvant setting. The

estrogen receptor (ER) and HER signaling pathways are the dominant drivers of cell proliferation and survival in the majority of human breast cancers. Not surprisingly, targeting these pathways provides the most effective therapies in appropriately selected patients[19,20] . However, *de novo* and acquired resistance remain major obstacles to successful treatment. By increasing the understanding of the molecular mechanisms of combined HER2-targeted therapies, we aim to be better able to select patients who would respond to these treatments and understand some of the escape mechanisms of HER2-targeted treatments.

The HER family of transmembrane type I receptor tyrosine kinases play an important role in cell processes like cell proliferation and survival. Upon ligand binding to the active domain of HER1, HER3, or HER4, these receptors preferentially recruit HER2 into a heterodimeric complex in which the HER2 kinase can modulate receptor internalization and prolong signal transduction. Conformational changes occur upon dimerization, leading to autophosphorylation and initiation of divergent signal transduction cascades[21]. These signaling pathways from these receptor heterodimers are not absolutely linear and some of their functions may overlap, laboratory data generally indicate that HER1/HER2 heterodimers activate cell proliferation by the ERK1,2 MAPK pathway[22], while HER2/HER3 heterodimers predominantly activate the PI3K/AKT cell survival pathway[23].

Several drugs have been developed and are in clinical use to block the HER pathway, most aimed at the receptor level. The anti-HER2 antibody trastuzumab is approved for treatment of breast cancer. Pivotal multicenter efficacy trials showed improved survival in patients who received trastuzumab[24]. Lapatinib is an orally active dual HER1/HER2 kinase inhibitor that blocks signal transduction pathways. It reduces tyrosine phosphorylation of HER1 and HER2, as well as activation of ERK1,2 MAPK and PI3K/AKT, affecting downstream effectors of both proliferation and survival[25]. It recently has shown activity in patients with HER2-overexpressing breast cancers after escape from trastuzumab[26-28]. Pertuzumab, a recombinant humanized monoclonal antibody (2C4), binds to extracellular domain II of the HER-2 receptor and blocks its ability to dimerize with other HER receptors in particular HER2-HER3 complex[29].

In addition to these receptor targeted therapies, a new class of antibody-drug conjugates has recently shown superior clinical activity. Trastuzumab-emtansine (TE) is an antibody–drug conjugate that incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent mertansine (DM1) (derivative of maytansine); the antibody and the cytotoxic agent are conjugated by means of a unique stable linker. TE allows intracellular drug delivery specifically to HER2-overexpressing cells, thereby improving the therapeutic index and minimizing exposure of normal tissue. Earlier this year, TE was approved for the treatment of HER2 overexpressing breast cancer patients[30]. TE has shown superiority over lapatinib/capecitabine combinations, and has recently been approved for the treatment of metastatic HER2 overexpressing breast cancer patients[30].

Despite some success of these agents that target the HER family as single agents, there are a number of escape mechanisms from HER-targeted therapies. Clinically, a more complete blockade of the HER receptor layer has been shown to be therapeutically meaningful in prolonging survival in patients. With incomplete blockade of the receptor input layer, proliferative and survival signals can be generated from several different dimer pairs. The idea that the redundancy in the input layer of the network might provide an escape mechanism around a single-agent block has been explored. Using combinations of inhibitors (*e.g.* trastuzumab+pertuzumab or lapatinib+trastuzumab), higher responses with higher pathologic complete responses (pCR) have been observed. In a recently completed randomized phase 2 study, patients given dual blockade with pertuzumab and trastuzumab plus taxane, compared to trastuzumab and taxane (NeoSphere study), had a significantly improved pathological complete response rate (46% vs. 29%; p=0·0141)[31]. Similar improved efficacy was observed with dual blockade with trastuzumab and lapatinib (NeoAltto study). In this randomized phase 3 study, the pCR rate was significantly higher in the group given lapatinib and trastuzumab plus taxane vs. trastuzumab plus taxane (51% vs.30%; p=0·0001)[32]. To date, these studies have shown the highest pathologic complete responses in HER2 overexpressing patients with the combinations of trastuzumab and either pertuzumab or lapatinib, together with paclitaxel chemotherapy. Here, we aim to build on these observations, and propose the use of trastuzumab-emtansine, that incorporates the antibody antitumor effect with trastuzumab with a cytotoxic agent, together with

lapatinib to overcome incomplete blockade of the HER receptor in the neoadjuvant setting so as to improve the pathologic complete responses and thus survival of women with HER2 overexpressing cancers.

Amplification of the PI3K pathway, as a result of low levels of the phosphatase PTEN or *PIK3CA* mutations, has been also been associated with resistance to trastuzumab in clinical patient samples[33,34]. PTEN loss has been described in approximately 50% of breast tumors. Nagata *et al.* reported that trastuzumab resulted in activation of PTEN by inhibiting Src tyrosine kinase, thus preventing Src binding to HER2[33,34]. Mechanisms for lapatinib resistance are less well established. Recent *in vitro* data suggests that, unlike trastuzumab, loss of PTEN function was not associated with lapatinib resistance[35]. We determined in biopsies obtained from women enrolled in two prior neoadjuvant studies that *PIK3CA* mutations or loss of PTEN predicted resistance to trastuzumab, but sensitivity to a lapatinib-containing regimen[36]. In a third recently completed study, we determined that *PIK3CA* mutations or loss of PTEN might also predict for resistance to the combination of lapatinib and trastuzumab (*Preliminary Studies*).

In this last decade, the availability of next-generation high-throughput technologies, many pioneered at Baylor College of Medicine (BCM), has opened up the potential to sequence entire tumor genomes to interrogate protein-encoding genes, non-coding RNA genes, and the mitochondrial genome. These technologies allows for comprehensive interrogation of the genetic landscape of residual tumors after therapy, to understand the mechanisms and pathways of resistance and escape. The Human Genome Sequencing Center (HGSC) at BCM is one of the three large-scale sequencing centers funded by the National Institutes of Health. The HGSC was a key member in the Cancer Genome Atlas Pilot Network (TCGA) which entered a pilot phase in 2006 to identify important genetic changes involved in lung, brain, and ovarian cancers. TCGA constitutes a comprehensive effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies, especially large-scale genome sequencing. We propose here to interrogate clearly annotated tissues obtained in a clinical trial, that have known response to HER2-targeted therapy, to determine mutational profiles, along with PI3K pathway alterations, that might predict for differential response to HER2-targeted therapies. To our knowledge, such studies have not as yet been performed. Summary of significance The HER pathway is the driving force behind 30% of human breast cancers, and understanding how targeted therapies block different cellular pathways, and mechanisms of escape, is crucial in the development of strategies to overcome resistance. Understanding the mechanisms of escape from HER pathway inhibitors may reveal general mechanisms of escape from other therapies as well. The neoadjuvant platform is especially attractive for evaluation of promising novel combinations, as this approach will allow for early assessment of response and access to primary tumors for serial tissue sampling to examine *in vivo* mechanisms of action and predictive markers. In addition, we are proposing to comprehensively sequence these HER2-overexpressing cancers, in order to identify potential somatic changes that may better select patients who will benefit from therapy, and to determine new targets that may overcome resistance and improve outcome with known current HER2-targeted therapies.

2.1 Innovation

Therapies directed at HER2 establish a successful treatment paradigm, but *de novo* and acquired resistance exist. With this neoadjuvant model, we have previously demonstrated that single agent HER2-targeted therapies are efficacious but response is incomplete. Consistent with large randomized clinical trials, we have also demonstrated that dual HER2- targeted combinations with trastuzumab/lapatinib are synergistic. Recently, the antibody-drug conjugate trastuzumab-emtansine, which targets the HER2 receptor conjugated to the potent antimicrotubule agent emtansine allowing for intracellular release of the cytotoxic drug, has recently been approved. Here, we propose a rational combination of dual HER2- targeted treatments with trastuzumab-emtansine (TE) and lapatinib (L), together with nab-paclitaxel to demonstrate improved efficacy in patients. By determining somatic mutations in HER2-overexpressing tumors, we will comprehensively characterize these alterations and identify those patients most likely to respond, as well as discovering new targets that may overcome resistance to HER2-directed therapy.

We propose a randomized neoadjuvant clinical trial in HER2-overexpressing breast cancer patients who will receive TE+L+A vs. T+L together with paclitaxel before definitive surgery. We will determine the efficacy of

TE+L+A gather data germane to the mechanisms of action, and discover predictive markers for sensitivity and resistance.

2.2 Approach Preliminary Studies

Preclinical MCF-7/HER2 mouse xenograft studies Trastuzumab (T), pertuzumab (P), lapatinib (L), and gefitinib (G) represent a group of therapeutic agents that target the HER family by different molecular mechanisms. These drugs, when used as single agents in the MCF7/HER2-18 xenograft model, restored or enhanced sensitivity to tamoxifen. However, tumor growth inhibition lasted only 2-3 months before resistance to treatments occurred and tumor growth resumed. We next investigated the efficacy of various drug combinations. The addition of the HER1 inhibitor G to the two-antibody (T+P) regimen to block signals from HER1 dimers resulted in complete disappearance of nearly all tumors with evidence of complete tumor eradication in >50% of the mice. The combination of lapatinib + trastuzumab (L+T) was highly effective (Fig. 1). The combination HER-targeting therapy more effectively induced apoptosis and inhibited proliferation and more effectively reduced levels of p-AKT and MAPK.

Three completed phase II neoadjuvant HER2-targeted clinical studies Over the past 10 years, our group has carried out neoadjuvant trials of HER pathway blockers. The first study (40 patients) used trastuzumab for a 3-week period with serial tissue sampling, and major endpoints have been published[37]. The second completed trial (49 patients) investigated the dual kinase inhibitor lapatinib but for a longer duration, 6 weeks, before chemotherapy was added. Again, dramatic responses were observed in most patients, with clinical response (>50% tumor regression) in 73% (33/45) by 6 weeks of lapatinib. In the third study, the combination of lapatinib plus trastuzumab (L+T) was studied as neoadjuvant therapy. Sixty-six patients were enrolled, and 64 were eligible and evaluable for response. Median tumor size was 6 cm (range, 1.5 to 30 cm). Adverse events were mainly grades 1 to 2 (GI, 63%; skin, 46%). Grade 3 metabolic, GI, and liver (18%; 12 patients) and grade 4 liver toxicities (one patient) were also observed. Overall, pCR rate was 27% (ER positive, 21%; ER negative, 36%) with targeted dual blockade alone without chemotherapy[38]

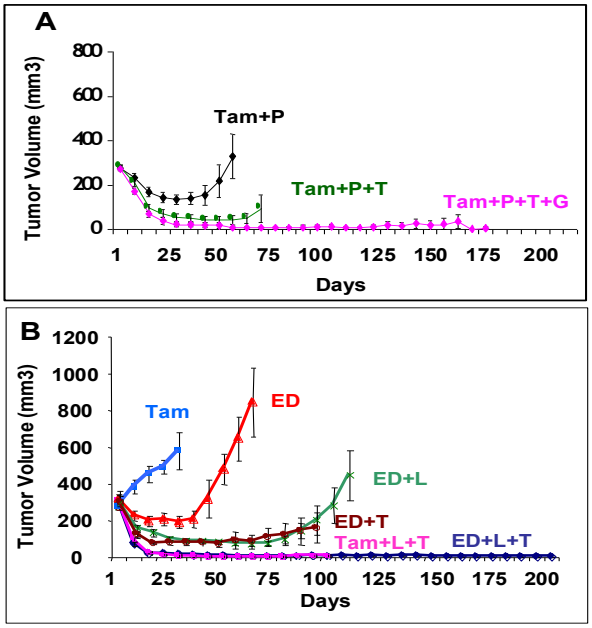

Figure 1. Inhibitory effects of various HER2 drug combinations on MCF7/HER2-18 xenograft growth and endocrine sensitivity. The combinations of P+T+G in the presence of tamoxifen (A) and L+T with tamoxifen or estrogen deprivation (ED) lead to complete tumor regression in almost all mice in the presence of ED (B).

Biologic correlative studies from clinical studies

Neoadjuvant trastuzumab: We completed the first single-agent neoadjuvant trastuzumab study from 2000 to 2003 (R21CA 87649-01 from the National Cancer Institute, NCI). Core biopsies of the primary cancers were taken before administration of single-agent trastuzumab as neoadjuvant treatment. Apoptosis (cleaved caspase 3, CC3) was significantly induced with a median increase from 2.6% to 4.0% (p=0.004) within one week after starting trastuzumab therapy, as shown in Fig. 2A. Trastuzumab did not decrease cell cycle proliferation, suggesting that trastuzumab primarily exerts its effects through the PI3K/AKT survival pathway. *Neoadjuvant lapatinib:* Next, a neoadjuvant study with lapatinib (R01CA112305, NCI) was conducted from 2004-2009. Unlike with trastuzumab, the apoptosis index did not change significantly. On the other hand, lapatinib decreased Ki67 significantly by week 2, and this decrease in proliferation continued through weeks 4 and 6 (p<0.0001) (Fig. 2B). Consistent with this decrease, p-MAPK showed a significant decrease by week 2 through week 4 (p=0.02). These data suggest that lapatinib exerts its effects by decreasing proliferation through the MAPK pathway.

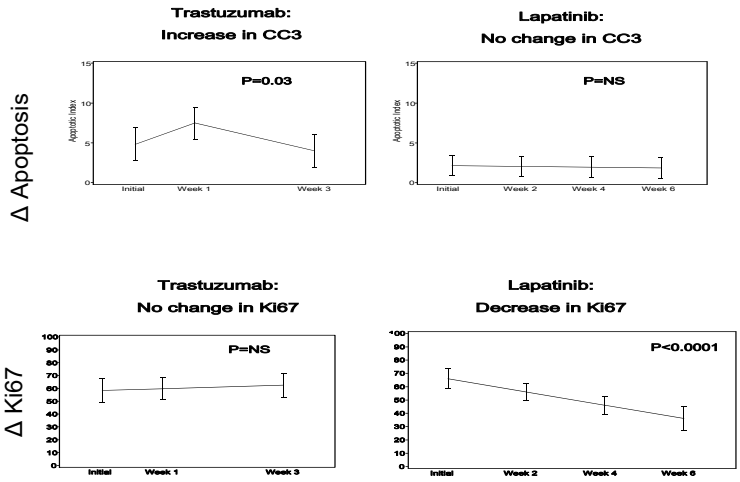

Figure 2A. Change in apoptosis as measured by cleaved caspase 3. With trastuzumab, CC3 (apoptosis) was increased in week 1, p=0.03. With lapatinib, no change in CC3 was observed.

Figure 2B. Change in proliferation as measured by Ki67. With trastuzumab, Ki67 was unchanged. With lapatinib, Ki67 was significantly decreased by week 2, which continued in weeks 4 and 6 (p<0.0001).

Activation of the PI3K pathway as a pretreatment predictive marker of response: Considering next the biomarkers in the pretreatment specimens that might be predictive indicators, we examined primarily activation of the PI3K/AKT pathway. Activation of the PI3K pathway was statistically significantly associated with *resistance* to trastuzumab[33,34]. Only 18.2% (4/22, 95% exact CI = 5.2% - 40.3%) patients with PI3K activation achieved pCR compared to 66.72% (6/9, 95% exact CI = 29.9% - 92.5%, p=0.015). With lapatinib, the opposite effect was observed - activation of this pathway led to increased sensitivity, with 86.7% (13/15) of patients achieving pCR when compared to 45.5% (5/11, p=0.038)[36]. The interaction between low PTEN/*PI3KCA* mutations and trastuzumab or lapatinib response was highly statistically significant, p=0.0016[36]. For dual blockade with T+L, of 64 evaluable patients, tissue was available on 59 for PTEN assay, and sufficient DNA was available on 33 for the mutation panel. PTEN was correlated with pCR (32% in high PTEN vs. 9% in low PTEN, p=0.04). Activating PIK3CA mutations were identified in 12 out of 33 tumors (36%). None of the patients whose tumors harbored a PIK3CA mutation achieved pCR (p=0.06). When PIK3CA mutations were considered along with PTEN status, 0/17 cases (0%) with a mutation and/or PTEN low expression had a pCR compared to 5/14 cases (36%) with no mutation or high PTEN (p=0.01), suggesting that the PI3K pathway activation results in resistance to the combination of T+L. These findings needs validation in larger cohorts, as planned in the control arm of this proposed study.

Large-scale mutation profiling in human cancers For the past 5 years, the technologies of high throughput DNA sequencing have been increasingly brought to bear on the problem of cancer. Results from these global and high throughput "genomic" approaches promise a new understanding of cancer biology in terms of a) classification of disease, b) identification of novel genes overlooked in previous studies due to insufficient breadth (sampling of too few genes) or depth (too few patients, and therefore insufficient statistical power), and c) a view of inter-

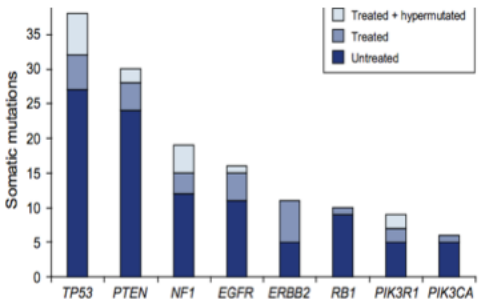

Figure 3. Gene mutation profile from large-scale study of Glioblastoma Multiforme (GBM). The genes shown in this figure were significantly mutated ($p < 0.0001$) above the expect background rate. In this data set, some patients had been treated with Temozolomide which causes a hypermutation phenotype in patients treated long enough; patients were tallied separately by treatment status.

dependence of the critical pathways, important for biological interpretation, as well as new treatment strategies. Recently, the HGSC began a collaborative project with two other sequencing centers to sequence 623 genes in 188 lung adenocarcinoma patients[39]. The approaches developed in lung adenocarcinoma project were applied to glioblastoma multiforme (GBM) tumors, with 1,300 genes and 153 patients as part of The Cancer Genome Atlas project[40]. These studies are among the largest undertaken and have dramatically revealed the power of genome-wide mutational analysis in cancer. The gene mutation profile of GBM (Fig. 3) revealed for the first time that ERRB2, NF1 and PIK3R1 play a significant role in GBM. Moreover, the first two are drug targets in other cancers. Genes mutated in a significant portion of tumors re considered to be "drivers" of the tumor phenotype; presumably they confer growth advantage and/or evasion of the body's natural defenses against cancer. These significantly mutated genes in GBM (Fig. 3) were found to affect three primary pathways: "Apoptosis", "Cell Cycle Control", and "Mitogenic Stimulus". Over 90% of all mutations found in GBM were in genes in these three pathways. Results similar to these were found in the mutation profile of lung adenocarcinoma but with different genes involved. Thus, in addition to TP53, EGFR, and NF1 found in GBM, the KRAS, STK11 and LRPB1 were also significantly mutated in lung adenocarcinomas. In contrast, ERBB2 and RB1 that were

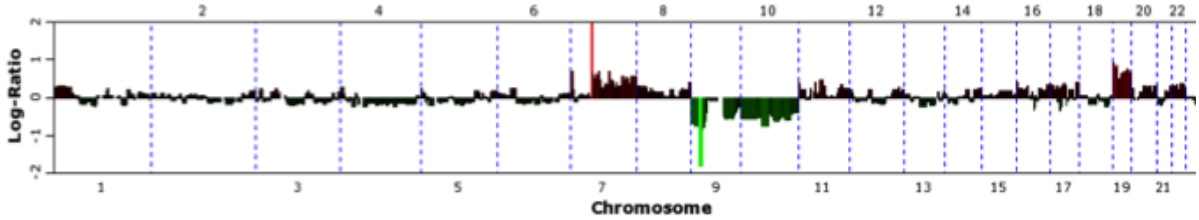

Figure 4. Somatic chromosomal copy number alterations are readily detected by DNA sequencing. Chromosomal gain, red bars and loss, green. The most dominant gain is at Chr7 EGFR locus and loss at Chr9 CDKN2A (in green). In addition, large segments of chr1, chr7 and chr19 show strong gain while

mutated significantly in GBM were not significantly mutated in lung adenocarcinoma. Thus, not unexpectedly, different cancers vary in which genes and which pathways drive the tumor phenotype. With the advent of next generation sequencers that afford even more comprehensive surveys, we now use targeted oligonucleotide arrays to capture exons across the entire genome (whole exome capture, WEC). Whole genome shotgun sequencing enables detection of copy number alterations (CNA) frequent in cancer. We have accurately mapped somatic structural variants in GBM, ovarian and pancreatic cancers by comparing sequencing coverage from tumor and matched normal genomes. Reads from tumor sample are partitioned into variably sized bins, averaging 10Kb. Figure 4 shows two major changes identified in a GBM patient using these methods: an amplification of chromosome 7 at the EGFR locus and a deletion at chromosomal 19 at the tumor suppressor gene CDKN2A locus. These changes were mirrored in CNA data obtained by SNP array as part of the TCGA copy number alteration platform (data not shown).

