USC Norris Comprehensive Cancer Center
Part of the Keck School of Medicine of USC

Local Protocol #: 1B-12-10

Protocol Title: Phase II Trial of Metronomic Capecitabine and Cyclophosphamide with Lapatinib and Trastuzumab in Patients with HER2 Positive Metastatic Breast Cancer Who Have Progressed on a Previous Trastuzumab-Based Regimen
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UNIVERSITY OF SOUTHERN CALIFORNIA/KENNETH NORRIS, JR. COMPREHENSIVE CANCER CENTER AND HOSPITAL

1B-12-10
Phase II Trial of Metronomic Capecitabine and Cyclophosphamide with Lapatinib and Trastuzumab in Patients with HER2 Positive Metastatic Breast Cancer Who Have Progressed on a Previous Trastuzumab-Based Regimen

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Study Drugs: Capecitabine (Xeloda®)
Cyclophosphamide (Cytoxan®)
Lapatinib (Tykerb®)
Trastuzumab (Herceptin®)

IND Number: N/A

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____
(Please Print)

PI Signature: _____
(Please Sign)

Institutional Name: _____

Date: __ __ / __ __ / __ __ __ __
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CONTENTS

LIST OF ABBREVIATIONS

AE	ADVERSE EVENT
ALT	ALANINE AMINOTRANSFERASE
ALC	ABSOLUTE LYMPHOCYTE COUNT
AST	ASPARTATE AMINOTRANSFERASE
BUN	BLOOD UREA NITROGEN
CBC	COMPLETE BLOOD COUNT
CMP	COMPREHENSIVE METABOLIC PANEL
CR	COMPLETE RESPONSE
CT	COMPUTED TOMOGRAPHY
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
DLT	DOSE LIMITING TOXICITY
DSMB	DATA AND SAFETY MONITORING BOARD
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
IV (OR IV)	INTRAVENOUSLY
MTD	MAXIMUM TOLERATED DOSE
NCI	NATIONAL CANCER INSTITUTE
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PBMCS	PERIPHERAL BLOOD MONONUCLEAR CELLS
PD	PROGRESSIVE DISEASE
PFS	PROGRESSION FREE SURVIVAL
P.O.	PER OS/BY MOUTH/ORALLY
PR	PARTIAL RESPONSE
SAE	SERIOUS ADVERSE EVENT
SD	STABLE DISEASE
SGOT	SERUM GLUTAMIC OXALOACETIC TRANSAMINASE
SGPT	SERUM GLUTAMIC PYRUVIC TRANSAMINASE
WBC	WHITE BLOOD CELLS
IIT	INVESTIGATOR INITIATED TRIAL

LIST OF TABLES

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STUDY SUMMARY

Title	Phase II Trial of Metronomic Capecitabine and Cyclophosphamide with Lapatinib and Trastuzumab in Patients with HER2 Positive Metastatic Breast Cancer Who Have Progressed on a Previous Trastuzumab-Based Regimen
Short Title	Metronomic Capecitabine and Cyclophosphamide with Lapatinib and Trastuzumab in Patients with HER2 Positive Metastatic Breast Cancer
Protocol Number (CIC)	1B-12-10
Protocol Number (HSIRB)	TBA
Phase	Phase II
Methodology	Single Arm, Open Label
Study Duration	24 months
Study Center(s)	Single Center - USC
Objectives	To evaluate the combination of metronomic cycleophosphamide and capecitabine with lapatinib and trastuzumab in patients with HER-2 positive metastatic breast cancer.
Number of Subjects	40
Diagnosis and Main Inclusion Criteria	HER-2 positive metstatic breast cancer previously treated with trastuzumab
Study Product(s), Dose, Route, Regimen	Capecitabine (Xeloda®) 1500mg PO QD Cyclophosphamide (Cytoxan®) 50mg PO QD Lapatinib (Tykerb®) 1000mg PO QD Trastuzumab (Herceptin®) 6mg/kg IV Once
Duration of administration	In the absence of treatment delays due to adverse events, treatment may continue until: • Disease progression • Inter-current illness that prevents further administration of treatment • Unacceptable adverse event(s) • Patient decides to withdraw from the study, **OR** • General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator"