3. **Hypothesis**:

We hypothesize that combining antibody-drug conjugate trastuzumab-emtansine and lapatinib together with Abraxane will improve clinical efficacy by affecting both PI3K and ERK1,2 MAPK pathways. We are proposing in this randomized phase 2 study to perform comprehensive sequencing to better define novel mutations that could predict for response and to interrogate residual tumors after exposure to TE/L and abraxane to define mechanisms of resistance to HER2-targeted therapy.

Research Strategy General considerations The neoadjuvant setting is especially attractive for several reasons; these include early assessment of response to therapy, access to the tumor specimens for correlative studies, and fewer patient numbers compared to those required in the adjuvant setting. The aims of this study are first to demonstrate the superior clinical efficacy of combined trastuzumab-emtansine/ lapatinib/Abraxane vs. lapatinib/trastuzumab, in combination with paclitaxel in the neoadjuvant setting; second, to comprehensively interrogate the genomic landscape by next generation whole exome sequencing to define novel predictive markers of sensitivity and resistance; and third, to validate predictors by protein markers on tissue microarrays.

4. Objectives and endpoints

Primary Objective:

- To evaluate the pathological complete response rate (pCR) in the breast after treatment with Trastuzumab Emtansine plus Lapatinib follow by Abraxane in women with HER2 Neu over-expressed breast cancer patients.

Secondary Objective(s):

- To determine the clinical response rate in patients with palpable disease.
- To determine the imaging response to neoadjuvant therapy.
- To compare overall objective response rate in both treatment groups.
- To assess toxicity, safety and efficacy of Trastuzumab Emtansine when combine with Lapatinib follow by Abraxane

Exploratory Objective(s):

- To determine predictive markers for sensitivity and resistance
- To determine baseline transcriptional profiling
- To evaluate the somatic mutational analysis
- To validate predictors of response and resistance with protein biomarkers

Endpoints

The primary endpoint will be the evaluation of the Pathological Complete Response (pCR) in the breast when TDM-1 plus Lapatinib plus Abraxane is combined.

Secondary endpoints will include the evaluation of a) clinical and radiological response b) toxicity related with the study arm treatment (toxicities will be defined as any treatment- related death or any **≥ Grade 3 non-hematological toxicity** excluding alopecia and constitutional symptoms as assessed by NCI-CTC AE ver. 4.0.). c) biological tissue effect of the proposed combination on HER2 expression levels, Gene expression analysis, sub typing Characterization, Transcriptional profiling, PTEN, PI3K and possibly other candidate markers related to the drug's mechanism of action, and d) pathologic CR in axillary nodes.

5. Study design

5.1 Description of study design

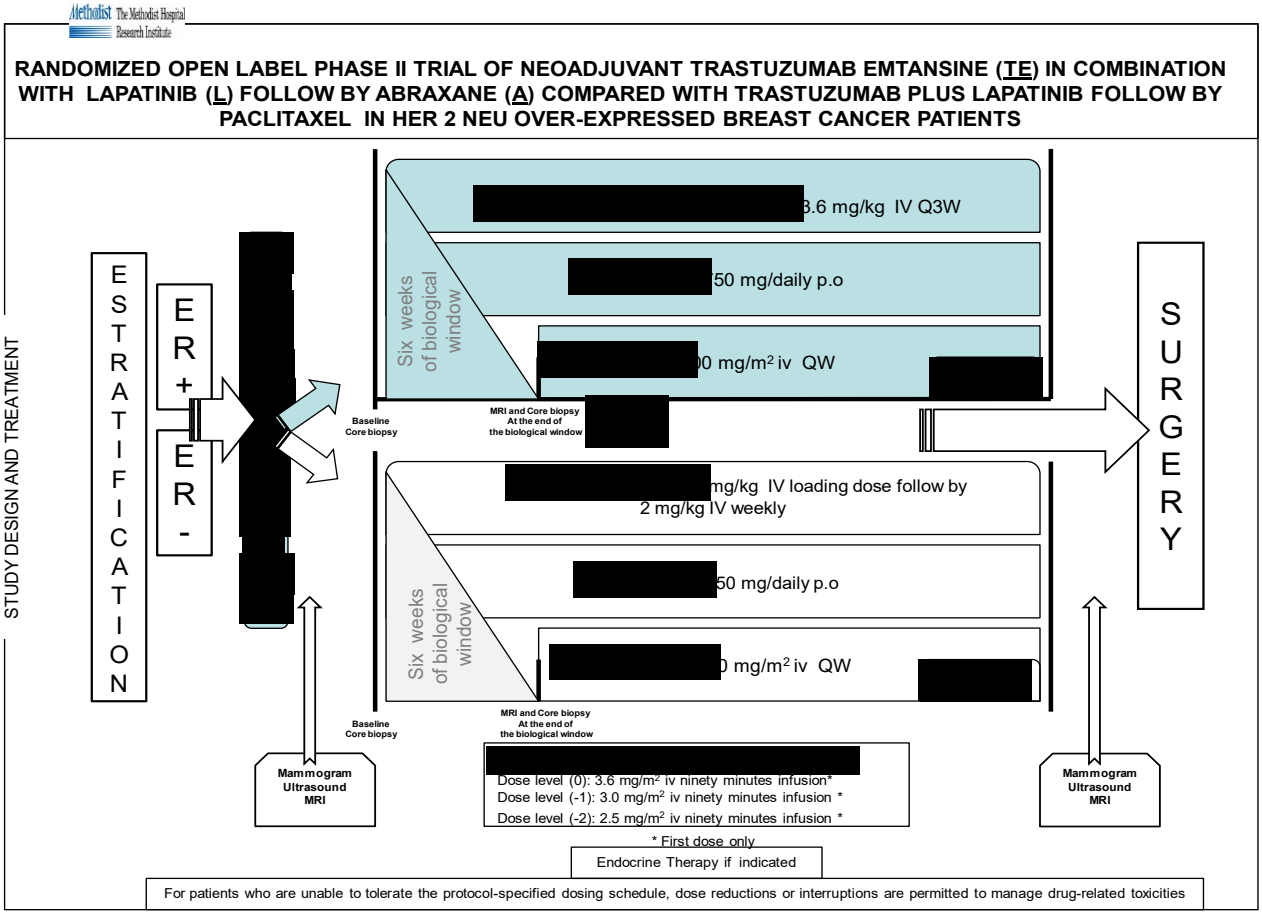

Figure 5

6. Treatment Arms

This is a randomized, open label Phase II neo-adjuvant study comparing the efficacy of neoadjuvant trastuzumab Emtansine plus lapatinib follow by Abraxane, versus trastuzumab plus Lapatinib follow by paclitaxel, given as neoadjuvant treatment in HER2/ErbB2 over-expressing and/or amplified primary breast cancer.

Arm 1: Trastuzumab Emtansine 3.6 mg/kg IV every three weeks plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks, after this biological window patients will continue the same targeted therapy plus Abraxane 100 mg/m^2 IV weekly for twelve (12) weeks

Arm 2: Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly plus Lapatinib 750 mg/daily for a total of 6 weeks, after this biological window, patients will continue on the same weekly targeted therapy plus weekly paclitaxel 80 mg/m^2 for a further 12 weeks, up to definitive surgery.

GCSF allowed after taxane (Nab or Taxol) chemotherapy. After surgery Trastuzumab will continue for 52 weeks (off study).
Pegfilgrastim (Neulasta®) is not allowed.

All patients will have an initial core needle biopsy at time of diagnosis, with additional biopsies at week 6 after the biologic window. Surgical specimens will be obtained after week 18. Biopsies will also be performed in primary cancers that do not respond to therapy.

7. Population

The study is being designed for Her2 Neu over-expressed breast cancer patients. The investigator or designee must ensure that the patient meets all the following inclusion and none of the exclusion criteria before being offered enrollment in the study.

Study Duration:

The duration of patient participation in the study treatment will be a total of 6 to 7 months, which is counted from the start of treatment. Study Follow-up for all patients will include medical history update (30 days after the last dose of the study drug)

Safety Criteria:

All participants will be assessed by a physician for pre-existing medical conditions and baseline physical abnormalities prior to the initiation of investigational therapy. Patients presenting with any medical history, physical exam, or laboratory abnormality that, in the in the opinion of the treating physician, would put the subject's safety at risk will be excluded. Baseline signs and symptoms are to be recorded and followed throughout the trial. These will be monitored throughout the study and recorded if they increase in severity or frequency during treatment or within the follow up period. Participants will be assessed for adverse events by a physician or designated midlevel provider prior to each chemotherapy infusion while the patient is on study. Vital signs including blood pressure, heart rate and temperature should be performed at each physical exam. Assessments may be performed more frequently if clinically indicated. In addition, hematology and serum chemistry profiles will be drawn prior to the initiation of treatment and prior to every infusion to determine whether the study drug combination affects hematologic values, electrolytes or liver function tests. Laboratory assessments will be performed more frequently if clinically indicated. This clinical and laboratory data will be used to determine whether these women in the study with trastuzumab Emtansine plus laptinib plus Abraxane therapy have any symptoms or side effects associated with the study medications. Subjects will be followed for adverse events for a period of 30 days after the completion of investigational therapy (Six (6) to seven (7) months). Patients with abnormal laboratory or clinical findings that are believed to be treatment related will be followed every four weeks until the condition resolves or stabilizes, or until the laboratory values are no longer considered clinically significant. CTC Version 4.0 will be used to grade toxicities. Laboratory tests may be done more frequently if medically indicated. If CTC Grade 4 hematologic toxicity is seen; CBC + differential + platelets should be repeated every 3 - 4 days until recovery.

At suspected recurrence: CT scans of the chest, abdomen, pelvis, and additional directed evaluation as appropriate. Recurrence should be documented by biopsy and/or evidence of metastatic disease on radiologic studies. Abnormal blood studies alone (e.g., elevated liver function tests, CA 15-3, CEA, etc.) are not sufficient evidence of relapse.

8. Inclusion and Exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

8.1 Inclusion criteria:

Patient must meet all of the following criteria:

- Female gender;
- Age ≥18 years;
- Performance Status- Eastern Cooperative Oncology Group (ECOG) 0-1
- Histologically confirmed invasive breast cancer:
- Primary tumor greater than 1 cm diameter, measured by clinical examination and mammography or ultrasound.
- Any N,
- No evidence of metastasis (M0) (isolated supra-clavicular node involvement allowed);
- Over expression and/or amplification of HER2 in the invasive component of the primary tumor and confirmed by a certified laboratory prior to randomization.
- Known hormone receptor status.
- Hematopoietic status:
- CBC not less than .75 of institutional lower limit.
  Absolute neutrophil count ≥ 1,5 x 10^9/L,
  Platelet count ≥ 100 x 10^9/L,
  Hemoglobin at least 9 g/dl,
- Hepatic status:
  Serum total billirubin ≤ 2 x upper limit of normal (ULN). In the case of known Gilbert's syndrome, a higher serum total billirubin (< 1.5 x ULN) is allowed,
  Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 3.5 times ULN,
  Alkaline phosphatase ≤ 2.5 times ULN,
- Renal status:
  Creatinine ≤ 1.5mg/dL,
- Cardiovascular:
  Baseline left ventricular ejection fraction (LVEF) ^{3} ≥50% measured by echocardiography (ECHO) or Multiple Gate Acquisition (MUGA) scan,
- Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential within 2-weeks (preferably 7 days) prior to randomization.
- Fertile patients must use effective contraception (barrier method - condoms, diaphragm - also in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not allowed)
- Signed informed consent form (ICF)
- Patient accepts to make available tumor samples for submission to central laboratory to conduct translational studies as part of this protocol.

8.2 Exclusion criteria:

- Previous (less than 5 years) or current history of malignant neoplasms, except for curatively treated: Basal and squamous cell carcinoma of the skin; Carcinoma in situ of the cervix.
- Patients with a prior malignancy diagnosed more than 5 years prior to randomization may enter the study.
- Preexisting peripheral neuropathy ≥ grade 2
- Known history of uncontrolled or symptomatic angina, clinically significant arrhythmias, congestive heart failure, transmural myocardial infarction, uncontrolled hypertension (≥180/110), unstable diabetes mellitus, dyspnea at rest, or chronic therapy with oxygen;
- Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety;
- Unresolved or unstable, serious adverse events from prior administration of another investigational drug;
- Dementia, altered mental status, or any psychiatric condition that would prevent the understanding or rendering of ICF;
- Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel. Subjects with ulcerative colitis are also excluded;
- Concurrent neoadjuvant cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy other than the trial therapies);
- Concurrent treatment with an investigational agent or participation in another therapeutic clinical trial;
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trastuzumab Emtansine, trastuzumab, lapatinib, paclitaxel, abraxane or their components;
- Pregnant or lactating women;
- Concomitant use of CYP3A4 inhibitors or inducers
- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol
- Patients have an active infection and require IV or oral antibiotics.
- Pregnant or breast-feeding women
- Patients unwilling or unable to comply with the protocol

9. Treatment

Table 1 Trastuzumab Emtansine dose modifications

Trastuzumab Emtansine Dose Level	Trastuzumab Emtansine Dose and Schedule
Starting dose level (0)	3.6 mg/m^2 iv ninety minutes infusion first dose only
Dose level – 1	3.0 mg/m^2 iv ninety minutes infusion first dose only
Dose level – 2	2.5 mg/m^2 iv ninety minutes infusion first dose only

First infusion: Administer infusion over 90 minutes. Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusionrelated reactions. Subsequent infusions: Administer over 30 minutes if prior infusions were well tolerated. Patients should be observed during the infusion and for at least 30 minutes after infusion.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event including abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Dose interruptions should be reported on the appropriate Dosage Administration CRF. The maximum time allowed for treatment interruption due to toxicity is 21 days (3 weeks) from the intended dosing day. If interruption is > 3 weeks, the patient must be discontinued from the study treatment. However, the patient will continue to be followed for toxicity.

9.1 Trastuzumab Emtansine (TDM-1) General Infortmation [41]

DRUG NAME: Trastuzumab emtansine

SYNONYM(S): **T-DM1, Trastuzumab-DM1, Trastuzumab-MCC-DM1 antibody-drug conjugate; ado-trastuzumab emtansine (USA)**

COMMON TRADE NAME(S): KADCYLA® (USA)

MECHANISM OF ACTION:

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate incorporating the monoclonal antibody trastuzumab and the cytotoxic agent emtansine (DM1). The trastuzumab moiety binds to the human epidermal growth factor 2 (HER2) receptor on the tumour surface. Once internalized, the emtansine moiety binds to tubulin, the protein component of microtubules, and disrupts the assembly and disassembly of the microtubules, leading to inhibition of mitosis and proliferation of cancer cells with HER2 overexpression.

USES: ***Primary uses:***

Breast cancer

SPECIAL PRECAUTIONS:

Contraindications: patients with known hypersensitivity reaction to trastuzumab or Chinese hamster ovary cell proteins

Caution: in patients with ***pre-existing cardiac dysfunction*** or a left ventricular ejection fraction (LVEF) of 50% or less

in patients with ***pre-existing pulmonary disease***: patients who experience dyspnea at rest due to complications of advanced malignancy and co-morbidities may be at an increased risk of pulmonary events and/or a fatal infusion reaction

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials.

ORGAN SITE	SIDE EFFECT
blood and lymphatic system/ febrile neutropenia	anemia (10%, severe 3%) bleeding (30%, severe 1%) neutropenia (6%, severe 2 %) ***thrombocytopenia*** (28%, severe 13%)
cardiac	left ventricular dysfunction (2%)
gastrointestinal	emetogenic potential: low5 diarrhea (23%, severe 2%) mucosal inflammation (7%, severe <1%) nausea (40%, severe <1%) vomiting (19 %, severe <1%)
general disorders and administration site conditions	extravasation hazard: non-vesicant6
	fatigue (35%, severe 2%)
immune system	infusion-related reactions (7%, severe <1%)1; see paragraph following Side Effects table
investigations	hypokalemia (9%, severe 2%) ALT, elevated (17%, severe 3%) AST, elevated (22%, severe 4%)

musculoskeletal and connective tissue	arthralgia (19%, severe <1%) myalgia (14%, severe <1%) musculoskeletal pain (36%, severe 2%)
respiratory	pneumonitis (1%) dyspnea (12%, severe <1%) cough (18%, severe <1%) epistaxis (22%, severe <1%)
skin and subcutaneous tissue	palmar–plantar erythrodysesthesia (1%)

Table 2

In a recent communication from Genentech/ROCHE, nine (9) fatal cases of bleeding including six central nervous system (CNS) hemorrhages have been reported among approximately 4,200 patients exposed to trastuzumab emtansine as a single agent or in combination with other drugs in clinical trials. Six of the 9 patients were exposed to trastuzumab emtansine as a single agent. Three patients received trastuzumab emtansine in combination: one case with pertuzumab, one case with blinded pertuzumab, and one case with paclitaxel. Six cases were associated with decreased platelet counts ranging from Grade 1 to Grade 4, and in 3 cases platelet counts were not provided. In 4 cases the patients were also receiving anticoagulation therapy. These cases occurred independent of ethnicity. Per investigator assessment, one of the nine fatal cases (with Grade 4 thrombocytopenia) was related to trastuzumab emtansine and the other eight cases were not related to drug.