1.0 BACKGROUND AND HYPOTHESES

1.1 METRONOMIC CHEMOTHERAPY

Cytotoxic chemotherapy has traditionally been administered at the highest possible dose that does not cause life-threatening toxicity, and this is called the 'maximum tolerated dose' (MTD). MTD-based chemotherapy does not target tumor cells specifically, but interferes with cell division, thus damaging the normal dividing cells of rapidly regenerating tissues. This results in toxic side effects such as myelosuppression, alopecia, and mucosal damage. Prolonged therapy breaks of 2-3 weeks are required between cycles to allow recovery from these side effects.
'Metronomic chemotherapy' is an emerging new paradigm in cancer therapy, in which frequent low doses of chemotherapeutic agents are administered at frequent intervals. Metronomic chemotherapy targets the endothelial cells that are dividing in the growing blood vessels of tumors, rather than the tumor cells themselves, resulting in an anti-angiogenic effect.[1, 2] In preclinical models, virtually every class of chemotherapeutic agent has been shown to inhibit angiogenesis, which contributes to their antitumor efficacy.[3] However, the anti-angiogenic effects of chemotherapy are masked by the long breaks between drug administrations, which enable the tumor vasculature to be repaired.[4] Frequent low-dose therapy has been shown to have impressive anti-angiogenic and antitumor effects in mice along with reduced toxicity.[4]

The major advantage of metronomic chemotherapy is the low toxicity, which significantly improves patients' quality of life, enables prolonged administration of chemotherapeutic agents without dose reductions or delays, and provides opportunities to combine different classes of agents that would otherwise be difficult with full dose regimens. Ideally metronomic chemotherapy would be administered on a daily basis. However, there are few chemotherapy agents that are available in an oral formulation. Nonetheless, the administration of a daily oral outpatient regimen has the additional practical benefit of decreasing clinic visits for patients. These benefits are most pronounced in the setting of metastatic cancer, where the goal is to prolong survival while maintaining quality of life for as long as possible.

1.2 METRONOMIC CHEMOTHERAPY IN METASTATIC BREAST CANCER

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer mortality in women.[5] Approximately 20% of patients will be diagnosed with metastatic breast cancer initially, while of the patients with initial localized disease 20-80% will ultimately develop metastatic disease. Despite recent advances in therapy, metastatic breast cancer (MBC) remains an incurable disease, with 5-year survival of 23%,[6] and further improvements in systemic therapy are necessary.

Metronomic chemotherapy has been found to have moderate activity with low toxicity in several phase II clinical trials in patients with MBC. In an initial study by Colleoni et al, sixty-four women with MBC were given oral cyclophosphamide 50mg daily and oral methotrexate 2.5mg bid on two days per week.[7] Fifty-two of the patients had previously received at least 1 line of chemotherapy. The overall clinical benefit was 32%, with 2 complete remissions (CR), 10 partial remissions (PR), and 12 patients with stable disease (SD) lasting 6 months or longer. Toxicity was minimal, with 12% grade ≥ 2 neutropenia, 2% grade ≥ 2 alopecia, and no grade ≥ 2 mucositis, nausea or vomiting. Levels of serum vascular endothelial growth factor (VEGF) decreased significantly after treatment, supporting an anti-angiogenic mechanism of therapy.

Another trial by Schott et al looked at the combination of metronomic cyclophosphamide and capecitabine.[8] Cyclophosphamide was given 100mg daily on days 1-14 and capecitabine was given 1500mg bid on days 8-21 of a 21-day cycle. The overall response rate was 36%, with four CRs and 25 PRs among 80 patients with measurable disease. The median progression-free survival was 5.9 months, and median overall survival was 18.8 months. These outcomes compared favorably with those of full-dose capecitabine monotherapy, or combination therapy with bevacizumab, sorafenib or ixabepilone. Most common toxicities were lymphopenia (grade 3-4 in 13 patients) and hand-foot syndrome (grade 3 in 7 patients). One case of grade 4 thromboembolism was reported.