These hemorrhagic events are not considered to impact the overall risk/benefit of trastuzumab emtansine. Patients with thrombocytopenia and patients on anti-coagulant treatment should be monitored closely while on trastuzumab emtansine treatment. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose.

Infusion-related reactions ranging from flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials. In most cases, these symptoms were not severe and reactions resolved over several hours to one day after the infusion was terminated. Consider discontinuing treatment for severe hypersensitivity reactions, including anaphylaxis, angioedema, or acute respiratory distress syndrome. Interrupt infusion for patients developing dyspnea or clinically significant hypotension. Symptoms are managed with diphenhydramine, acetaminophen, epinephrine, corticosteroids, oxygen, or intravenous fluids.

SUPPLY AND STORAGE:

TDM-1 will be considered part of the study arm and will be provided by the sponsor for those patients randomized in this arm. Genentech, Inc. produces trastuzumab Emtansine as 100 mg or 160 mg vials of sterile, preservative-free lyophilized powder. Sterile water for injection (containing benzyl alcohol) is supplied for reconstitution. Refrigerate.

SOLUTION PREPARATION AND COMPATIBILITY:

Intermittent infusion

Initial dose: over 90 minutes (observe at least 90 minutes post-infusion) Subsequent doses: over 30 minutes (observe 30 minutes post-infusion)

DOSAGE GUIDELINES:

Cycle Length: 3 weeks

Intravenous:

3.6 mg/kg (range 2.4-3.6 mg/kg) IV for one dose on day 1 (total dose per cycle 3.6 mg/kg [range 2.4-3.6 mg/kg])

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

9.2 Trastuzumab (Herceptin) General Infortmation[42]

DRUG NAME: Trastuzumab
SYNONYM(S): anti-c-erB-2; anti-ERB-2; MOAB HER2; rhuMAb HER2
COMMON TRADE NAME(S): HERCEPTIN®
CLASSIFICATION: Monoclonal antibody
Special pediatric considerations are noted when applicable, otherwise adult provisions apply.
MECHANISM OF ACTION:
Trastuzumab is a human monoclonal IgG antibody which selectively targets HER2, a human epidermal growth factor receptor (EGFR). Trastuzumab inhibits the growth of tumour cells that overexpress HER2 on the surface of breast, gastric, ovarian, lung, and prostate cancer cells. Mechanisms involved include: decreasing VEGF production, activating antibody-dependent cell-mediated cytotoxicity, G0/G1 cell cycle cytotoxicity, and inhibiting intracellular signaling pathways.
PHARMACOKINETICS:

Interpatient variability	interpatient variability noted in clearance and volume of distribution	
Distribution	steady state, AUC, C_{max}, C_{min} are lower in metastatic gastric cancer than metastatic breast cancer; steady state trough levels are similar between weekly and 3-weekly regimens	
	cross blood brain barrier?	unlikely, due to large molecule size
	volume of distribution	3-4L
	plasma protein binding	no information found
Metabolism	no information found	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	via the reticuloendothelial system	
	urine	no information found
	feces	no information found
	terminal half life	12-29 days; shorter half life in metastatic gastric cancer due to increased clearance
	clearance	0.225-0.378 L/day; increased with more metastatic sites
Elderly	no differences reported	

Table 3

USES: ***Primary uses:***
Other uses:
*Breast cancer *Gastric cancer
SPECIAL PRECAUTIONS:
Contraindications: history of hypersensitivity reaction to trastuzumab or Chinese hamster ovary cell proteins
Caution: in patients with pre-existing cardiac dysfunction or a left ventricular ejection fraction (LVEF) of 55% or less; see paragraph following **Side Effects** table.
In patients with pre-existing pulmonary disease or extensive pulmonary tumor involvement; patients who experience dyspnea at rest due to comorbidities or advanced malignancy may be at increased risk of a fatal infusion reaction.
Special populations:
Patients aged 65 years and older may be at greater risk for cardiac dysfunction and hematologic toxicities

(leukopenia and thrombocytopenia).
Patients who received prior adjuvant therapy with anthracyclines for treatment of early breast cancer are at greater risk of developing cardiotoxicity.
Carcinogenicity: no information found
Mutagenicity: Not mutagenic in Ames test. Trastuzumab is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.
Fertility: Formal fertility studies have not been conducted in women. No evidence of impaired fertility was reported in animal studies.
Pregnancy: FDA Pregnancy Category D. There is evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Impaired fetal renal growth and function, intrauterine growth retardation, and skeletal abnormalities associated with oligohydramnios during the second and third trimesters have been reported. Women of childbearing potential are advised to use effective contraception during treatment and for at least 6 months post treatment.
Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, trastuzumab was detected in the milk of lactating monkeys, although no adverse effects on growth or development were seen.
SIDE EFFECTS:
The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
blood and lymphatic system/ febrile neutropenia	Anemia (4%), leukopenia (3%)
cardiac	Arrhythmia (3%), ***congestive heart failure*** (2%; severe <1%), palpitations (3%) , tachycardia (1%)
gastrointestinal	emetogenic potential: low, abdominal pain (2%) , constipation (2%) , diarrhea (7%) , dyspepsia (2%) , gastritis (1%) , nausea (6-14%)2,18 , stomatitis (2%) , vomiting (4-28%)
general disorders and administration site conditions	Extravasation hazard: none , asthenia (5%) , chills (5%) fatigue (8%) , fever (6%) , influenza-like illness (2%) , infusion-related reaction (21-40%, severe 1%); , non-cardiac chest pain (3%) , peripheral edema (5%)
immune system	Allergic reaction (3%)
infections and infestations	Herpes zoster (1%) , influenza (4%) , nasopharyngitis (8%) pharyngitis (1%) , rhinitis (2%) , sinusitis (2%) , upper respiratory tract infection (3%) , urinary tract infection (2-5%)
investigations	alkaline phosphatase, elevated , ALT, elevated, AST, elevated bilirubin, elevated (1%) , ejection fraction, decreased (4-10%) weight gain (2%)
musculoskeletal and connective tissue	Arthralgia (8%) , back pain (5%) , bone pain (3%) , chest wall pain (2%) , muscle spasms (3%) , myalgia (4%) , pain in extremity (4%) , shoulder pain (2%)
nervous system	Dizziness (4%) , headache (10%) , paresthesia (2%) , vertigo (2%)
psychiatric	Anxiety (2%) , depression (3%) , insomnia (4%)

renal and urinary	Cystitis (1%)
reproductive system and breast disorders	Breast pain (1%)
respiratory, thoracic and mediastinal	Cough (5%) , dyspnea (3%) , epistaxis (1%) , pharyngolaryngeal pain (2%) , rhinitis (2%)
skin and subcutaneous tissue	Erythema (1%) , nail disorder (3%) , pruritus (2%) , rash (4%)
vascular	Hot flashes (6%) , hypertension (4%) , lymphedema (3%)

Table 4

Cardiotoxicity has been reported with trastuzumab. Signs and symptoms include: dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, congestive heart failure (CHF), or a reduced ejection fraction of 10% or greater. Cardiac dysfunction from trastuzumab is not dose-related and is reported to be highly reversible so patients have relatively good prognosis following CHF or LVEF dysfunction. LVEF usually returns toward baseline during the 1.5 months post-trastuzumab treatment; however, some cases have resulted in disabling heart failure, thrombosis and stroke, and/or death.

Risk factors for trastuzumab-related cardiotoxicity include: older age (>65 years), prior or concurrent use of antihypertensive medications, higher cumulative dose of anthracycline prior to trastuzumab, a lower left ventricular ejection fraction (LVEF) at baseline, a declining LVEF (<55%), a low LVEF prior to or following paclitaxel treatment, a higher body mass index (>25) at screening

An increase in cardiac events is observed when trastuzumab is administered after anthracycline-containing chemotherapy compared to non-anthracycline-containing chemotherapy. The incidence is more marked when trastuzumab is administered concurrently, rather than sequentially, with a taxane. There is some uncertainty whether smoking, diabetes, hypothyroidism, or hyperlipidemia is associated with trastuzumab-related cardiotoxicity. Prior or concurrent radiation does not increase cardiac events, but may increase the incidence of leukopenia. There is inadequate long term data, however, to correlate cardiac dysfunction from trastuzumab with concurrent or prior radiation. Trastuzumab interrupts the HER2 signalling pathway in the heart which maintains normal growth, repair, and survival of cardiac cells. This results in changes to cardiac contractility, but does not cause myocardial cell death. Suggested management for trastuzumab-related cardiotoxicity includes withholding trastuzumab for approximately 3 weeks if LVEF falls 10-15 ejection points below baseline and/or below 50%. Trastuzumab can be resumed once LVEF improves. If the LVEF does not improve within approximately 3 weeks, consider discontinuing trastuzumab. Trastuzumab may be considered in patients with a LVEF less than 50% if their risk of disease recurrence is very high. The LVEF should be assessed prior to starting trastuzumab, repeated every 3 months during treatment, and then, every 6 months following completion of treatment until 24 months from the last dose of trastuzumab. For early breast cancer patients who received anthracycline-based chemotherapy, yearly monitoring of LVEF up to 5 years or longer from the last dose of trastuzumab is suggested. Refer to protocol by which patient is being treated.

Infusion-related reactions range from mild reactions of chills and/or fever (occurring in 40% of patients with first infusion) to mild-moderate reactions of nausea, vomiting, pain, rigors, headache, cough, dizziness, dyspnea, rash, and asthenia. Severe reactions include hypotension, hypertension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. Pre-existing pulmonary disease or co-morbidities may increase risk of pulmonary toxicities or a fatal reaction. Clinical course is variable; initial improvement may be followed by clinical deterioration and death. Management of infusion-related reactions includes decreasing the rate for mild or moderate reactions and interrupting the infusion in patients experiencing dyspnea or hypotension. Consider discontinuing treatment for severe reactions such as anaphylaxis, angioedema, pneumonitis, or respiratory distress. Patients who react to the initial trastuzumab infusion may receive further treatment after complete resolution of symptoms. Infusion duration may be increased at the physician's discretion. Symptoms are managed with diphenhydramine, acetaminophen, meperidine, epinephrine, corticosteroids, oxygen, bronchodilators, or IV fluids. Patients experiencing infusion-related symptoms should not drive or use machines until symptoms resolve completely.

INTERACTIONS: AGENT	EFFECT	MECHANISM	MANAGEMENT
anthracycline chemotherapy	increase in trastuzumab-induced cardiac dysfunction	negative inotropic effect on the heart	avoid use of anthracyclines concurrently with trastuzumab
paclitaxel	1.5 fold increase in trastuzumab serum levels	mechanism unclear; animal studies report a 2 fold decrease in trastuzumab clearance	monitor for signs of cardiac dysfunction

Table 5

SUPPLY AND STORAGE:

Trastuzumab (Herceptin) will be considered standard of care and will be provided by the insurance company for those patients randomized for the control arm. Hoffmann-La Roche Limited produces trastuzumab as 440 mg vials of sterile, preservative-free lyophilized powder. Bacteriostatic water for injection (containing benzyl alcohol) is supplied for reconstitution. Refrigerate.

SOLUTION PREPARATION AND COMPATIBILITY: Benzyl alcohol should not be administered intrathecally due to the risk of anaphylaxis and increased potential for neurotoxicity.

For intrathecal administration of trastuzumab or in patients with a known hypersensitivity to benzyl alcohol: reconstitute vial with sterile water for injection instead of the supplied preservative-containing diluent.use immediately; discard unused portion.

PARENTERAL ADMINISTRATION: over 30-90 minutes 3-weekly dosing: loading dose over 90 minutes; 1st maintenance dose over 60 minutes; 2nd and further maintenance doses over 30 minutes if no adverse reactions. Weekly dosing: loading dose over 60 minutes; maintenance doses over 30 minutes if no adverse reactions

Intrathecal has been used (not approved to use in this protocol)

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

Cycle Length:	
Intravenous: ***weekly***	***Loading dose: 4 mg/kg IV for one dose on day 1 of first cycle*** ***Maintenance dose: 2 mg/kg IV for one dose on day 1 of each subsequent cycle***
3 weeks	***Loading dose: 8 mg/kg IV for one dose on day 1 of first cycle*** ***Maintenance dose: 6 mg/kg IV for one dose on day 1 of each subsequent cycle***
3 weeks	Loading dose: 6 mg/kg IV for one dose on days 1, 8, and 15 of first cycle. Maintenance dose: 6 mg/kg IV for one dose on day 1 only of each subsequent cycle

Using a reloading dose has been recommended to quickly regain a therapeutic serum level after a treatment delay; however the optimal way to reload trastuzumab after interruption of maintenance therapy is unclear. Trastuzumab has a long elimination half-life so serum level declines slowly with short treatment delays. In addition, the minimal therapeutic serum level is not clearly defined, since the targeted serum level in dosing design is based on *in vitro* tumor growth inhibition and is lower than the actual steady state level observed in efficacy trials.

Concurrent radiation: ***3 weeks***	***Loading dose: 8 mg/kg IV for one dose on day 1 of first cycle*** ***Maintenance dose: 6 mg/kg IV for one dose on day 1 of subsequent cycles***
Dosage in myelosuppression:	modify according to protocol by which patient is being treated;
Dosage in renal failure:	no adjustment required
Dosage in hepatic failure:	no information found
Dosage in dialysis:	no significant removal

Table 6

9.3 Lapatinib General Infortmation[43]

DRUG NAME: Lapatinib

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

SYNONYM(S): lapatinib ditosylate monohydrate, lapatinib tosylate, GW572016

COMMON TRADE NAME(S): TYKERB®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Lapatinib is an orally active small molecule tyrosine kinase inhibitor. It is a potent, reversible, and selective inhibitor of both EGFR and HER2 receptors, and induces growth arrest or apoptosis in EGFR-dependent or HER2-dependent tumour cell lines. Lapatinib binds to the intracellular cytoplasmic ATP-binding site of the tyrosine kinase domain, blocking receptor phosphorylation and activation, thereby blocking downstream signaling pathways.

PHARMACOKINETICS:

Oral Absorption	incomplete and variable; increased when administered with food	
Distribution	highly protein bound; peak plasma concentrations in 4h	
	cross blood brain barrier?	yes
	volume of distribution	no information found
	plasma protein binding	>99% to albumin and alpha-1 acid glycoprotein
Metabolism	extensive; primarily by CYP 3A4 and CYP 3A5, minor metabolism by CYP 2C19 and CYP 2C8 to oxidized metabolites	
	active metabolite(s)	activity not characterized
	inactive metabolite(s)	activity not characterized
Excretion	primarily in feces; increased systemic exposure with moderate to severe hepatic impairment	
	urine	<2%
	feces	3-67% as unchanged drug and oxidized metabolites
	terminal half life	14 h after single dose, 24 h with repeated dosing
	clearance	no information found

Table 7

USES: ***Primary uses:*** *Breast cancer

SPECIAL PRECAUTIONS:

Caution: lapatinib is associated with QT/QTc prolongation. Patients who are at risk for developing torsades de pointes (an atypical ventricular tachycardia with changes in QT interval) include those with cardiac disease, history of arrhythmias, electrolyte disturbances, nutritional deficits, etc. and should be closely monitored. Baseline and periodic electrolyte measurements and electrocardiograms with QT measurement should be considered. Concurrent therapy with other QT prolonging drugs may increase the risk of potentially fatal arrhythmias and should be avoided if possible; see paragraph in **Interactions** section. Concurrent medication should be carefully reviewed for potential drug interactions, particularly in regard to CYP 3A4, CYP 2C8, P-glycoprotein, BCRP and OATP1B11; see paragraphs in **Interactions** section.

Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to treatment initiation. Caution is advised with concurrent medications that disrupt electrolyte levels, including diuretics, laxatives, and high dose corticosteroids. Lapatinib has been reported to decrease left ventricular ejection fraction (LVEF). LVEF should be evaluated prior to initiation of therapy and periodically throughout treatment (eight week intervals have been used in clinical trials); see table and paragraph in **Side Effects** section.

Interstitial lung disease and pneumonitis have been associated with treatment. Patients should be monitored for pulmonary symptoms, and treatment discontinued if reported symptoms are Grade 3 or greater.

Hepatoxicity has been observed. Liver function should be monitored prior to initiation of therapy, every four to six weeks during treatment, and as clinically indicated; see table and paragraph in **Side Effects** section.

The presence of food significantly alters the bioavailability of lapatinib, with 3-5 fold increases in AUC reported with low and high fat meals relative to fasting. Multiple mechanisms are believed to be involved. Administration on an empty stomach is believed to be the most reliable way to achieve consistent systemic exposure and reduce

potential toxicity during chronic therapy.

Carcinogenicity: No evidence of carcinogenicity in mammalian studies at doses up to twice the expected human clinical exposure.

Mutagenicity: Not mutagenic in Ames test or clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: No effects on mammalian gonadal function, mating, or fertility at doses up to 3-8 times the expected human clinical exposure.

Pregnancy: FDA Pregnancy Category D.9 Lapatinib was not teratogenic in mammalian studies, but decreased pup survival, decreased fetal body weights, and minor skeletal anomalies in mammals have been reported. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

Table 8. Adverse Reactions Occurring in ≥10% of Patients						
	lapatinib1,250 mg/day + Capecitabine 2,000 mg/m2/day			Capecitabine 2,500 mg/m2/day		
	(N = 198)			(N = 191)		
	All Grades a	Grade 3	Grade 4	All Grades a	Grade 3	Grade 4
Reactions	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash b	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0
Laboratory Abnormalities						
Hematologic						

Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	22	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	1	0

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

Table 9. Adverse Reactions Occurring in ≥10% of Patients						
	lapatinib 1,500 mg/day + Letrozole 2.5 mg/day (N = 654)			Letrozole 2.5 mg/day (N = 624)		
	All Grades a	Grade 3	Grade 4	All Grades a	Grade 3	Grade 4
Reactions	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	64	9	<1	20	<1	0
Nausea	31	<1	0	21	<1	0
Vomiting	17	1	<1	11	<1	<1
Anorexia	11	<1	0	9	<1	0
Skin and subcutaneous tissue disorders						
Rashb	44	1	0	13	0	0
Dry skin	13	<1	0	4	0	0
Alopecia	13	<1	0	7	0	0
Pruritus	12	<1	0	9	<1	0
Nail Disorder	11	<1	0	<1	0	0
General disorders and administrative site conditions						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
Nervous system disorders						
Headache	14	<1	0	13	<1	0
Respiratory, thoracic, and mediastinal disorders						
Epistaxis	11	<1	0	2	<1	0
Hepatic Parameters						
AST	53	6	0	36	2	<1
ALT	46	5	<1	35	1	0
Total Bilirubin	22	<1	<1	11	1	<1

a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.
b In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment arm had rash under "Infections and infestations"; none were Grade 3 or 4.