Of note, capecitabine, an orally available tumor selective fluropyrimidine carbamate, has been approved by the United States Food and Drug Administration for treatment of MBC at a dose of 2500 mg/m^2/day for 2 weeks followed by a 1-week drug-free period. However, significant toxicity is encountered in clinical practice at this dose, in the form of diarrhea, mucositis and hand-foot syndrome. Therefore, capecitabine is routinely administered at a lower dose of 2000 mg/m^2/day, and data from non-randomized clinical trials suggest that activity is maintained while toxicity is decreased at this dose.[9] At USC we routinely treat patients with metastatic breast cancer using a low fixed dose of 1000 mg po bid, which is approximately 1130mg/m^2/day, given continuously without a drug-free interval. The activity of this regimen appears to be comparable to that of published studies using more conventional doses but with reduced toxicity.[10-12]

1.3 HER2 TARGETED THERAPIES IN BREAST CANCER

Human epidermal growth factor receptor 2 (HER2) plays a significant role in the pathogenesis of breast cancer. Around 20-30% of all breast cancers have overexpression of HER2, which is associated with earlier recurrence and shorter overall survival.[13] Trastuzumab, a recombinant humanized monoclonal antibody against the extracellular domain of HER2, is an integral part of the treatment of HER2-positive breast cancer. Studies have shown that trastuzumab improves disease-free and overall survival in HER2 positive patients in both the adjuvant and metastatic disease settings.[14-16] Trastuzumab monotherapy for HER2-positive MBC has a response rate of 13-26%,[16, 17] and in combination with chemotherapy, such as taxanes and vinorelbine, response rates are 60-70% in the first line setting.[18-20] However, patients invariably progress after initial response, and the response rates decrease in subsequent lines of therapy.[21] Also, in patients previously treated with trastuzumab in the adjuvant setting, response rates to HER2 targeted regimens are significantly lower when retreated in the metastatic setting. A recent report looking at the activity of HER2 targeted frontline chemotherapy for MBC found a response rate of 48% for patients who had not received adjuvant trastuzumab, while the response in the patients who had received it was only 13%.[22] Therefore, further treatment options need to be explored for patients with HER2-positive MBC who have already received trastuzumab in the adjuvant setting.

Trastuzumab is usually continued in patients with HER2-positive MBC even after they experience progression of disease while receiving trastuzumab. Preclinical data indicate that withdrawal of trastuzumab results in rapid tumor cell regrowth. The German Breast Group 26/Breast International Group 03-05 trial compared capecitabine with continuation of trastuzumab versus capecitabine alone in patients who progressed on a prior trastuzumab-containing regimen. Overall response rates were 48% in the combined arm and 27% in the capecitabine alone arm (P=0.01). Median time to progression was 8.2 months in the combined arm and 5.6 months in the capecitabine alone arm (P=0.03). Continuation of trastuzumab beyond progression was not associated with increased toxicity.

Lapatinib is an orally active small molecule that inhibits the tyrosine kinases of HER2 and epidermal growth factor receptor type 1 (EGFR). A phase III, randomized, open-label study showed that lapatinib in combination with capecitabine is also active in women with HER2-positive MBC who had previously received trastuzumab.[23] The overall response rate for the combination therapy was 22%, compared to 14% for patients receiving capecitabine monotherapy (P=0.09). The median time to progression was 8.4 months with the combination therapy and 4.4 months with monotherapy (P<0.001). The treatment was well tolerated, with the most common grade ≥ 3 toxicities being diarrhea (13%) and hand and foot syndrome (7%). These toxicities were similar to those observed with capecitabine alone. Therefore, the combination of lapatinib and capecitabine now represents a standard approach for patients with HER2-positive MBC after treatment with trastuzumab.

Trastuzumab and lapatinib have non-overlapping mechanisms of action, and synergistic interaction between these two agents has been well characterized in in-vitro breast cancer models.[24-26] In a randomized phase III study of patients with trastuzumab-refractory HER2 positive MBC, lapatinib 1000mg daily in combination with trastuzumab 2mg/kg weekly (after initial 4mg/kg loading dose) showed an improved median progression-free survival of 12 weeks compared to 8 weeks with lapatinib alone (P=0.008).[27] Adverse events were similar in both groups, with a higher rate of grade 1-2 diarrhea with combination therapy. Another large phase III study looked at lapatinib plus trastuzumab in the neoadjuvant setting and found a significantly higher rate of pathologic complete response compared to either agent alone.[28] These studies suggest that dual HER2 inhibition is better than single agent anti-HER2 therapy in the treatment of HER2-positive breast cancer.

1.4 HER2 TARGETED THERAPY WITH ANTI-ANGIOGENIC THERAPIES

Tumor neovascularization, or angiogenesis, has been demonstrated to be a critical pathway in the development and progression of cancer. Inhibition of angiogenesis represents an important and promising therapy in the management of solid tumors.[29] Agents that target angiogenesis such as bevacizumab, sunitinib, and pazopanib are now approved for the treatment of various tumors, including lung, colon and renal cancer. In breast cancer the addition of bevacizumab to cytotoxic chemotherapy led to statistically significant improvements in disease-free survival and overall response rates, although a benefit in overall survival was not observed.[30]

Vascular endothelial growth factor (VEGF) is the most potent and specific regulator of both normal and pathologic angiogenesis.[31] HER2 overexpression is associated with VEGF upregulation in breast cancer.[32] In xenograft models, increased efficacy is observed when anti-HER2 antibody trastuzumab is given in combination with anti-VEGF antibody bevacizumab.[33]

Rugo et al reported encouraging clinical activity for the combination of lapatinib and bevacizumab in heavily pretreated patients.[34] A response rate of 13% and clinical benefit of 34% was observed among 32 patients with metastatic breast cancer who had a median of 5 prior chemotherapy regimens. Most of these patients had received 2 or 3 prior lines of trastuzumab containing regimens.
Preliminary data from a phase I trial reported by Falchook et al suggests that the combination of trastuzumab, bevacizumab and lapatinib is active in heavily pretreated patients with metastatic breast cancer.[35] Three out of 5 patients previously refractory to lapatinib and trastuzumab achieved a response.

The most compelling data evaluating the clinical activity of combining HER2 and anti-angiogenic therapies comes from a phase II trial of bevacizumab and trastuzumab as front line therapy for metastatic breast cancer conducted by Hurvitz et al.[36] In this trial of 50 patients a response rate of 48% and a clinical benefit of 60% were obtained. Treatment was well tolerated with the expected toxicity profile of these agents.

1.5 METRONOMIC CHEMOTHERAPY COMBINED WITH TARGETED THERAPY

A phase II trial by Dellapasqua et al evaluated bevacizumab, a recombinant humanized monoclonal antibody against VEGF, in combination with metronomic cyclophosphamide and capecitabine in MBC.[37] Bevacizumab was given 10mg/kg intravenously every 2 weeks, with cyclophosphamide 50mg daily and capecitabine 500mg three times a day. An overall response rate of 48% was observed in 47 patients who had received 0-3 prior chemotherapy regimens. Median time to progression was 42 weeks. Treatment was well tolerated, and grade 3 or 4 toxicities were uncommon.

Another phase II trial by Montagna et al evaluated the activity of a 4-drug regimen of metronomic capecitabine and cyclophosphamide given with bevacizumab and erlotinib in patients with MBC.[38] Erlotinib is a tyrosine kinase EGFR inhibitor with a mechanism of action and toxicity profile similar to that of lapatinib. Patients received bevacizumab 15mg/kg intravenously every 21 days in combination with cyclophosphamide 50mg daily, capecitabine 500mg three times a day and erlotinib 100mg daily. In this trial an overall response rate of 62% was observed among 26 patients with HER2 negative disease who had not received prior chemotherapy for metastatic disease, although two thirds of the patients had received prior adjuvant chemotherapy.

A particularly relevant finding from these 2 studies is that the 3 drug combination (metronomic capecitabine, cyclophosphamide and bevacizumab) and the 4 drug combination (metronomic capecitabine, cyclophosphamide, bevacizumab and erlotinib) were found to be well tolerated, with very few grade 3 or 4 toxicities. Diarrhea and myelosuppression, the main toxicities of concern, are summarized in the following table:

TABLE 1: MAIN TOXICITIES RELATED TO DRUG COMBINATION

Type of Comb	***Diarrhea***		***Neutropenia***	
	All Grades	***Grade 3-4***	***All Grades***	***Grade 3-4***
3-Drug Comb	34%	0%	32%	4%
4-Drug Comb	76%	1%	20%	0%

In preclinical models the combination of metronomic cyclophosphamide plus trastuzumab was significantly more effective than either therapy used alone. The combination of metronomic chemotherapy and trastuzumab has comparable efficacy to that of trastuzumab in combination with the maximal tolerated dose of cyclophosphamide, while toxicity is significantly reduced.[39]

The activity of metronomic chemotherapy and trastuzumab was reported in a small clinical trial by Orlando et al, looking at 22 patients with HER2 positive MBC previously treated with trastuzumab.[40] Treatment consisted of methotrexate 2.5mg twice daily on day 1 and 4 every week, with cyclophosphamide 50mg daily and trastuzumab 6mg/kg every three weeks, after an

initial loading dose of 8mg/kg. A response rate of 18% and a clinical benefit of 46% were observed in patients who had received 2-8 prior chemotherapy regimens.