Gastrointestinal adverse events

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

Nausea, vomiting, or both. In subjects who have emesis and are unable to retain lapatinib, every attempt should be made to obtain control of nausea and vomiting. A dose may be repeated if tablets can be visually found after the vomiting episode.

Diarrhea is commonly reported, mainly as grade 1 or 2 events. Moderate to severe diarrhea may be complicated by severe cramping, nausea or vomiting, fever or dehydration. Diarrhea incidence appears to be related to dose, but not serum concentration, suggesting a local effect on the gut as opposed to a systemic effect. Proactive management with anti-diarrheal agents is important. A loperamide dosing regimen, including an initial dose of 4 mg, followed by 2 mg every four hours, and continued until twelve hours diarrhea-free, has been suggested. Therapy interruption or discontinuation may be required until recovery, and severe cases may also require oral or intravenous electrolytes and fluids.

Diarrhea management

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

Common clinical sense with the onset of uncomplicated Grade 1-2 diarrhea: stop all lactose containing products: drink 8-10 large glasses of clear liquids a day; eat frequent small meals; for Grade 2 diarrhea hold cytotoxic chemotherapy, and consider hold lapatinib (discuss with medical monitor); **It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below.**

Initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool. It is suggested to continue loperamide until the subject is free from diarrhea for 12 hours.

For Grade 3 or 4 diarrhea or Grade 1 or 2 with complicating features ((CTCAE) Version 4.0) severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration) use intravenous fluids as appropriate, consider hospital administration. Use prophylactic antibiotics as needed (example fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is a fever or Grade 3-4 neutropenia, hold both cytotoxic chemotherapy and lapatinib and discuss with medical monitor. (See Algorithm for the management of diarrhea appendix F)

Treatment of gastrointestinal adverse events

Diarrhea can be debilitating, and on rare occasions, it is potentially life-threatening. Based on experience with lapatinib alone or in combination with taxanes and/or trastuzumab, diarrhea should be managed proactively to avoid complications or worsening of the patient's condition. Guidelines developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea are abstracted below. Pharmacological approaches include the following:

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.

Hepatoxicity, although reported in less than 1%, may be severe and may occur days to several months after treatment initiation. ALT or AST greater than three times the upper limit of normal and total bilirubin of 1.5 times the upper limit of normal have been described. Deaths have been reported, although causality is uncertain. Monitor liver function tests (transaminases, bilirubin, and alkaline phosphatase) before treatment initiation, every four to six weeks during treatment, and as clinically indicated. Lapatinib should be discontinued and not restarted if liver

function changes are severe or if severe hepatotoxicity develops during treatment, as moderate to severe hepatic impairment has been associated with 56-85% increases in systemic exposure. Clinical experience with severe pre-existing hepatic impairment is limited and safety and efficacy data are not available. Based on pharmacokinetic modeling, it has been suggested that a dose reduction from 1250 mg/day to 750 mg/day is warranted.

Hepatotoxicity Addition to SAE Definition

Hepatobiliary events have been seen in subjects taking lapatinib and other tyrosine kinase inhibitors. As a precaution, the following will be reported as an SAE:

- ALT >3×ULN and total bilirubin >2.0×ULN (>35% direct; bilirubin fractionation required).

NOTE: If bilirubin fractionation testing is unavailable and a subject meets the criterion of total bilirubin >2.0 × ULN, then the event should still be reported as an SAE.

Other hepatic events should be documented as an AE or an SAE as appropriate.

Safety: Ensure LFT assessment is included in the protocol as follows:

- During treatment phase: every 4-6 weeks (to best fit protocol schedule) for first 6 months, then every 8 – 12 weeks (or more frequently, if clinically indicated) for remainder of treatment period
- During post-treatment phase: continue to monitor any liver chemistry abnormalities noted during treatment or within 30 days after last dose of investigational product until values return to normal or baseline

Liver Chemistry Stopping Criteria

Liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology. All subjects who meet liver chemistry criteria requiring permanent discontinuation of investigational product must continue to be followed per the Liver Chemistry Follow-up Criteria below.

If a subject experiences ALT >3 × ULN and total bilirubin >2.0 × ULN (>35% direct; bilirubin fractionation required), or ALT>3 x ULN and INR>1.5 (if INR measured), then the following actions must be taken:

immediately and permanently discontinue investigational product;

complete the SAE data collection tool, the liver event CRF, and the liver imaging and/or liver biopsy CRFs, if these tests are performed;

in addition to the liver event follow up assessments, the following are suggested: specialist or hepatology consultation; anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies; and liver imaging and/or liver biopsy to evaluate liver disease;

promptly report the event to GSK within 24 hours of learning its occurrence

monitor every week until liver chemistries resolve, stabilize or return to within baseline values;

Do not re-challenge with investigational product.

***NOTE**: If bilirubin fractionation testing is unavailable and a subject meets the criterion of total bilirubin >2.0 × ULN, then the aforementioned actions must still be performed. If bilirubin fractionation testing is unavailable, record the presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

If a subject experiences:

ALT >8 × ULN or

ALT >5 × ULN persisting for ≥2 weeks : retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists or

ALT >3 × ULN with signs or symptoms of hepatitis or hypersensitivity (the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) then hold investigational product for 2 weeks, repeat liver chemistry testing in 2 weeks, and then call the GSK Medical Monitor to discuss the possibility of re-challenging with investigational product. Liver chemistries and aforementioned signs and symptoms should be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol.

If a subject experiences ALT >3 × ULN **but** <5 × ULN **and** total bilirubin ≤2 × ULN, without signs or symptoms of hepatitis or hypersensitivity, **and** who can be monitored weekly, then the following actions should be taken:

continue investigational product; monitor weekly until liver chemistries resolve, stabilize, or return to within

baseline, then monitor liver chemistries as per protocol assessment schedule; If ALT >3 and < 5 × ULN persists for > 4 weeks, discontinue treatment.

for subjects who have ALT >3 × ULN **and** total bilirubin >2.0 × ULN (>35% direct; bilirubin fractionation required*), or ALT>3 x ULN and INR>1.5 (if INR measured), promptly report the event as SAE to GSK within **24 hours** of learning its occurrence (refer to pages 34 & 35) for guidance on prompt reporting to GSK);

complete the SAE data collection tool for all other subjects only if the event meets the criteria for an SAE;

complete the liver event CRF and the liver imaging and/or liver biopsy CRFs, if these tests are performed;

monitor every week until liver chemistries resolve or return to within baseline values

Do not re-challenge with study treatment.

If a subject experiences ALT >3 × ULN **but** <5 × ULN **and** total bilirubin ≤2 × ULN, without signs or symptoms of hepatitis or hypersensitivity, **and** who can be monitored weekly, then the following actions should be taken:

continue study treatment;

monitor weekly until liver chemistries resolve or return to within baseline, then monitor liver chemistries as per protocol assessment schedule;

if at any time the subject meets any of the liver chemistry stopping criteria, then proceed as described above;

Liver Chemistry Follow-up Criteria

For all subjects who meet any of the liver chemistry criteria described above, make every attempt to carry out the liver event follow up assessments described below:

Viral hepatitis serology including:

Hepatitis A IgM antibody;

Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);

Hepatitis C RNA;

Cytomegalovirus IgM antibody;

Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);

Hepatitis E IgM antibody (if subject resides or has traveled outside USA or Canada in past 3 months);

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);

Complete blood count with differential to assess eosinophilia;

Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on an AE report form;

Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, other putative hepatotoxins, and/or alcohol use

The following assessments are required for subjects with ALT≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other liver chemistries:

A specialist or hepatology consultation is recommended;

Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;

Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;

Refer to Appendix E, for a liver safety algorithm detailing stopping and follow up criteria.

Left ventricular ejection fraction (LVEF) has been reported to decrease with lapatinib. Events are usually reversible and asymptomatic. Caution is advised in patients with conditions that impair left ventricular function. Previous anthracycline or trastuzumab treatment are suggested as possible risk factors for cardiotoxicity, although similar rates of occurrence have been reported for pretreated patients in pooled data. The majority of LVEF decreases (69%) occurred within the first 9 weeks of treatment during clinical trials, but long-term data is limited. Events resolved or improved in 62% of patients, with 42% of this continuing treatment. Average event duration was reported to be 4 weeks. Symptomatic events responded to standard CHF therapy in most. Baseline LVEF should be evaluated in all patients prior to initiation of treatment and periodically throughout treatment. LVEF was monitored at eight week intervals during clinical trials. Lapatinib should be discontinued in patients with symptoms associated with decreased LVEF (grade 3 or greater), or if LVEF drops 20% or greater relative to baseline or below the lower limit of normal.

Concentration dependent QT/QTc interval prolongation has been reported with lapatinib. Events of ventricular fibrillation, cardiac arrest, and sudden death have been reported. Risk factors for experiencing torsade de pointes during treatment with a QT/QTc prolonging drug include female gender, age ≥65 years, family history, history of cardiac disease or arrhythmias, electrolyte disturbances, acute neurological events, hepatic dysfunction, diabetes, and nutritional deficits. Concurrent therapy with other QT/QTc prolonging drugs should be avoided where possible. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to lapatinib treatment.

Addition to SAE definition:

Cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines, and interstitial pneumonitis has been reported in subjects taking compounds that inhibit ErbB1. As a precaution, the following will be reported as an SAE:

- Cardiac dysfunction will be reported as an SAE and will be defined as any signs or symptoms of deterioration in left ventricular cardiac function that are Grade 3 (NCI CTCAE) or a ≥20% decrease in left ventricular cardiac ejection fraction (LVEF) relative to baseline which is below the institution's lower limit of normal.

Refer to NCI CTCAE grading of left ventricular cardiac function.

Criteria for Evaluating Cardiac Events

Asymptomatic cardiac events:

Subjects who have a ≥20% decrease in LVEF relative to baseline, and the ejection fraction is below the institution's lower limit of normal, should have a repeat evaluation of ejection fraction 1-2 weeks later while still receiving investigational product.

- If the repeat ejection fraction evaluation confirms a ≥20% decrease in LVEF, and the ejection fraction is below the institution's lower limit of normal, then investigational product should be temporarily discontinued.
- If repeat ejection fraction evaluation still shows a decrease ≥20% in LVEF relative to baseline, and the value is below the institution's lower limit of normal, then the subject should be withdrawn from investigational product.

Symptomatic cardiac events:

Subjects with an NCI CTCAE grade 3 or 4 LVEF relative decrease must be withdrawn from study medication.

Rash (including rash, acne, and dermatitis acneiform) is generally mild to moderate in intensity. Skin rash generally appears on the trunk, and sometimes the face. Rash incidence does not appear to relate to dose, serum concentration or clinical response to treatment.3 Onset of rash and ***other dermatologic events*** tends to develop early in treatment, usually occurring between days 2 to 66, with a median duration of 29 days. Most dermatologic events with lapatinib monotherapy resolve without dose adjustment or treatment interruption. Treatment should be permanently discontinued for intolerable grade 3 or 4 reactions or for grade 3 or 4 reactions which recur after treatment interruption and rechallenge. Patients are advised to moisturize dry skin with a thick alcohol-free emollient upon treatment initiation and minimize sun exposure for treatment duration. Appropriate use of sunscreen is recommended to prevent exacerbation of dermatologic toxicity. Treatment of dermatologic events is anecdotal and is based on type of reaction and severity of toxicity: skin rash may respond to short-term oral steroids; topical or systemic antihistamines may be beneficial for pruritic reactions; antiseptic baths, potent local corticosteroids, and silver nitrate are recommended to treat paronychia; and topical or systemic antibiotics are indicated for superinfection.

Management of interstitial lung disease

If a patient develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, lapatinib or trastuzumab therapy should be interrupted and a thorough evaluation performed. If NCI-CTCAE v3.0 Grade 3 or 4 pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to lapatinib and/or trastuzumab cannot be excluded), lapatinib and/or trastuzumab must be permanently discontinued. All incidences of interstitial lung disease/ interstitial pneumonitis regardless of grade must be reported as serious adverse events (SAEs).

Other adverse events

For any other NCI-CTCAE v3.0 Grade 3 or 4 adverse events or any clinically significant, lower-grade adverse event, treatment with lapatinib should be interrupted for a maximum of 14 days until the patient recovers completely or the adverse event reverts to NCI-CTCAE v3.0 Grade 1 or to baseline grade.

If recurrence of adverse event after drug holiday / interruptions is observed a dose reduction by 250mg is recommended. Dose reduction should only be implemented when all supportive care measures have been exhausted without an improvement of patient status.

Dermatologic (skin) adverse events

Significant skin adverse events (Grade 3 or more) resulting from lapatinib are rare (1-3%). For NCI-CTCAE v4.0 Grade 4 rash manifested as toxic epidermal necrolysis (i.e. Stevens-Johnson's Syndrome etc) lapatinib must be permanently discontinued.

Severe Skin Events

Lapatinib-related severe dermatological events are infrequent (1-3%). Table 1 displays the NCI-CTCAE (version 4.0) ≥ Grade 3 skin events, which are defined as:Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL

Surgical intervention or IV antibiotics indicated; limiting self care ADL

Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated

Covering >30% BSA and associated with pruritus; limiting self care ADL

Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs

Despite the rarity of these events among subjects treated with lapatinib, it is recommended that subjects which present with these events be assessed for shortness of breath, angioedema, or generalized mucosal/cutaneous affectation with blisters or ulcers, suggestive of Type I hypersensitivity and/or NCI-CTCAE Grade 4 rash or dermatologic event, manifested as toxic epidermal necrolysis (i.e., Stevens-Johnson's Syndrome etc). If Grade 4 rash or dermatologic event occurs, lapatinib must be permanently discontinued.

Stopping and holding rules

If any Grade 4 dermatologic event occurs, lapatinib must be permanently discontinued.

Stopping rules

Lapatinib should be permanently discontinued if an NCI-CTCAE Grade 3 dermatological reaction is intolerable to the patient despite recommended treatment interventions, or if a Grade 3 reaction recurs after one drug interruption/re-challenge cycle. For any occurrence of Stevens Johnson syndrome (toxic epidermal necrolysis), study therapy must be immediately and permanent discontinued.

Holding rule

For NCI-CTCAE Grade 3 dermatological reactions, or a Grade 2 dermatological reaction which is not improved after 2 weeks with recommended management strategies, a brief (up to 14 days) therapy interruption is recommended; the daily dose of lapatinib should then be reinstated. In some cases, the skin event may improve without the need for interrupting therapy with lapatinib. In the lapatinib clinical program to date, many subjects were able to resume lapatinib therapy at the same dose after resolution of skin event; these subjects had less extensive and/or severe skin events.

Re-challenge

One re-challenge may be considered, if indicated in the opinion of the investigator, for subjects who present with NCI-CTCAE Grade 3 skin events which recover briskly to NCI-CTCAE Grade 1 (within 14 days) after holding lapatinib.

Subjects with poorly tolerated skin adverse events may be successfully managed by providing a brief (up to 14 days) therapy interruption; the daily dose of lapatinib should then be reinstated. However, the rash may improve without the need for interrupting therapy with lapatinib. Of note in current studies, many subjects were able to resume lapatinib therapy at the same dose after resolution of rash, and they then had less extensive and/or severe

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

General Summary of dose holding/interruptions

(graded according to NCI-CTCAE v3.0)

Adverse events	Action
Non-hematological, Grade 3 or 4	Apply maximum supportive care recommendations. Hold lapatinib therapy until recovery to Grade ≤ 1 (up to 14 days). Grade 3 or 4 left ventricular cardiac dysfunction - please refer to Appendix C. For NCI-CTCAE v3.0 Grade 3 or 4 interstitial pneumonitis or Grade 4 rash manifested as toxic epidermal necrolysis (e.g. Stevens-Johnson Syndrome etc) lapatinib must be permanently discontinued If recurrence of adverse event after drug hold / interruptions is observed, and maximum supportive care measures applied, a dose reduction must be considered
Non-hematological, Grade 3 or 4 and adverse events NOT resolved to Grade ≤ 2 within a maximum of 2 weeks from last planned administration	Evaluate risk benefits, Contact the PI for further guidance.
Cardiac* (asymptomatic drop in LVEF or symptomatic congestive heart failure)	Lapatinib therapy to be discontinued permanently in case of symptomatic NYHA class III and IV CHF. Lapatinib therapy to be hold continued or resumed according to appendix B, for patients with NYHA class I or II CHF.
Hematological adverse events: Absolute neutrophil count (ANC) <1.0 x 10^9/L Platelets <75 x 10^9/L Hemoglobin <9.0 g/dL (after transfusion if needed)	Hold chemotherapy if lapatinib given simultaneously; if the adverse event is related to chemotherapy please refer to appropriate label (until recovery to Grade ≤1). If ANC recovers to 1.5 x 10^9/L within 7days, then merely delaying dose is acceptable. If no recovery to ANC of 1.5 x 10^9/L within 7 days then decrease chemotherapy as indicated above. Dose modifications for thrombocytopenia, at the start of subsequent courses of therapy are the same as recommended for neutropenia above. Next cycle should not begin until the platelet count has recovered to 100 x 10^9/L or more.
	In case of multiple short interruptions of dose due to either adverse events or drug supply or other reasons the sum of days without lapatinib treatment should not exceed 21 days in any 90 day treatment period.

*Severity corresponding to NYHA criteria

Table 10

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit and grapefruit juice	may increase plasma level of lapatinib	may inhibit CYP 3A4 metabolism of lapatinib in the intestinal wall	avoid grapefruit and grapefruit juice

Table 11

Lapatinib is a weak base with low, pH dependent solubility that declines above pH 4.8 Clinical significance is unknown. It has been suggested that antacids which modify gastric pH may affect lapatinib absorption and should be avoided for 1 hour pre and post lapatinib doses.

Lapatinib is a substrate for CYP 3A4. Strong inducers and inhibitors (see appendix G) of this enzyme may alter lapatinib pharmacokinetics. Concurrent use with strong inducers or inhibitors should be avoided as clinical data for dose adjustment is lacking. Based on pharmacokinetic studies, however, it is suggested that if co-administered with a strong CYP 3A4 inhibitor, lapatinib dose reduction from 1250 mg/day to 500 mg/day could be considered, with a washout period of 1 week if the inhibitor is discontinued, or if co-administered with a strong CYP 3A4 inducer, gradual titration of lapatinib to 1250-4500 mg/day (based on tolerability), with gradual dose reduction over 2 weeks if the inducer is discontinued. Lapatinib is an inhibitor of CYP 3A4, therefore, it may decrease the metabolism or increase bioavailability of substrates of this enzyme. Concurrent therapy is discouraged. Dose reduction of the substrate drug should be considered. Lapatinib inhibits CYP 2C8 *in vitro* and may decrease the metabolism of substrates of this enzyme. Dose reduction of the substrate drug should be considered. Lapatinib is a substrate for the transport proteins P-glycoprotein and BCRP. Inhibitors or inducers of these proteins may alter the exposure or distribution of lapatinib and QT prolongation is expected to be increased in the presence of inhibitors of these proteins. Drugs that prolong QT/QTc interval should be avoided due to the risk of potentially fatal arrhythmias. *In vitro,* lapatinib is an inhibitor of the transport proteins P-glycoprotein, BCRP, and OATP1B1. Clinical relevance of this effect has not been established but elevated bilirubin may occur due to inhibition of hepatic uptake or reduced excretion into bile. Reduced metabolism of substrates of these proteins is considered likely, resulting in increased concentrations of the substrate drugs.