The following table summarizes the clinical trials previously discussed using metronomic chemotherapy and/or targeted therapy in metastatic breast cancer.

TABLE 2: CLINICAL TRIALS USING METRONOMIC CHEMOTHERAPY

Trial	***N***	***Prior therapy***	***Treatment***	***ORR***	***CB***	***Toxicity***
Metronomic chemotherapy						
Colleoni et al.	63	0-3	Cyclophosphamide 50mg daily Methotrexate 2.5mg bid D1, 2	19%	32%	Grade 3/4: transaminitis (n=9); leukopenia, neutropenia, anemia (n=1)
Schott et al.	96	0-2	Cyclophosphamide 100mg daily D1-14 Capecitabine 1500 bid D8-21 q21 days	36%	68%	Grade 3/4: leukopenia (n=15); neutropenia, hand-foot syndrome (n=7); fatigue, dehydration, diarrhea (n=2); dyspnea, febrile neutropenia, transaminitis, anemia, thrombocytopenia, hypokalemia, hyponatremia, depression, nausea, puritis, rash, thrombosis (n=1)
Trial	***N***	***Prior therapy***	***Treatment***	***ORR***	***CB***	***Toxicity***
HER2 targeted therapy + anti-angiogenic therapy						
Rugo et al.	52	0-12	Lapatinib 1500mg daily Bevacizumab 10mg/kg q2weeks	13%	32%	Grade 3: hypertension, rash (n=2); diarrhea, transaminitis (n=1)
Falchook et al.	24	6	Lapatinib 750mg daily Trastuzumab 4mg/kg q3weeks Bevacizumab 7.5mg/kg q3weeks	60%	N/A	N/A
Hurvitz et al.	50	0	Trastuzumab 2mg/kg weekly Bevacizumab 10mg/kg q2weeks	48%	60%	Grade 5: perforated ulcer (n=1) Grade 3/4: HTN (n=18); proteinuria (n=4); dyspnea, leukopenia, infusion reaction, headache (n=2); fatigue, diarrhea, inflammatory demyelination, hyperglycemia, hyponatremia, irregular menses, cardiac event (n=1)

TABLE 2: CONTINUED

Trial	*N*	*Prior therapy*	*Treatment*	*ORR*	*CB*	*Toxicity*
Metronomic chemotherapy + targeted therapy						
Dellapasqua et al.	46	0-3	Capecitabine 500mg tid Cyclophosphamide 50mg daily Bevaciumab 10mg/kg q2weeks	48%	68%	Grade 3: hypertension (n=8); transaminitis, nausea/vomitting, neutropenia, leukopenia (n=2)
Montagna et al.	26	0	Capecitabine 500mg tid Cyclophosphamide 50mg daily Bevacizumab 15mg/kg q3weeks Erlotinib 100mg daily	62%	75%	Grade 3: hypertension (n=2); diarrhea, thrombosis (n=1)
Orlando et al.	22	2-8	Cyclophosphamide 50mg daily Methotrexate 2.5mg bid D1, 4 Trastuzumab 6mg/kg q3weeks	18%	46%	Grade 3: transaminitis (n=2)

1.6 HYPOTHESIS

Based on the above we propose a phase II clinical trial using metronomic chemotherapy (capecitabine and cyclophosphamide), in combination with dual HER2 inhibition (lapatinib and trastuzumab), in HER2 positive MBC patients previously treated with trastuzumab. Each of these agents has been shown to have activity in MBC, although they have never been combined in this 4-drug regimen. We postulate that this combination regimen will be highly active in patients with HER2 positive MBC while also having a favorable toxicity profile.

2.0 OBJECTIVES AND PURPOSE

The primary and secondary objectives listed below apply to the combination of metronomic cyclophosphamide and capecitabine with lapatinib and trastuzumab in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab.

2.1 Primary Objective

- To estimate the progression free survival (PFS)

2.2 Secondary Objectives

- To evaluate the overall response rate (ORR)
- To evaluate the clinical benefit rate (CBR; complete response, partial response, and stable disease for ≥24 weeks)
- To estimate the overall survival (OS)
- To assess the safety and tolerability

3.0 SELECTION AND WITHDRAWAL OF PARTICIPANTS

Study participants (N=40) will be recruited from the Los Angeles County + University of Southern California (LAC+USC) Healthcare Network and the Keck Medical Center of USC, Norris Comprehensive Cancer Center in Los Angeles, California. Because of the multi-ethnic nature of this catchment area, the inclusion of minority groups into study enrollment will be supported.