Prohibited Medications

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

Drug Class	Specific Agents	Wash-out[1]
CYP3A4 Inducers		
rifamycin antibiotics	rifampicin, rifabutin, rifapentine	2 weeks
anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)	
antiretrovirals	efavirenz, nevirapine, tipranivir, etravirine	
glucocortical steroids (oral only)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)[2]	
other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
antibiotics	clarithromycin, erythromycin, troleandomycin, flucloxacillin	1 week
antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
antiretrovirals	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir, atazanavir	
calcium channel blockers	verapamil, diltiazem	
antidepressants	nefazodone, fluvoxamine	
gastrointestinal agents[3]	cimetidine	
fruit juices	grapefruit, star fruit, and papaw	
other	amiodarone	6 months

Miscellaneous		
antacids	Mylanta, Maalox, Tums, Rennies	1 hour before and after dosing
herbal supplements[4]	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	2 weeks

Table 12

1. Time period between last dose of listed drug and first dose of lapatinib, required to avoid drug-drug interaction potential for toxicity (inhibitors) or loss of efficacy (inducers) that could make the patient unevaluable. Clinically appropriate substitution of drugs not on the list is recommended.
2. A standard 3-5 day course of dexamethasone at a dose following the institutions standard of care for the prevention and/or treatment of platinum-induced nausea and vomiting is allowed. Glucocortical steroid oral dose equivalents (in parentheses) to dexamethasone 1.5 mg (or less) given daily are allowed. Intravenous dosing should be considered if clinically appropriate.
3. Emetogenic chemotherapy may require 3-4 daily doses of aprepitant. CYP3A4 inhibition by oral (not IV) Oral aprepitant will be contraindicated in this trial.
4. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact a GSK Medical Monitor or Clinical Scientist.

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

Agent Accountability

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

REGULATORY AND REPORTING REQUIREMENTS

It is the responsibility of the investigator to document all adverse events which occur during the investigation. An adverse event is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product. *An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.* Anticipated day-to-day fluctuations of the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered an adverse event.

All adverse events occurring from the first dose of investigational product until five days after the last dose must be recorded **REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.** In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported. It is the responsibility of the IND holder to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32.

Assessment of Causality

Every effort should be made by the investigator to explain each adverse event and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: no (not related), or yes (reasonable possibility).

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The event having often been reported in literature for similar drugs as drug related (e.g. skin rashes, blood dyscrasia)
- The event being related by time to drug administration terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting Serious Adverse Events

Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined stopping criteria will be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT >3 × ULN **and** bilirubin[0] >2 × ULN (35% direct) ***or*** ALT>3xULN and INR>1.5, if INR measured	24 hours	Liver Event and Liver Imaging and/or Biopsy CRFs, if applicable	24 hours	Updated Liver Event CRF

Table 13

a. bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >2.0 × ULN, then the event should still be promptly reported as defined

Any serious adverse events which occur during the clinical study or within 5 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All related and unexpected adverse events, in addition to being reported to the local IRB by the investigator, must be reported by facsimile within 24 hours to GlaxoSmithKline as follows:

Oncology MDC Fax: (610) 917-6715

For medical emergencies contact:

Michael Arbushites: Office: (610) 917-4039

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

GlaxoSmithKline

1250 S. Collegeville Road, UP4420

Collegeville, PA 19426-0989

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to GSK within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of lapatinib and considered by the investigator to be related or possibly related to lapatinib must be reported to GSK if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Investigators should notify GlaxoSmithKline of the pregnancy within 14 days of notification.

Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within five days after the treatment period.

Whenever possible a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported to GlaxoSmithKline after delivery.

SUPPLY AND STORAGE:

Oral: GlaxoSmithKline Inc. supplies lapatinib ditosylate as 250 mg film-coated tablets. Store at room temperature.

DOSAGE GUIDELINES:
Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.
***Adults*:** *Oral:* 1250 mg PO once daily. Administer on an empty stomach (one hour before or one hour after meals). Do not take with food. The protocol will require 750 mg no dose reduction will be needed except for severe adverse events.
Dosage in myelosuppression: modify according to protocol by which patient is being treated; *Dosage in renal failure:* dosage adjustment likely not required; less than 2% eliminated by kidneys
Dosage in hepatic failure: moderate and severe impairment have been associated with increased systemic exposure; consider dose reduction to 750 mg PO once daily; treatment should be stopped if severe hepatotoxicity develops (See appendix E)
Recommended Dosing Procedure for Slurry Preparation of Lapatinib Kool-Aid Suspension
Prepare Lemonade or Tropical Punch Kool-Aid as directed on the package. Place 2 or 4 oz of Kool-Aid in a glass container, then add three lapatinib tablets to the container. 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 mixture for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and repeat the administration process. This completes the administration process (total of 4-6 oz of liquid is dispensed).
How Supplied: lapatinib is supplied as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. The tablets contain 410 mg of lapatinib Ditosylate Monohydrate, equivalent to 250 mg lapatinib free base per tablet. The tablets are packaged into HDPE bottles with child-resistant closures.
Excipients present in the tablet include: Microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat contains: Hydroxypropyl methylcellulose, titanium dioxide, triacetin/glycerol triacetate, and yellow iron oxide.
Storage: The intact bottles should be stored at controlled room temperature (15°C-30°C).
Stability: Shelf life surveillance studies of the intact bottle are on-going. Current data indicates lapatinib is stable for at least 2 years at controlled room temperature (15°C - 30°C).

9.4 Abraxane General Infortmation[44]

DRUG NAME: ABRAXANE
SYNONYM(S): Albumin-Bound Paclitaxel
COMMON TRADE NAME(S): ABRAXANE®
CLASSIFICATION: antimicrotubule agent
MECHANISM OF ACTION:
ABRAXANE ABRAXANE for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents. The active agent in ABRAXANE is paclitaxel. Abraxane is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intralumminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic

complex via these caveolae to the underlying tumor interstitium (Desai et al, 2004). A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane (Desai et al, 2004). ABRAXANE is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.

INDICATION

In the United States, ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

PRECLINICAL STUDIES WITH ABRAXANE

Preclinical studies comparing ABRAXANE to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for ABRAXANE compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, ABRAXANE treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for ABRAXANE versus solvent based paclitaxel, indicating more effective intratumoral accumulation of ABRAXANE (Desai et al, 2006).

CLINICAL STUDIES WITH ABRAXANE

Every-Three-Week (Q3W) Schedule in Metastatic Breast Cancer

In a phase I study, the maximum tolerated dose (MTD) of ABRAXANE was determined to be 300 mg/m^2 by 30 minute infusion Q3W, without premedication or G-CSF support (Ibrahim et al, 2002). No severe hypersensitivity reactions occurred with ABRAXANE despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2.

Two multicenter phase II studies have evaluated 2 dose levels of ABRAXANE (300 mg/m^2, n=63, and 175 mg/m^2, n=43) in patients with metastatic breast cancer (Ibrahim et al 2005 and Investigator's Brochure, respectively). The overall response rates in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m^2 dose, and 48% (95% CI 35-60%) for the 300 mg/m^2 dose. Of 39 patients receiving 300 mg/m^2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

A Phase III trial in patients with metastatic breast cancer compared ABRAXANE 260 mg/m^2 (n=229) to Taxol 175 mg/m^2 (n=225) given Q3W (Gradishar et al 2005). Efficacy analyses were based on the ITT population. The ORR was significantly greater for ABRAXANE than for Taxol for all patients (33% *v* 19%, respectively; $P = 0.001$), patients who received first-line therapy (42% *v* 27%, respectively; $P = 0.029$), patients who received second-line or greater therapy (27% *v* 13%, respectively; $P = 0.006$), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% *v* 18%, respectively; $P = 0.002$) or the metastatic setting only (27% *v* 14%, respectively; $P = 0.010$). Tumor response rate was also significantly higher for ABRAXANE than for Taxol in patients with visceral dominant lesions (34% *v* 19%, respectively; $P = 0.002$) and in patients aged younger than 65 years (34% *v* 19%, respectively; $P < 0.001$). ORR also was greater for ABRAXANE compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% *v* 19%, respectively) and in patients ≥ 65 years old (27% *v* 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

Median TTP was significantly longer with ABRAXANE than with Taxol for all patients (23.0 *v* 16.9 weeks, respectively; hazard ratio [HR] = 0.75; $P = 0.006$).

There was a trend for greater median survival for all patients treated with ABRAXANE than with Taxol (65.0 *v* 55.7 weeks, respectively; *P* = 0.374). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received ABRAXANE, compared to Taxol, as second-line or greater therapy (56.4 *v* 46.7 weeks, respectively; HR = 0.73; *P* = .024) [Gradishar et al, 2005].

The incidence of hypersensitivity reactions (any grade) was low for both arms (1% for ABRAXANE and 2% for Taxol). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the ABRAXANE group despite the absence of premedication. In contrast, grade 3 hypersensitivity reactions occurred in the Taxol group despite standard premedication (chest pain, two patients; allergic reaction, three patients). Per protocol, corticosteroids and antihistamines were not administered routinely to patients in the ABRAXANE group; however, premedication was administered for emesis, myalgia/arthralgia, or anorexia in 18 patients (8%) in the ABRAXANE group in 2% of the treatment cycles, whereas 224 patients (> 99%) in the Taxol group received premedication in 95% of the cycles.

Although the patients in the ABRAXANE group received an average paclitaxel dose-intensity 49% greater than that received by patients in the Taxol group, the incidence of treatment-related grade 4 neutropenia was significantly lower in the ABRAXANE group than in the Taxol group (9% *v* 22%, respectively; *P* < 0.001), with a higher mean neutrophil nadir (1.67 *v* 1.31x10^9/L, respectively; *P* = 0.046), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard (solvent-based) paclitaxel.

As expected with a higher dose of paclitaxel, treatment-related grade 3 sensory neuropathy occurred more frequently in the ABRAXANE arm than in the Taxol arm (10% *v* 2%, respectively; *P* < 0.001); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

The only clinical chemistry value that was notably different between the two treatment arms was higher serum glucose levels in the Taxol–treated patients, who also had a higher incidence of hyperglycemia reported as an AE compared with ABRAXANE–treated patients (7% *v* 1% respectively; *P* = 0.003).

Subgroup analyses revealed that the safety profiles of ABRAXANE (n=97) and Taxol (n=30) in patients who received the drugs as first-line therapy were similar to those in the overall study population. In subgroup analyses by age, the reported AEs were similar in patients less than 65 years old and patients ≥ 65 years old in both groups. Of the patients ≥ 65 years old, the incidences of the following AEs were notably lower in the ABRAXANE group (n=30) than in the Taxol group (n=32): neutropenia (23% *v* 59%, respectively), leukopenia (10% *v* 31%, respectively), nausea (20% *v* 38%, respectively), hyperglycemia (0% *v* 19%, respectively), and flushing (0% *v* 16%, respectively). These data indicate no additional safety concerns for ABRAXANE in patients ≥ 65 years old compared with younger patients.

Six patients (3%) in the ABRAXANE group and eight patients (4%) in the standard paclitaxel group died during the study, all as a result of disease progression. No treatment-related deaths occurred in the ABRAXANE group; one patient (< 1%) in the Taxol group died of multiorgan failure, which was considered by the investigator to be possibly related to treatment but may also have been a result of sepsis and/or progressive disease.

Weekly (QW) for 3 Weeks, Every 4 Weeks Schedule in Metastatic Breast Cancer

Thirty-nine patients were enrolled into A Phase I study of ABRAXANE administered QW for 3 weeks followed by a 1 week rest in patients with advanced solid tumors (Nyman et al, 2005). The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m^2 respectively. Dose limiting toxicities included grade 4 neutropenia and grade 3 sensory neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed.

In a Phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 14% of women treated with ABRAXANE 100 mg/m^2 QW schedule. ABRAXANE weekly regimen was well tolerated; 91% of 106 patients were treated at the full dose of 100 mg/m^2 of ABRAXANE without dose reductions. Based on the activity and low toxicity documented with this schedule, the study was expanded to

evaluate the efficacy and safety/tolerability of a higher dose of ABRAXANE 125 mg/m^2 weekly regimen in 75 additional patients. Results of this dose-finding study confirm the dose of ABRAXANE 100 mg/m^2 as the appropriate dose for further study in this patient population (Blum et al, 2007). [45]

In a open-label, randomized, multicenter phase II study comparing the antitumor response and toxicity of in two QW dosing regimens, ABRAXANE dosed Q3W, and Taxotere® (polysorbate solvent-based docetaxel Sanofi-Aventis] Q3W for the first-line treatment of metastatic breast cancer (Gradishar et al, EBCC 2008). Total of 300 patients were randomized to one of four treatment arms: (A) ABRAXANE 300 mg/m^2 IV Q3W, (n=76); (B) ABRAXANE 100 mg/m^2 (n=76); (C) ABRAXANE 150 mg/m^2 QW (n=74) QW every 28 days; or (D) Taxotere 100 mg/m^2 Q3W (n=74). The primary objective of the trial was to evaluate the antitumor activity and safety of three different ABRAXANE regimens to determine the optimal dose and frequency to be used. Secondary objectives included the comparisons of each treatment group with respect to efficacy and safety, specifically: ABRAXANE to Taxotere; ABRAXANE QW regimens to ABRAXANE Q3W regimen; and the two dose levels of QW ABRAXANE. Patients received ABRAXANE as a 30-minute IV infusion without premedication; Taxotere was administered as a 60-minute infusion with corticosteroid premedication. The primary efficacy endpoint was ORR assessed every 8 weeks in all treatment arms by using the RECIST* guidelines. The secondary efficacy endpoints included total response (ORR + SD ≥16 weeks) and PFS. Tumor response results underwent an evaluation by the investigators, as well as an Independent Radiology Review (IRR). If a pre-set level of congruence was observed between the tumor responses described by the investigators and the IRR, only the tumor response assessed by investigators was reported. Total of 75% of all patients were post-menopausal with a mean age of 53.9 years at randomization. Both ORRs and total response rates were higher in all ABRAXANE arms compared to the Taxotere arm. The investigator-reported ORRs were 46%, 63%, 74%, and 39%, for arms A, B, C, and D, respectively. This difference was statistically significant for both QW dosing arms of ABRAXANE compared with Taxotere, (P = 0.002 for arm B *v* D, and P <0.001 for arm *v* D). The corresponding investigator-reported total response rates were 72%, 83%, 91% and 69% for the four arms, respectively. This difference reached statistical significance for arms B and C compared to Taxotere (P = 0.009 for arm B *v* D, and p=0.005 for arm C *v*. D). No significant difference in ORR was noted between the two weekly dosing arms (arm B vs. C, P = 0.24). A significant increase in PFS was observed in the 150 mg/m^2 QW arm compared to the Taxotere arm (14.6 *v* 7.8 months, respectively, P = 0.012, hazard ratio 0.57). No significant difference in PFS was found between the ABRAXANE 300 mg/m^2 Q3W arm and Taxotere arm (A and D). Similarly, PFS was not significantly different between arms A and C, or arms B and D. Figure I depicts the Kaplan-Meier curves comparing PFS for the four treatment arms.

All three ABRAXANE arms demonstrated a favorable safety profile when compared with the Taxotere arm. Toxicity data occurring in >25% of patients is summarized in Table II. The most frequent hematologic adverse event was neutropenia, with significantly lower rates of Grade 3/4 neutropenia in all ABRAXANE arms (Grade 4, 5%, 5%, 9%, 75% for arms A, B, C, D, respectively). ABRAXANE also had lower rates of febrile neutropenia (1%, 1%, 1%, 8% for arms A, B, C, D, respectively) and fatigue (Grade 3, 5%, 0%, 3%, 19% for arms A, B, C, D, respectively) compared to Taxotere. While the incidence of sensory neuropathy was similar in the ABRAXANE and Taxotere arms, the median time to improvement in patients with Grade 3 neuropathy was shorter in all three ABRAXANE arms (22, 22, 19 and 37 days in arms A, B, C and D, respectively).The ABRAXANE arms demonstrated improved safety and increased efficacy compared with Taxotere. All three ABRAXANE regimens produced lower rates of neutropenia, febrile neutropenia, and fatigue than Taxotere.

Continuous Weekly (QW) Schedule in Neoadjuvant Breast Cancer

The NSABP studied the administration of ABRAXANE in a neoadjuvant setting to patients with locally advanced breast cancer at a dose of 100 mg/m2 QW for 12 weeks, with no break (Robidoux et al, 2010). Four cycles of FEC were administered sequentially based on patients' HER2 status: HER2 negative patients received FEC-100 (F: 500 mg/m2, E: 100 mg/m2, C: 500 mg/m2 Q3 weeks) and HER2 positive patients received weekly trastuzumab in addition to FEC-75 (F: 500 mg/m2, E: 75 mg/m2, C: 500 mg/m2 Q3 weeks). Weekly trastuzumab was permitted during ABRAXANE and FEC-75 treatment at the discretion of the investigator. The primary objective of the trial was to determine the pathologic complete response rate (pCR) in the breast. At the time of initial report at SABCS

2006, 65 patients had been entered on study and were evaluable for cCR and safety. Following 12 weeks of ABRAXANE, a clinical complete response rate (cCR) of 32% was noted. The therapy was well tolerated, with 48/65 patients receiving 12 doses in 12 weeks and 13/65 receiving 12 doses in 13-14 weeks. The incidence of peripheral (sensory) neuropathy was low (11% grade 2, 5% grade 3) as was neutropenia (3% grade 3 and no grade 4). The authors concluded that the administration of ABRAXANE 100 mg/m2 QW x 12 was both effective and tolerable.

At the time of this update, more than 20 abstracts and publications have been presented at major oncology conferences or published in medical journals related to ABRAXANE QW schedule in breast cancer, including completed and ongoing studies.

ABRAXANE Toxicities

Myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia, arthralgia, and myalgia. During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred.

Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Q3W Schedule

	Percent of Patients	
	ABRAXANE 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6

Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

Table 14

[a] Based on worst grade [b] ABRAXANE dose in mg/m^2/duration in minutes [c] paclitaxel injection dose in mg/m^2/duration in hours [d] paclitaxel injection pts received premedication [e] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing. [f] Severe events are defined as at least grade 3 toxicity [g] During study drug dosing.

STUDY MEDICATION ADMINISTRATION

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of ABRAXANE. In any event, filters of pore-size less than 15 micrometers must not be used.

ABRAXANE Premedication

Patients do not require premedication prior to ABRAXANE administration, as hypersensitivity reactions are rare. Although the solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their detergent-like nature and known ability to induce histamine release (Ten Tije et al, 2003), the administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. However, the hypersensitizing role of the taxane molecules themselves cannot be ruled out. In the unlikely event

of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel.

In the rare event of a severe hypersensitivity reaction, discontinue ABRAXANE.

Dose Modifications/Reductions

Administration of Study Drug to Patients with Abnormal Hematologic Function

ABRAXANE dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to ≥1.5 x 10^9 cells/L and the platelet count returns to >100 x 10^9 cells/L. For patients receiving weekly ABRAXANE, for each subsequent dose of ABRAXANE within a cycle (Days 8 and 15), patients must have an ANC ≥ 1.0 x 10^9 cells/L and platelets > 75 x 10^9 cells/L. If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose will be omitted and the total cycle length remains the same.

Administration of Study Drug to Patients with Abnormal Hepatic Function

Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

Dose Modification Table

Use this table as a guideline to determine any necessary dose modifications. The modification is dependant on the starting dose for the study. The below modifications are aligned with the most recent data presented at the SABCS.

Dose Modification

Table 15

Dose Level	ABRAXANE (mg/m²)
1	100
-1	80
-2	60

Dose Reductions and guidelines for optional use of Growth Factors for Hematologic Toxicity. The table below provides a guideline for implementing dose reductions and optional use of growth factor treatment for hematologic toxicity:

Use of G-CSF and Dose reductions for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken
ANC < 500 cells/mm³ (nadir count) with neutropenic fever > 38° OR Delay of next cycle due to persistent neutropenia (ANC < 1000 cells/mm³) OR Neutropenia < 500 cells/mm³ for > 1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), the same dose is maintained and G-CSF is given as outlined below. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1500 cells/mm³. If G-CSF will be given if needed concurrently with weekly ABRAXANE; its administration may begin the day after ABRAXANE is given and should stop at least 48 hours prior to when ABRAXANE is given the following week.
Thrombocytopenia Grade 3 or Grade 4*	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

Table 16

*See NCI Toxicity Criteria Scale for definition of Grade 3 and Grade 4 events.

G-CSF Administration. For QW study drug administration administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care) 24 hours after chemotherapy and hold 48 hours prior to the next dose

Pegfilgrastim (Neulasta®) is not allowed.

Sensory Neuropathy

ABRAXANE should be withheld in patients who experience ≥ Grade 3 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Table 14) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event

reporting. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2; see Table 14) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. Note: the investigator may elect to dose modify for Grade 2 sensory neuropathy.

Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reactions to ABRAXANE should not be re-challenged. It is not recommended to administer ABRAXANE to patients with prior hypersensitivity to a taxane.

Other Toxicities

If toxicities are ≥ grade 3, except for anemia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 2).

Concomitant Medications

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates is allowed. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

Packaging, Labeling, and Storage of Study Drug

Availability ABRAXANE will be supplied by Celgene Corporation. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

Storage and Stability

Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.

Stability: Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 8 hours.

Study Medication Administration

ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter is not recommended.

Reconstitution and use of ABRAXANE

Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10% by using the formula provided in the study manual.

Calculate the total dose (in mg) to be administered by:

Total Dose (mg) = BSA x (study dose mg/m2)

Calculate the total number of vials required by:

$$\textbf{Total Number of Vials} = \frac{\textbf{Total Dose (mg)}}{\textbf{100 (mg/vial)}}$$

Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted). Using sterile technique, prepare the vials for reconstitution. Swab the rubber stoppers with alcohol. Aseptically, reconstitute each ABRAXANE vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP. **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.

DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.

Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.

Gently swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. Each ml of reconstituted product will contain 5 mg of paclitaxel. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:

Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)

The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Once the exact volume of reconstituted ABRAXANE has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted ABRAXANE suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Administer the calculated dosing volume of reconstituted ABRAXANE suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

Drug Distribution and Destruction

Supplier

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Industry Contact:

TBN
Manager, Medical Operations
Celgene Corporation
400 Connell Drive, 7th Floor
Connell Corporate Park
Berkeley Heights, NJ 07922
Mobile: 908-723-6919
Fax: 908-673-2779
Email: Mkennedy@celgene.com

Drug Distribution

ABRAXANE® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.

For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

9.5 Paclitaxel General Infortmation[46]

DRUG NAME: Paclitaxel

SYNONYM(S): benzenepropanoic acid

COMMON TRADE NAME(S): TAXOL®, ONXOL®

CLASSIFICATION: antimicrotubule agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Paclitaxel is a taxane. Paclitaxel binds to tubulin, the protein component of microtubules, simultaneously promoting their assembly and disassembly to form stable, nonfunctional microtubules. Although some reports indicate a cross-reactivity rate of 90% between docetaxel and paclitaxel, others suggest it does not occur consistently. Stabilization of microtubules blocks cells in the M phase of the cell cycle, inhibiting cell division and causing cell death. Paclitaxel acts as a radiosensitizing agent by blocking cells in the G_2phase. Paclitaxel is an immunosuppressant.

PHARMACOKINETICS:

Distribution	biphasic: initial distribution to peripheral compartment, then slow efflux from the peripheral compartment; widely distributed into body fluids and tissues[1,7]; small changes in dose may lead to large changes in peak plasma concentrations and total drug exposure due to saturable, nonlinear pharmacokinetics	
	cross blood brain barrier?	no
	volume of distribution	67 L/m² for 1-6 h infusion; varies with dose and infusion time; 198-688 L/m² for 24 h infusion
	plasma protein binding	88-98%
Metabolism	extensively metabolized in liver via CYP 2C8 (primarily) and CYP 3A4; activity of metabolites is unknown	
	metabolite(s)	67% as 6α-hydroxypaclitaxel via CYP 2C8; 37% as 3-p-hydroxypaclitaxel and 6α,3-p-dihydroxypaclitaxel via CYP 3A4
Excretion	primarily via bile	
	urine	14% (1-13% as unchanged drug)
	feces	71% (5% as unchanged drug)
	terminal half life	10 h; varies with dose and infusion time
	clearance	12 L/h/m²; varies with dose and infusion time

Children	clearance: 19 to 260 L/m²	Table 17

USES: ***Primary uses:***

*Breast cancer, Lung cancer, small cell, *Lung cancer, non-small cell, Esophageal cancer , *Ovarian cancer Bladder cancer, *Kaposi's sarcoma, Head and Neck cancer, Cervical cancer, Endometrial cancer.

SPECIAL PRECAUTIONS:

Preexisting liver impairment may impair elimination of paclitaxel , dose reduction is suggested; see **Dosage Guidelines**.

Special populations: Elderly patients may have more myelosuppression, neuropathy and cardiovascular toxicities

Patients with ***AIDS-related Kaposi's sarcoma*** may have more hematologic toxicities, infections and febrile neutropenia.

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Paclitaxel is clastogenic in human lymphocytes *in vitro* but not in other mammalian *in vivo* chromosome tests.

Fertility: In animal studies, reduced fertility has been observed, with decreased pregnancy rates and increased embryo loss in females and testicular atrophy/degeneration in males.

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Paclitaxel has shown to be embryotoxic and fetotoxic in animal studies; soft tissue and skeletal malformations have been reported.

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials.

ORGAN SITE	SIDE EFFECT
blood and lymphatic system/ febrile neutropenia	***anemia*** (62-78%, severe 6-16%)
	febrile neutropenia (2%)
	leukopenia (86-90%, severe 4-17%)
	neutropenia (87-90%, severe 27-52%) nadir 10-12 days, recovery 15-21 days; may require dose reduction
	thrombocytopenia (6-20%, severe 1-7%); nadir 8-9 days
cardiac	bradycardia (3-4%); first 3 h of infusion;
	cardiovascular events (severe 1-2%);
ear and labyrinth	hearing loss, tinnitus, vertigo, ototoxicity (<1%)
eye	optic nerve and/or visual disturbances, photopsia, visual floaters (<1%); generally reversible, may be dose-related

gastrointestinal	*emetogenic potential: low-moderate* abdominal pain; with intraperitoneal administration anorexia (25%) constipation (18%) ***intestinal obstruction*** (4%) mucositis (20-31%); more common with 24 h infusion ***nausea and vomiting*** (44-52%) taste changes
general disorders and administration site conditions	*extravasation hazard: irritant*
	edema (17-21%, severe 1%); localized under skin at no specific site
	fever (12%)
	injection site reactions (4-13%)
immune system	***hypersensitivity reactions*** (5-42%, severe 1-2%)
infections and infestations	infections (18-30%, severe 1%); primarily urinary tract and upper respiratory tract
injury, poisoning, and procedural complications	radiation recall dermatitis
investigations	***ECG abnormalities*** (8-14%, severe <1%); alkaline phosphatase, elevated (18-22%, severe 1%) AST, elevated (18-19%, severe 1%) bilirubin, elevated (4-7%, severe 1%)
musculoskeletal and connective tissue	***arthralgia/myalgia*** (54-60%, severe 8-12%);
nervous system	autonomic neuropathy, resulting in paralytic ileus and orthostatic hypotension (<1%) motor neuropathy, with resultant minor distal weakness (<1%) ***peripheral neuropathy*** (52-64% severe 2-4%)
respiratory, thoracic and mediastinal	dyspnea (2%) radiation recall pneumonitis
skin and subcutaneous tissue	***alopecia*** (87-93%); usually complete, generally occurs 14-21 days after administration of paclitaxel; onset sudden, often occurring in a single day // nail discoloration (2%) //r ash (12-14%)
vascular	hypotension (11-24%); during first 3 h of infusion phlebitis

Table 18

Hypersensitivity reactions typically occur within the first 10 minutes of the first two cycles. Reactions are caused by either a histamine release in response to polyoxyl 35 castor oil (Cremophor® EL), or a non-IgE mediated reaction to the taxane moiety. Frequent, minor hypersensitivity reactions include: flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%), and hypertension (1%). Chills, abdominal pain, and back pain are more rare. Severe hypersensitivity reactions include: dyspnea requiring bronchodilators, hypotension requiring treatment, flushing, chest pain, tachycardia, angioedema, and generalized urticaria. Severe reactions rarely occur after the third cycle of treatment. The incidence and severity of hypersensitivity reactions are reduced with premedication although rare, fatal reactions may occur despite premedication. A single IV dexamethasone dose with an antihistamine and an H_2-antagonist reduces the incidence of hypersensitivity reactions from 40% to 2-3%.

The frequency and severity of hypersensitivity reactions are not affected by the dose or duration of infusion of paclitaxel. For management of hypersensitivity reactions.

Rechallenge after a severe hypersensitivity reaction:

The occurrence of hypersensitivity reactions does not preclude rechallenge with paclitaxel. In the event of a hypersensitivity reaction, the patient may be rechallenged the same day after additional premedication, slowing the rate of infusion, and close monitoring. Subsequent cycles may benefit from a regimen of oral dexamethasone given 12 and 6 hours before paclitaxel, plus antihistamines and H_2-antagonists given 30 minutes to 1 hour before paclitaxel. Consider substituting paclitaxel with docetaxel or implementing a desensitization protocol if a patient develops a reaction following a rechallenge. For management of

Arthralgia/myalgia may be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of paclitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after paclitaxel administration, and resolving within days. If arthralgia/myalgia is not relieved by adequate doses of ibuprofen, or short-term, low-dose dexamethasone or prednisone, gabapentin may be tried. Dose reducing paclitaxel may lessen the severity of arthralgias/myalgias; however, there is no data on efficacy of reduced doses in a curative setting. Dose reduction should be considered only if symptom severity precludes continuing paclitaxel.

Peripheral sensory neuropathy presents with numbness and tingling in a stocking-and-glove distribution, perioral numbness, and hyperesthesia. Onset of symptoms can be within days following infusion. Frequency of symptoms increases with repeated exposure and cumulative dose. Pre-existing neuropathies from prior therapies are not a contraindication for treatment with paclitaxel; however, the incidence of neuropathy appears to be increased in this patient population. A dose reduction of 20% is recommended for all subsequent cycles of paclitaxel for patients who experience severe peripheral neuropathy. Sensory neuropathy usually improves or resolves within months of paclitaxel discontinuation.

Cardiovascular effects present as bradycardia, hypotension and ECG changes. Bradycardia and hypotension typically occur during the first 3 hours of infusion; however, they are usually asymptomatic and do not require treatment. Paclitaxel administration may require interruption or discontinuation in some cases. Frequency of hypotension and bradycardia is not influenced by dose, schedule or prior anthracycline therapy. Common ECG changes are non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia, and premature beats. Among patients with normal ECG at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities. Severe cardiovascular effects are rarely reported, including cases of atrial fibrillation, supraventricular tachycardia, myocardial infarction, congestive heart failure, and thromboembolic events. When reported, these patients had underlying disease or previous radiotherapy or chemotherapy which was thought to have contributed to the event.

INTERACTIONS: AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin	may increase neutropenia when paclitaxel is given *after* cisplatin	paclitaxel clearance is decreased by 25-33% when given *after* cisplatin	preferred method is to give paclitaxel first when administering as sequential infusions
dexamethasone		does not affect protein binding of paclitaxel	
diphenhydramine		does not affect protein binding of paclitaxel	
disulfiram	development of acute alcohol intolerance reactions	inhibition of aldehyde dehydrogenase by disulfiram, leading to development of toxic metabolites of ethanol (found in the solution)	avoid disulfiram concurrently with paclitaxel administration
doxorubicin	may increase cardiac toxicity from	doxorubicin clearance is decreased leading to increased plasma levels of doxorubicin and	monitor for increased cardiotoxicity

	doxorubicin when given concurrently with paclitaxel	doxorubicinol	
metronidazole and derivatives	development of acute alcohol intolerance reactions; the risk for most patients appears slight	inhibition of aldehyde dehydrogenase by metronidazole, leading to development of toxic metabolites of ethanol (found in solution)	avoid metronidazole and its derivatives concurrently with paclitaxel administration
vaccines, live	enhanced viral replication may increase the risk of disseminated disease	decreased immune response allows live vaccine to produce infection	avoid live vaccines during treatment
warfarin	may increase anticoagulant effect of warfarin when given concurrently with paclitaxel	paclitaxel may displace warfarin from plasma protein binding sites when given concurrently	monitor INR and adjust warfarin dosing accordingly; consider use of LMWH with chemotherapy

Table 19

Paclitaxel is a substrate of CYP 3A4 and CYP 2C8 isoenzymes. Strong inhibitors of CYP 3A4 or 2C8 may decrease paclitaxel metabolism resulting in increased plasma levels and toxicity. Avoid concurrent use if possible; if unavoidable, consider reducing the paclitaxel dose. Strong inducers of CYP 3A4 or 2C8 may increase paclitaxel metabolism, potentially resulting in a reduced therapeutic effect of paclitaxel.

SUPPLY AND STORAGE:

Paclitaxel (TAXOL) will be considered standard of care and will be provided by the insurance company for those patients randomized for the control arm. Biolyse Pharma produce paclitaxel as 30 mg and 100 mg single dose vials and a 300 mg multi-dose vial in a concentration of 6 mg/mL. Refrigerate. Do not freeze. Potency is not affected when transported or stored for up to 2 months at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 49.7%(v/v) alcohol.

***Adults*:**

3 weeks 80 mg/m^2 IV for one dose on days 1, 8 and 15 (total dose per cycle 240 mg/m^2), for atotal of 12 weeks

Concurrent radiation: has been given

Dosage in dialysis:

No dosage adjustment required for creatinine clearance less than 50 mL/min *Dosage in myelosuppression:*

Dosage in hepatic failure	Suggested guidelines for first course; subsequent courses should be based on individual tolerance			
	ALT or AST	**bilirubin**		**dose**
	<10 X ULN	and	≤1.25 X ULN	175 mg/m²
	<10 X ULN	and	1.26-2 X ULN	135 mg/m²
	<10 X ULN	and	2.01-5 X ULN	90 mg/m²
	≥10 X ULN	or	>5 X ULN	not recommended

modify according to protocol by which the patient is being treated. Table 20

Dosage in renal failure hemodialysis: no significant removal; may give standard dose before or after hemodialysis *chronic ambulatory peritoneal dialysis*(CAPD): no significant removal; may give standard dose before or after CAPD

Bristol-Myers Squibb supplies paclitaxel as 30 mg, 100 mg and 300 mg vials in a concentration of 6 mg/mL. Store at room temperature. Product may precipitate if refrigerated; precipitate redissolves at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 49.7%(v/v) ethanol.

Healthcare supplies paclitaxel as 30 mg, 100 mg, 150 mg, and 300 mg multi-use vials in a concentration of 6

mg/mL. Store at room temperature. Protect from light. If refrigerated, product may precipitate; precipitate redissolves at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 46.5%(v/v) alcohol.

SOLUTION PREPARATION AND COMPATIBILITY:

Additional information:

Concentrated solution must be diluted prior to IV infusion. To prevent extraction of plasticizer DEHP from container, prepare solutions in non-PVC (or non-DEHP) containers and administer using non-PVC administration sets.

PARENTERAL ADMINISTRATION:

Intermittent infusion over 1-3 h

Continuous infusion has been given

Intraperitoneal infuse into abdominal cavity as rapidly as possible by gravity

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

10. Prohibited concomitant therapy

Anti-neoplastic therapies

Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than the protocol treatment is not permitted until disease progression is documented per RECIST1.1.

11. Visit schedule and assessments

11.1 Study flow and visit schedule

Table 21 Visit evaluation schedule Arm 1

Clinical trial T-DM1-L-Nab SOE

Period				Cycle 1			Cycle 2			Cycle 3			Cycle 4			EOT
				Week			Week			Week			Week			
Screening [a]		Base-line [b]	Biological Window [c]	1	2	3	1	2	3	1	2	3	1	2	3	
Informed Consent	X															
Inclusion/ Exclusion	X															
Demographics	X															
Medical History	X															
Physical Exam [d]	X	X	X	X			X			X			X			X
Height	X															
Weight	X	X	X	X			X			X			X			X
ECOG Performance Status	X	X	X	X			X			X			X			X
Vital Signs [e]	X	X	X	X			X			X			X			X
12-Lead ECG and MUGA or Echocardiogram [f]	X							X								X
Concomitant Therapies	**Continuous from Screening period**															
Hematology [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy (β-hCG) [i]	X	X														
Tumor Assessments (Mammogram & Ultrasound) [j]	X															X
Bilateral MRI [j]		X	X													X
Biopsy [k]	X		X													X
Tumor Tissue [l]	X		X													X
Adverse Events and Serious Adverse Events			**From signing of informed consent up to and including 30 days after the last dose of treatment [n]**													
Trastuzumab Emtansine Administration [m]			X	X			X			X			X			
lapatinib Administration [m]			**Daily continuous from the Biological Window through cycle 4**													
Abraxane Administration [m]				X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ANC = absolute neutrophil count; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG= Performance Status Scale; h = hour(s); min = minute(s); WBC = white blood cell. Each treatment cycle is 28 days in length. Tests and procedures should be done on schedule, but visit windows of ± 2 days are allowed (except as otherwise specified) occasionally for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled assessment within this time frame, the patient may continue in the study only with written permission of the medical monitor. Additional schedules that specify study days on which these assessments are to be performed will be provided in the study manual as needed.

a. Within 28 days prior to the Cycle 1, Day 1 dose of Trastuzumab Emtansine

b. Within 3 days prior to the Cycle 1, Day 1 dose of Trastuzumab Emtansine . Only screening procedures not performed within 3 days of dosing are required at baseline. Treatment cycles are to be repeated every 28 days.

c. The Biological window (BW) will be covered by targeted therapy only (Trastuzumab Emtansine 3.6 mg/kg IV every three weeks plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks)

d. The baseline symptom- directed medical history and physical examination are not required if the screening medical history and physical examination were conducted within 3 days prior to the Cycle 1, Day 1.

e. Vital signs (blood pressure, heart rate, and oral temperature) measurements will be obtained during screening and baseline and before every infusion.

f A 12-lead ECG will be performed during screening/before start treatment, at week 12 and EOT. In all patients enrolled in the study, MUGA or echocardiogram to be performed at screening and week 12 or when clinically indicated. MUGA or echo also required for all patients with history of cardiac dysfunction. Same method (ECHO or MUGA) must be used throughout the duration of the study.

g. A blood sample for complete blood count (CBC) with platelet count and differential white blood cell (WBC) count will be obtained during screening/baseline, and on day one, eight, and fifteen (1,8,15) of every chemo dose [±1 day], and before each Trastuzumab Emtansine infusion during the biological window. EOT and if clinically indicated.