3.1 INCLUSION CRITERIA

Female patients 18 years of age and older who meet the following inclusion criteria for participation in the study will be considered for study enrollment:

- Histologically confirmed HER2-positive metastatic breast cancer.
- HER2 overexpression of tumor by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). Tumors tested by IHC must be 3+ positive. Tumors tested by FISH must have a ratio of HER2:CEP17>2.0. When both tests are performed, the FISH result must be positive.
- Prior trastuzumab use in the adjuvant or metastatic setting.
- No more than two prior cytotoxic chemotherapeutic regimens for metastatic breast cancer. In addition, prior Trastuzumab emtansine (TDM-1, Kadcyla) is allowed.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
- Adequate organ and marrow function as follows:
  - ANC ≥ 1500/mm3
  - Platelets ≥ 100,000/mm3
  - Hemoglobin ≥ 9g/dL
  - Bilirubin ≤ 1.5 x the upper limit of normal
  - Serum creatinine ≤ 1.5 x the upper limit of normal or calculated creatinine clearance ≥ 60ml/min
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal.
- Fully recovered from toxicity due to prior therapy.

- Capable of understanding the informed consent and complying with the protocol and signed the informed consent document prior to any study-specific screening procedures or evaluations being performed.

- Patients must have the ability to swallow pills.

- Patients may have either measurable or non-measurable disease by RECIST 1.1 criteria.

- Sexually active participants must agree to the use of a medically accepted barrier method of contraception (i.e. male condom or female condom) during the course of the study and for 3 months following discontinuation of study treatments. For participants of childbearing potential, a barrier method and a second method of contraception must be used.

- Participants of childbearing potential must have a negative pregnancy test at screening and enrollment. Participants of childbearing potential are defined as premenopausal females capable of becoming pregnant, i.e. females who have had any evidence of menses in the past 12 months with the exception of those who had prior hysterectomy (oophorectomy or surgical sterilization). However, women who have been amenorrheic for ≥ 12 months are still considered to be of childbearing potential if the amenorrhea is possibly due to any other cause including prior chemotherapy, antiestrogens, or ovarian suppression.

3.2 EXCLUSION CRITERIA

Women with any of the following exclusion criteria for this study will be ineligible to participate in the study:

- The following restrictions on prior therapy apply:
  - Prior treatment with capecitabine or lapatinib.
  - Radiation therapy within 2 weeks before the first dose of study treatment
  - Hormonal therapy within 2 weeks before the first dose of study treatment
  - Cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) within 3 weeks before the first dose of study treatment
  - Biologic therapy (including antibodies [other than trastuzumab], immune modulators, cytokines) within 4 weeks before the first dose of study treatment. Note: There is no washout period required for trastuzumab.
  - Any other type of investigational agent within 4 weeks before the first dose of study treatment.
  - Major surgery, or not recovered from major surgery within 4 weeks before the first dose of study treatment

- Untreated, symptomatic, or progressive brain metastases. Participants must have no radiographic or other signs of progression in the brain for ≥1 month after completion of local therapy. Any corticosteroid use for brain metastases must have been discontinued without the subsequent appearance of symptoms for ≥ 4 weeks prior to first study treatment.

- Uncontrolled significant intercurrent illness that would preclude the patient from study participation per investigator assessment.

- Left ventricular ejection fraction (LVEF) ≤ 50% as documented by MUGA or echocardiogram performed within 28 days prior to the first study treatment.
- Currently receiving anticoagulation with therapeutic doses of warfarin (low-molecular weight heparin is permited).
- Pregnant or breastfeeding.
- Known to be positive for the human immunodeficiency virus (HIV) (a test for HIV at screening is not required).
- Have acute or currently active/requiring anti-viral therapy hepatic or biliary disease (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).
- Previously identified allergy or hypersensitivity or intolerance to components of the study treatment formulation (cyclophosphamide, capecitabine, lapatinib, trastuzumab).
- Any other diagnosis of malignancy or evidence of malignancy (except non-melanoma skin cancer, in-situ carcinoma of the cervix) within 2 years prior to screening for this study.
- Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

4.0 TREATMENT PLAN

This is a single institution, phase II, single arm, open-label study.