If a patient is found to have an absolute neutrophil count (ANC) <500/mm^3 or a platelet count < 25,000/mm^3, or both, the CBC with differential should be repeated at least every other day until the ANC and platelet count have exceeded these values on at least 2 occasions.

h. A blood sample for the clinical chemistry panel (sodium, potassium, carbon dioxide, chloride, magnesium, blood urea nitrogen [BUN], creatinine, total bilirubin, uric acid, LDH, alkaline phosphatase, aspartate transaminase [AST/SGOT], alanine transaminase [ALT/SGPT]) will be obtained at screening/ baseline, and on day one, eight, and fifteen (1,8,15) of every chemo dose [±1 day], and before each Trastuzumab Emtansine infusion during the biological window. EOT and if clinically indicated. Glucose and albumin are to be obtained at baseline only.

i. For women of childbearing potential, the results of a serum β-hCG pregnancy test must be negative within 7 days before the first dose of treatment is administered. If the screening serum β-hCG pregnancy test is performed more than 7 days before dosing, it must be repeated at baseline, with results known to be negative prior to first dose of study drug. To be repeated as clinically indicated.

j. Mammography and Ultrasound at baseline and before surgery, chest X-ray at baseline only or when clinically indicated, CT scans, abdomen at discretion of the treatment physician, or as a clinically indicated. Bilateral breast MRI at baseline, after the biological window before the first cycle of chemotherapy and before surgery.

k. Main tumor site biopsy will be completed during screening (within 56 days of Cycle 1, Day 1 is acceptable) In patients with accessible tumor, biopsies will be conducted at baseline, and before the second infusion of Trastuzumab Emtansine, and if the patient progresses while in treatment a new biopsy will be taken before the patient start the new treatment.

l.. Banked tumor tissue obtained as part of the patient's standard care and additional biopsies, will be evaluated for HER2 expression levels, PTEN, PI3K and possibly other candidate markers related to the drug's mechanism of action, tumor biology or the improvement of diagnostic assays.

m. Trastuzumab Emtansine 3.6 mg/kg IV every three weeks plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks, after this biological window patients will continue the same targeted therapy plus Abraxane 100 mg/m^2 IV weekly for twelve (12) weeks.

n. Serious adverse events (SAEs) will be captured from the time of informed consent through 30 days from the last dose of treatment. SAEs occurring beyond 30 days from last dose that are attributed to study treatment or any study patient death should be reported also.

*. Patients will be treated until completion of 4 cycles then a local therapy (surgery). Following surgery, patients will complete one year of anti-HER2 therapy with trastuzumab. Hormone positive patients will continue hormonal therapy. Chemotherapy and radiation will be given at the discretion of the treating physician.

Table 22 Visit evaluation schedule Arm 2

Clinical trial T-L-P SOE

Period				Cycle 1			Cycle 2			Cycle 3			Cycle 4			EOT
				Week			Week			Week			Week			
Screening [a]		Base-line [b]	Biological Window [c]	1	2	3	1	2	3	1	2	3	1	2	3	
Informed Consent	X															
Inclusion/ Exclusion	X															
Demographics	X															
Medical History	X															
Physical Exam [d]	X	X	X	X			X			X			X			X
Height	X															
Weight	X	X	X	X			X			X			X			X
ECOG Performance Status	X	X	X	X			X			X			X			X
Vital Signs [e]	X	X	X	X			X			X			X			X
12-Lead ECG and MUGA or Echocardiogram [f]	X							X								X
Concomitant Therapies	**Continuous from Screening period**															
Hematology [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy (β-hCG) [i]	X	X														
Tumor Assessments (Mammogram & Ultrasound) [i]	X															X
Bilateral MRI [j]		X	X													X
Biopsy [k]	X		X													X
Tumor Tissue [l]	X		X													X
Adverse Events and Serious Adverse Events			**From signing of informed consent up to and including 30 days after the last dose of treatment [n]**													
Trastuzumab Administration [m]			X	X	X	X	X	X	X	X	X	X	X	X	X	
lapatinib Administration [m]			**Daily continuous from the Biological Window through cycle 4**													
Paclitaxel Administration [m]				X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ANC = absolute neutrophil count; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECOG= Performance Status Scale; h = hour(s); min = minute(s); WBC = white blood cell. Each treatment cycle is 28 days in length. Tests and procedures should be done on schedule, but visit windows of ± 2 days are allowed (except as otherwise specified) occasionally for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled assessment within this time frame, the patient may continue in the study only with written permission of the medical monitor. Additional schedules that specify study days on which these assessments are to be performed will be provided in the study manual as needed.

a. Within 28 days prior to the Cycle 1, Day 1 dose of Trastuzumab

b. Within 3 days prior to the Cycle 1, Day 1 dose of Trastuzumab . Only screening procedures not performed within 3 days of dosing are required at baseline. Treatment cycles are to be repeated every 28 days.

c. The Biological window (BW) will be covered by targeted therapy only (Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks)

d. The baseline symptom- directed medical history and physical examination are not required if the screening medical history and physical examination were conducted within 3 days prior to the Cycle 1, Day 1.

e. Vital signs (blood pressure, heart rate, and oral temperature) measurements will be obtained during screening and baseline and before every infusion.

f. A 12-lead ECG will be performed during screening/before start treatment, at week 12 and EOT. In all patients enrolled in the study, MUGA or echocardiogram to be performed at screening and week 12 or when clinically indicated. MUGA or echo also required for all patients with history of cardiac dysfunction. Same method (ECHO or MUGA) must be used throughout the duration of the study.

g. A blood sample for complete blood count (CBC) with platelet count and differential white blood cell (WBC) count will be obtained during screening/baseline, and on day one, eight, and fifteen (1, 8, 15) of every chemo dose [±1 day], and every three weeks during the biological window, EOT and if clinically indicated. If a patient is found to have an absolute neutrophil count (ANC) <500/mm^3 or a platelet count < 25,000/mm^3, or both, the CBC with differential should be repeated at least every other day until the ANC and platelet count have exceeded these values on at least 2 occasions.

h. A blood sample for the clinical chemistry panel (sodium, potassium, carbon dioxide, chloride, magnesium, blood urea nitrogen [BUN], creatinine, total bilirubin, uric acid, LDH, alkaline phosphatase, aspartate transaminase [AST/SGOT], alanine transaminase [ALT/SGPT]) will be obtained at screening/ baseline, and on day one, eight, and fifteen (1, 8, 15) of every chemo dose [±1 day], and every three weeks during the biological window. EOT and if clinically indicated. Glucose and albumin are to be obtained at baseline only.

i. For women of childbearing potential, the results of a serum β-hCG pregnancy test must be negative within 7 days before the first dose of treatment is administered. If the screening serum β-hCG pregnancy test is performed more than 7 days before dosing, it must be repeated at baseline, with results known to be negative prior to first dose of study drug. To be repeated as clinically indicated.

j. Mammography and Ultrasound at baseline and before surgery, chest X-ray at baseline only or when clinically indicated, CT scans, abdomen at discretion of the treatment physician, or as a clinically indicated. Bilateral breast MRI at baseline, after the biological window before the first cycle of chemotherapy and before surgery.

k. Main tumor site biopsy will be completed during screening (within 56 days of Cycle 1, Day 1 is acceptable) In patients with accessible tumor, biopsies will be conducted at baseline, and before the third infusion of Trastuzumab, and if the patient progresses while in treatment a new biopsy will be taken before the patient start the new treatment.

l.. Banked tumor tissue obtained as part of the patient's standard care and additional biopsies, will be evaluated for HER2 expression levels, PTEN, PI3K and possibly other candidate markers related to the drug's mechanism of action, tumor biology or the improvement of diagnostic assays.

m. Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly plus Lapatinib 750 mg/daily for a total of 6 weeks, after this biological window, patients will continue on the same targeted therapy plus weekly paclitaxel 80 mg/m^2 for a further 12 weeks, up to definitive surgery.

n. Serious adverse events (SAEs) will be captured from the time of informed consent through 30 days from the last dose of treatment. SAEs occurring beyond 30 days from last dose that are attributed to study treatment or any study patient death should be reported also.

*. Patients will be treated until completion of 4 cycles then a local therapy (surgery). Following surgery, patients will complete one year of anti-HER2 therapy with trastuzumab. Hormone positive patients will continue hormonal therapy. Chemotherapy and radiation will be given at the discretion of the treating physician.

12. Assessment types

Tests and procedures should be done on schedule, but visit windows of ± 2 days are allowed (except as otherwise specified) occasionally for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled assessment within this time frame, the patient may continue in the study only with written permission of the medical monitor. Additional schedules that specify study days on which these assessments are to be performed will be provided in the study manual as needed.

Screening: Within 28 days prior to the Cycle 1, Day 1 dose of Trastuzumab or Trastuzumab Emtansine

Base line: Within 3 days prior to the Cycle 1, Day 1 dose of Trastuzumab or Trastuzumab Emtansine. Only screening procedures not performed within 3 days of dosing are required at baseline. Treatment cycles are to be repeated every 28 days.

The Biological window (BW) will be covered by targeted therapy only (Trastuzumab Emtansine 3.6 mg/kg IV every three weeks plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks) (in Arm 1 only).

The Biological window (BW) will be covered by targeted therapy only (Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks)(in Arm 2 only)

The baseline symptom- directed medical history and physical examination are not required if the screening medical history and physical examination were conducted within 3 days prior to the Cycle 1, Day 1.

Vital signs (blood pressure, heart rate, and oral temperature) measurements will be obtained during screening and baseline and before every infusion.

A 12-lead ECG will be performed during screening/before start treatment, at week 12 and EOT. In all patients enrolled in the study, MUGA or echocardiogram to be performed at screening and week 12 or when clinically indicated. MUGA or echo also required for all patients with history of cardiac dysfunction. Same method (ECHO or MUGA) must be used throughout the duration of the study.

A blood sample for complete blood count (CBC) with platelet count and differential white blood cell (WBC) count will be obtained during screening/baseline, and on day one, eight, and fifteen (1, 8, 15) of every chemo dose [±1 day], and every three weeks during the biological window, EOT and if clinically indicated. If a patient is found to have an absolute neutrophil count (ANC) <500/mm^3 or a platelet count < 25,000/mm^3, or both, the CBC with differential should be repeated at least every other day until the ANC and platelet count have exceeded these values on at least 2 occasions.

A blood sample for the clinical chemistry panel (sodium, potassium, carbon dioxide, chloride, magnesium, blood urea nitrogen [BUN], creatinine, total bilirubin, uric acid, LDH, alkaline phosphatase, aspartate transaminase [AST/SGOT], alanine transaminase [ALT/SGPT]) will be obtained at screening/baseline, and on day one, eight, and fifteen (1, 8, 15) of every chemo dose [±1 day], and every three weeks during the biological window. EOT and if clinically indicated. Glucose and albumin are to be obtained at baseline only.

For women of childbearing potential, the results of a serum β-hCG pregnancy test must be negative within 7 days before the first dose of treatment is administered. If the screening serum β-hCG pregnancy test is performed more than 7 days before dosing, it must be repeated at baseline, with results known to be negative prior to first dose of study drug. To be repeated as clinically indicated.

Mammography and Ultrasound at baseline and before surgery, chest X-ray at baseline only or when clinically indicated, CT scans, abdomen at discretion of the treatment physician, or as a clinically indicated. Bilateral breast MRI at baseline, after the biological window before the first cycle of chemotherapy and at the end of the study before surgery. Main tumor site biopsy will be completed during screening (within 56 days of Cycle 1, Day 1 is acceptable) In patients with accessible tumor, biopsies will be conducted at baseline, and before the third infusion of Trastuzumab, and if the patient progresses while in treatment a new biopsy will be taken before the patient start the new treatment.

Banked tumor tissue obtained as part of the patient's standard care and additional biopsies, will be evaluated for HER2 expression levels, PTEN, PI3K and possibly other candidate markers related to the drug's mechanism of action, tumor biology or the improvement of diagnostic assays.

Arm 1; Trastuzumab Emtansine 3.6 mg/kg IV every three weeks plus Lapatinib 750 mg/daily p.o for a total of six (6) weeks, after this biological window patients will continue the same targeted therapy plus weekly Abraxane 100 mg/m^2 for a further 12 weeks, up to definitive surgery.

Arm 2: Trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly plus Lapatinib 750 mg/daily for a total of 6 weeks, after this biological window, patients will continue on the same targeted therapy plus weekly paclitaxel 80 mg/m^2 for a further 12 weeks, up to definitive surgery.

Serious adverse events (SAEs) will be captured from the time of informed consent through 30 days from the last dose of treatment. SAEs occurring beyond 30 days from last dose that are attributed to study treatment or any study patient death should be reported also.

*. Patients will be treated until completion of 4 cycles with the chemo agent then a local therapy (surgery). Following surgery, patients will complete one year of anti-HER2 therapy with trastuzumab. Hormone positive patients will continue hormonal therapy. Chemotherapy and radiation will be given at the discretion of the treating physician.

Clinical evaluation will include a record of the date and site(s) of recurrence, subsequent breast cancer treatment administered, and late treatment-related toxicity.

The duration of patient participation in the study will be a total of six(6) to seven (7) months from the start of treatment. Follow-up for all patients will include: ·Medical history update (30 days after the last dose of the study drug) Evaluate subjects who discontinue the protocol for reasons other than disease progression (AEs) every 4 weeks until progression or until they receive additional anti-cancer therapy.

12.1 CRITERIA FOR RESPONSE

The main endpoint in this study is to determine the pathologic complete response rate (pCR) in the breast, when TDM-1 is given in combination with Lapatinib and Abraxane in patients with Her 2 Neu over-expressed Breast carcinoma and who are candidates for pre-operative chemotherapy.

12.2 RECIST Criteria

The clinical tumor response will be assessed using RECIST criteria at baseline and before surgery.

RECIST criteria offer a simplified, conservative, extraction of imaging data for wide application in clinical trials. They presume that linear measures are an adequate substitute for 2-D methods and register four response categories[47]

- CR (complete response) = disappearance of all target lesions
- PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
- PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions
- SD (stable disease) = small changes that do not meet above criteria

12.3 Withdrawal of subjects from study

Withdrawal

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at her own request or at the request of her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up.
- Death.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.

- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Severe allergic reaction to Everolimus (such as stomatitis or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable. In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

12.4 Pregnancy and assessments of fertility

Pregnancy testing is required at screening or whenever pregnancy is suspected. Serum pregnancy testing should be performed at screening and at the end of the study or if clinically indicated.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

13. Safety monitoring and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

13.1 Adverse events

13.1.1 Definitions and reporting

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates or if continuing at the Safety Follow-up Visit)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 14.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome. Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure]. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment

13.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event. Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

14. Serious Adverse Events

14.1 Definitions

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

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

14.1.1 Reporting

The principal investigator has the obligation to report all related and unexpected adverse events to the local, IRB. To ensure patient safety, every SAE, regardless of suspected causality, occurring:

- after the patient has provided informed consent and until atleast 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment must be reported to the institutional IRB within 24 hours of learning of its occurrence ; This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, may urgently require further information from the investigator to the local IRB. The Investigator and the local IRB may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities. For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the comapartor drug company by the investigator. The following categories and definitions of causal relationship to study drug should be considered for use for this clinical study.

- Certain: There is a known causal relationship between the study drug and the SAE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible. (>95% certainty)
- Probable: There is reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge. Rechallenge is not required. (65%-95% probability)
- Possible: There is reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear. (35%-65% probability of relatedness)
- Not likely: There is temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the SAE. (5-35% probability of relatedness)
- Not related: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is known causal relationship between the SAE and another drug, concurrent disease, or other circumstance. (<5% chance of relatedness)
- Adverse events classified as "serious" require expeditious handling and reporting to Houston Methodist Cancer Center (TMHCC) and local IRB to comply with regulatory requirements.
- All related or unexpected AEs of any of the study drugs must be immediately reported to local IRB by the investigator or designee within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.
- Report SAE to Celgene Drug Safety within 24 hours via email or fax.

  Celgene Corporation
  Global Drug Safety and Risk Management
  Connell Corporatke Park
  300 Connell Dr. Suite 6000
  Berkeley Heights, NJ 07922
  Fax 908-673-9115. Email
  Email: drugsafety@celgene.com
  All SAEs should be faxed or emailed to

  Houston Methodist Cancer Center at:
  Research@tmhs.org
  Fax Number: 713-793-1642
- For studies conducted under an Investigator IND expecion , any event that is both related and unexpected must be reported to the local IRB as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information.

14.1.2 Pregnancy

Preclinical data regarding reproductive toxicity is described in the most recent Investigator Brochure. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the local IRB/CELGENE/GSK within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local IRB/CELGENE/GSK Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study

treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

15. Statistical methods

15.1 Sample Size.

Two parallel arms (arm 1: Trastuzumab Emtansine plus Lapatinib followed by Abraxane and arm 2: Trastuzumab plus Lapatinib followed by paclitaxel) will be evaluated and a two-stage optimum Simon's design will be employed to perform interim analysis for each arm of the trial. The null hypothesis is that pathological complete response rate is equal to 50% versus an alternative hypothesis equal to 70%. A sample of 15 patients will be enrolled in each arm during the first stage. Decisions on how to proceed with the trial after enrollment has been completed in the first stage will involve all three parties (CELGENE, GSK, and HMRI). For the experimental arm only, a two-stage Simon's design with 80% power and 5% alpha level patient accrual will be terminated if 8 or fewer patients achieve pCR; otherwise decisions on how to proceed with the trial will involve all three parties. The interim analysis results will be treated as confidential as long as the study is ongoing, and may not be released to anyone other than those specified in the interim analysis plan (CELGENE, GSK, and HMRI). pCR rates will be estimated in each arm along with exact 95% confidence intervals. The safety profiles of the study will be assessed through summaries of adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, and treatment-related death. All patients who receive at least 1 dose of treatment will be included in the analysis for safety. The safety analysis will report the frequency of all AEs and laboratory abnormalities, as well as the frequency of dose interruptions, dose reductions, and treatment discontinuation for toxicity. Toxicity rates will be presented using the worst NCI CTCAE (V4) grade per patient. Blocked randomization will be used to randomly assign patients either to arm 1 or arm 2. Other secondary clinical outcomes will be summarized including clinical response rate, % tumor shrinkage, changes in imaging, operability and type of surgery, disease-free interval and time to progression. All subjects who received study drug will be included in the safety analysis.

16. Protocol amendments, or changes in study conduct

Any change or addition to this protocol requires a written protocol amendment that must be reviewed by the local IRB and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons must be notified to the IRB and other centers must be informed immediately. Amendments affecting administrative aspects of the study do not require formal protocol amendments. Amendments affecting administrative aspects of the study will require IRB approval.

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46. Paclitaxel Investigator Brochure
47. National Cancer Institute RECIST Guidelines and criteria.

18. Appendices

Appendix A: ECOG/ Karnofsky Performance Status Criteria

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

Appendix B: New York Heart Association (NYHA) Classifications

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

This table is an excerpt from the Oxford Textbook of Medicine, 2nd ed. Oxford; New York: Oxford University Press, 1987, p. 2228.

Appendix C: Version 4.0 (dated June-14-2010)

CTCAE Files

NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files and related documents are published here. The most current release files appear in this directory:

Files: Booklet	Content
CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf	Most recent release of core terminology: PDF document, traditional small booklet format.

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix D: WOCBP & Determination of Menopausal Status

WOCBP

Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation and up to 90 days following completion of therapy. Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms for the duration of the study and for 90 days following completion of therapy.

- Total abstinence from sexual intercourse (minimum one complete menstrual cycle).
- Vasectomized male subjects or vasectomized partner of female subjects.
- Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration.
- Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream).
- Intrauterine device (IUD).

The following criteria will be used in this trial to define postmenopausal:

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry;

Or

- Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) and with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard;

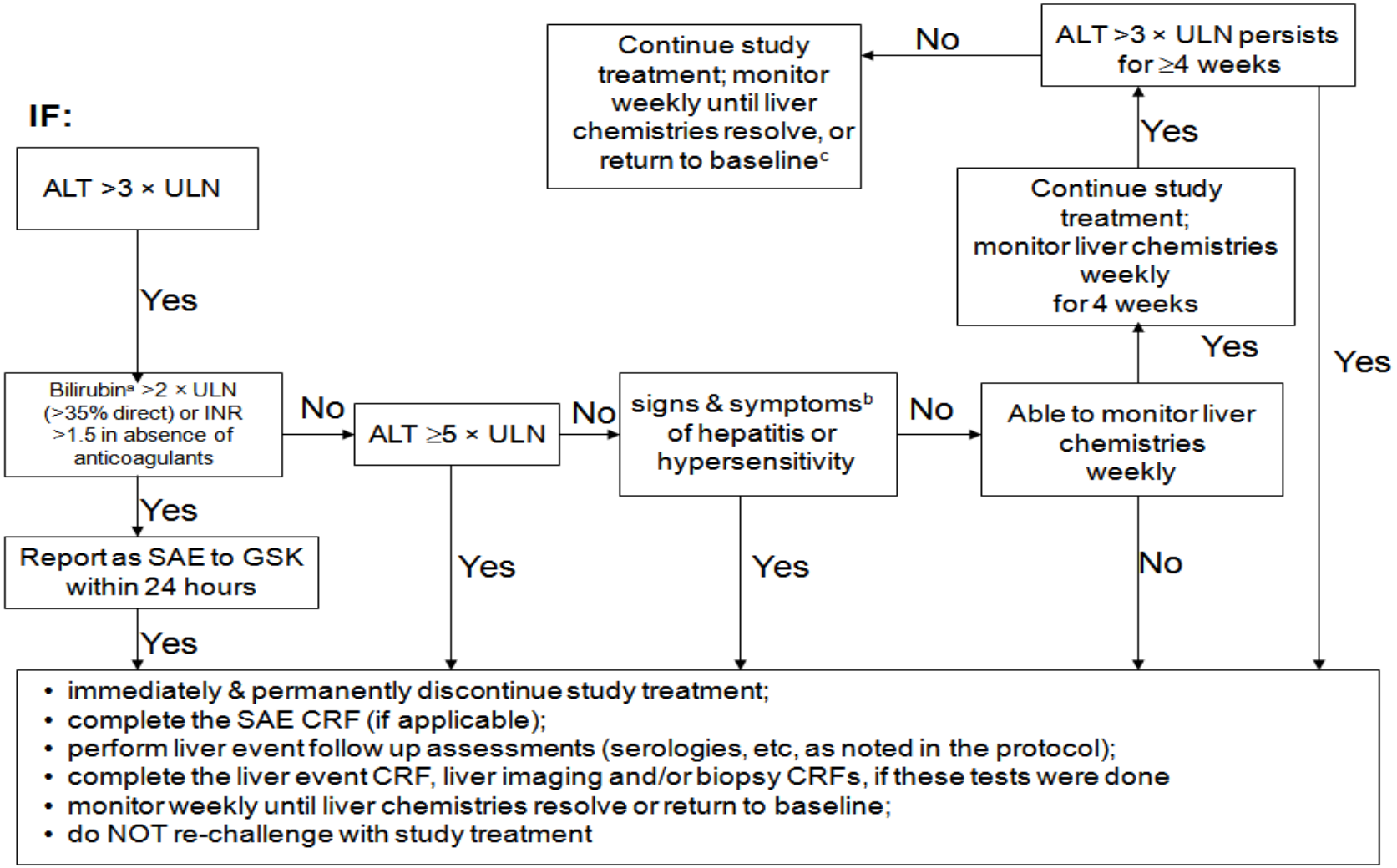
Or

- Documented bilateral oophorectomy.

Women failing to meet one of these criteria will be classified as pre-menopausal.

Apendix E: Lapatinib Liver Toxicity guidelines

LIVER TOXCIITY DISCONTINUATION AND FOLLOW-UP CRITERIA



a. Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >2.0 × ULN, then the event should still be reported as an SAE and actions taken as described

b. the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

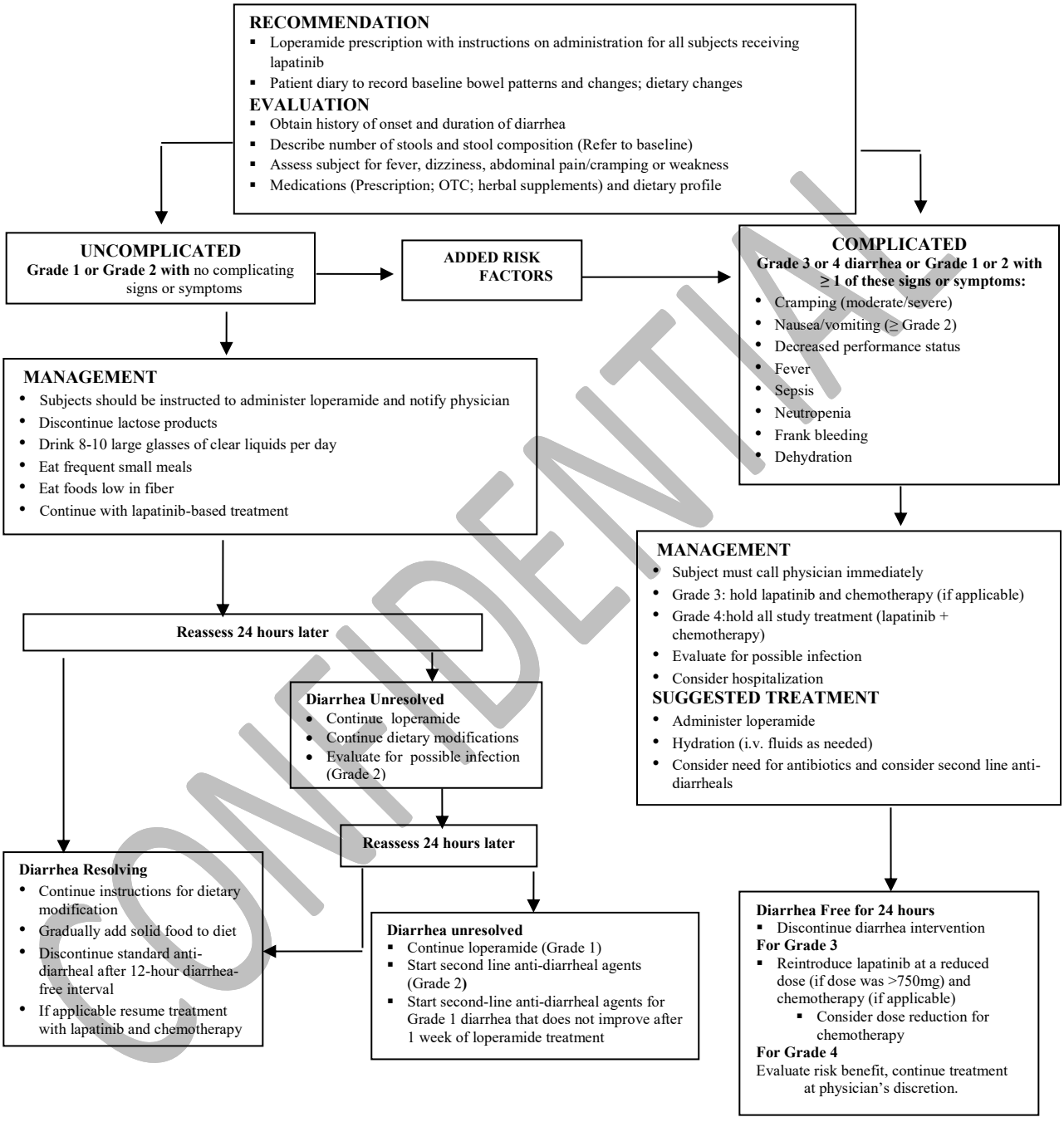
c. Hold Lapatinib and TDM-1 if grade 2(>3.0-5.0 x ULN) or grader ALT, until resolve, return to baseline or ≤ grade 1 (whichever is greater), once liver chemistries resolve, or return to baseline, then continue monitoring per the protocol assessment schedule, retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists

Apendix E continuation: Liver Chemistry Follow up Criteria

For all subjects who meet any of the liver chemistry criteria described above, make every attempt to carry out the liver event follow up assessments described below:

a. Viral hepatitis serology including:
b. Hepatitis A IgM antibody;
c. Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
d. Hepatitis C RNA;
e. Cytomegalovirus IgM antibody;
f. Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
g. Hepatitis E IgM antibody (if subject resides or has traveled outside USA or Canada in past 3 months);
h. Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
i. Complete blood count with differential to assess eosinophilia;
j. Pharmacokinetic (PK) testing for measurement of lapatinib concentrations"
k. Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
l. Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form;
m. Record alcohol use on the liver event alcohol intake case report form.

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



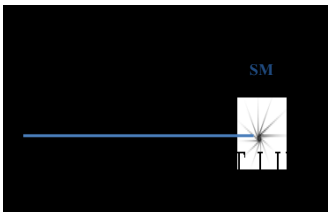
For Grade 1 diarrhea that persists for 2 weeks or longer, refer to Section 9.3
For Grade 2 diarrhea that persists longer than 3 days/72 hours, refer to Uncomplicated Diarrhea Section 9.3
For recurrent diarrhea, refer to Uncomplicated Diarrhea Section 9.3 for further management guidelines

Appendix G: Inducers and Inhibitors' list

INHIBITOR	Therapeutic class	Substrate
CYP2C8		
POTENT INHIBITORS		
gemfibrozil	Fibric acid derivatives	Repaglinide
MODERATE INHIBITORS		
deferasirox	Miscellaneous	Repaglinide
WEAK INHIBITORS		
trimethoprim	Antibiotics	repaglinide
ketoconazole	Antifungals	rosiglitazone
fluvoxamine	Selective Serotonin Reuptake Inhibitors	rosiglitazone
CYP3A4		
POTENT INHIBITORS		
indinavir /RIT	Protease Inhibitors	alfentanil
tipranavir/RIT	Protease Inhibitors	midazolam
ritonavir	Protease Inhibitors	midazolam
cobicistat (GS-9350)	None	midazolam
indinavir	Protease Inhibitors	vardenafil
ketoconazole	Antifungals	midazolam
troleandomycin	Antibiotics	midazolam
Saquinavir/RIT	Protease Inhibitors	midazolam
Itraconazole	Antifungals	midazolam
voriconazole	Antifungals	midazolam
telaprevir	Antivirals	midazolam
mibefradil	Calcium Channel Blockers	midazolam
clarithromycin	Antibiotics	midazolam
lopinavir / RIT	Protease Inhibitors	aplaviroc
elvitegravir / RIT	Treatments of AIDS	midazolam IV
posaconazole	Antifungals	midazolam
nelfinavir	Protease Inhibitors	simvastatin
telithromycin	Antibiotics	midazolam
grapefruit juice DS[2]	Food Products	midazolam
conivaptan	Diuretics	midazolam
nefazodone	Antidepressants	midazolam
saquinavir	Protease Inhibitors	midazolam
boceprevir	Antivirals	midazolam
MODERATE INHIBITORS		
fluconazole	Antifungals	midazolam
atazanavir / RIT	Protease Inhibitors	maraviroc
darunavir	Protease Inhibitors	saquinavir
erythromycin	Antibiotics	midazolam
diltiazem	Calcium Channel Blockers	midazolam
darunavir / RIT	Protease Inhibitors	sildenafil
dronedarone	Antiarrhythmics	simvastatin
atazanavir	Protease Inhibitors	maraviroc
aprepitant	Antiemetics	midazolam
casopitant	Antiemetics	midazolam
amprenavir	Protease Inhibitors	rifabutin
imatinib	Antineoplastic Agents	simvastatin
verapamil	Calcium Channel Blockers	midazolam
grapefruit juice	Food Products	midazolam
tofisopam	Benzodiazepines	midazolam
cyclosporine	Immunosuppressants	Imidazolam
ciprofloxacin	Antibiotics	sildenafil
schisandra sphenanthera	Herbal Medications	midazolam
cimetidine	H-2 Receptor Antagonists	midazolam
FK1706	Central Nervous System Agents	midazolam
WEAK INHIBITORS		
tabimorelin	Hormone Replacement	midazolam
ranolazine	Cardiovascular Drugs	simvastatin
fosaprepitant (IV)	Antiemetics	midazolam
Seville orange juice	Food Products	felodipine
chlorzoxazone	Muscle Relaxants	midazolam
M100240	Antihypertensive Agents	midazolam
fluvoxamine	Antidepressants	midazolam
ranitidine	H-2 Receptor Antagonists	midazolam
goldenseal	Herbal Medications	midazolam
clotrimazole	Antifungals	midazolam

tacrolimus	Immunosuppressants	midazolam
cilostazol	Antiplatelets	lovastatin
peppermint oil	Food Products	felodipine
roxithromycin	Antibiotics	midazolam
propiverine	Anticholinergics	midazolam
isoniazid	Antibiotics	triazolam
oral contraceptives	Oral contraceptives	triazolam
delavirdine	NNRTIs	indinavir
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	midazolam IV
tolvaptan	Vasopressin Antagonists	lovastatin
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	simvastatin
resveratrol	Food Products	buspirone
lacidipine	Calcium Channel Blockers	simvastatin
cranberry juice	Food Products	midazolam
pazopanib	Kinase Inhibitors	midazolam
nilotinib	Kinase Inhibitors	midazolam
AMD070	Fusion Inhibitors	midazolam
alprazolam	Benzodiazepines	buspirone
amlodipine	Calcium Channel Blockers	simvastatin
bicalutamide	Antiandrogens	midazolam
sitaxentan	Endothelin Receptor Antagonists	sildenafil
azithromycin	Antibiotics	midazolam
ginkgo	Herbal Medications	midazolam
INDUCER		Object
3A4		
POTENT INDUCERS		
rifampin		budesonide
mitotane		midazolam
avasimibe		midazolam
phenytoin		nisoldipine
carbamazepine		quetiapine
St John's Wort		midazolam
rifabutin		delavirdine
phenobarbital		verapamil
MODERATE INDUCERS		
ritonavir and St. Johns wort		midazolam
tipranavir and ritonavir		saquinavir
bosentan		sildenafil
nafcillin		nifedipine
[talviraline]		indinavir
efavirenz		simvastatin acid
modafinil		triazolam
etravirine		sildenafil
WEAK INDUCERS		
garlic		saquinavir
amprenavir		lopinavir
[troglitazone]		simvastatin
sorafenib		sirolimus
rufinamide		triazolam
[pleconaril]		midazolam
gingko		midazolam
vinblastine		midazolam IV
nevirapine		indinavir
armodafinil (R-modafinil)		midazolam
prednisone		tacrolimus
oxcarbazepine		felodipine
danshen		midazolam
echinacea		midazolam
pioglitazone		midazolam
dexamethasone		aprepitant
terbinafine		midazolam
glycyrrhizin		midazolam
aprepitant		midazolam IV
methylprednisolone		cyclosporine
topiramate		ethinyl estradiol

Appendix H : Trail Support and Development



We have recently created the **C**onsortium for the **A**dvancement of **R**esearch **E**xcellence (**CARE**) with seven (7) major academic medical and research institutions committed to translational and clinical cancer research.

CARE represent a consortium of clinical and laboratory investigators/Institutions with the primary objective as development of translational research studies incorporating innovative molecular diagnostics, targeted therapeutic interventions and utilizing advanced statistical design. The overall goal is to expedite the translational of laboratory research into the clinic and to develop a model for the implementation of effective personalized therapy. In this effort we will work closely with the Industry, the NCI, other federal and private funding agencies and advocate organizations.

Our Members are:

1) Massimo Cristofanilli, MD – Thomas Jeferson Philadelphia (PA)
2) Jenny Chang MD – The Methodist Hospital-Houston (TX)
3) Lyndsay Harris, MD- Case Comprehensive Cancer Center- Cleveland (OH)
4) Linda T Vahdat, MD- Weill Cornell Medical Center, NY (NY)
5) Stefan Gluck, MD- Sylvester Cancer Center Miami (FL)
6) Ruth O'Regan, MD-Georgia Cancer Center Emory University (GA)
7) Sunil Sharma, MD– Huntsman Cancer Institute University of Utah

Key Milestones:

FPFV / First Dose: With documented invasive disease and eligible for neo-adjuvant therapy

LPLV / Last Subject completed: Sep/2015

Database Lock: March/2016

Final Report: June/2016

Sponsoring Department: TMHCC &TMHRI

Prepared by: _____ Date _____