4.1 TREATMENT DOSAGE AND ADMINISTRATION

Each patient will be given the following treatment on a 21-day cycle, with an average of 8 cycles per patient:

TABLE 3: TREATMENT DOSAGE AND ADMINISTRATION

Drug	*Dose*	*Route*	*Frequency per Cycle*	*Days*
Capecitabine	1500mg	PO	Daily	1-21
Cyclophosphamide	50mg	PO	Daily	1-21
Lapatinib	1000mg	PO	Daily	1-21
Trastuzumab	6mg/kg*	IV	Once	1

* A loading dose of 8mg/kg will be given for the first cycle of trastuzumab.

Any patient who receives treatment on this protocol will be evaluable for toxicities (see Section 4.2). Each patient will be assessed for the development of toxicities according to the Study

Calendar (see Section 5.0). Dose adjustments will be made according to the system showing the greatest degree of toxicity (see Section 4.4).

4.2 TOXICITIES AND SPECIFIC MANAGEMENT GUIDLINES

Adverse events (AE) will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0, which can be accessed at: http://ctep.cancer.gov/reporting/ctc.html. Information related to Reporting of Adverse Events can be found in Section 7.5 of this document.

Participants experiencing one or more AEs due to the study treatment may require dose interruption and/or dose reduction for capecitabine, cyclophosphamide, lapatinib and/or trastuzumab. Guidelines for the management of AEs (ie, dose interruptions and dose reductions) are presented in the next sections. The study will be terminated if the incidence of unacceptable toxicities, as defined below, is greater than 15%.

4.2.1 UNACCEPTABLE TOXICITIES

Unacceptable toxicities are defined as any of the following attributable to study drug (definitely, probably, or possibly) during treatment.

- Any Grade 4 hematologic toxicity not resolving to Grade 1 or less by the time of the next scheduled blood draw a week later despite supportive care
- Grade 3 thrombocytopenia with bleeding
- Any Grade 3 or 4 non-hematologic toxicity not reversible to Grade 1 or less within 96 hours despite supportive care, excluding:
  - Alopecia
  - Transient myalgia or fatigue
  - Inadequately treated nausea, vomiting, or diarrhea
  - Any uncomplicated hyperglycemia and hypertriglyceridemia defined as not being associated with any other grade 3 or greater toxicity

4.2.2 SPECIFIC SYMPTOM MANAGEMENT – CARDIAC AND RESPRIATORY EVENTS

Asymptomatic cardiac events:
Participants who have a ≥20% decrease in left ventricular cardiac ejection fraction 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 lapatinib and trastuzumab.
If the repeat ejection fraction evaluation confirms a ≥20% decrease in left ventricular cardiac ejection fraction, and the ejection fraction is below the institution's lower limit of normal, then lapatinib and trastuzumab should be temporarily discontinued.

If the left ventricular ejection fraction recovers during the next 3 weeks, after consultation and approval of the medical monitor, the participant may be restarted on lapatinib and trastuzumab at a reduced dose. For such participants, monitoring of left ventricular ejection fraction will then be performed 2 weeks and 4 weeks after rechallenge, and then every 4 weeks thereafter.
If repeat ejection fraction evaluation still shows a decrease ≥20% in left ventricular ejection fraction relative to baseline, and the value is below the institution's lower limit of normal, then the participant should be withdrawn from study.

Symptomatic cardiac events:
Participants with an NCI CTCAE grade 3 or 4, LVEF relative decrease must be withdrawn from study.

Interstitial pneumonitis:
Participants with an NCI CTCAE Grade 3 or 4, interstitial pneumonitis must be withdrawn from study and must be reported as a SAE to GlaxoSmithKline (Section 7.5.1).

4.2.3 SPECIFIC SYMPTOM MANAGEMENT – DIARRHEA

Experience thus far suggests that when lapatinib is used as monotherapy 51% of patients experience diarrhea; most diarrhea presents as uncomplicated NCI CTCAE Grade 1 or 2 (G1 30%, G2 15%, G3 6%, G4<1%). In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances. Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea. Presented in the sections below are the recommended guidelines for the management of diarrhea in participants receiving lapatinib-based therapy; these guidelines were derived from the recommendations published by the ASCO panel.

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

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

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

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

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

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

Definitions:

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

TABLE 4: NCI COMMON TERMINOLOGY CRITERIA FOR GRADING DIARRHEA

Adverse Event Grade	Diarrhea
Grade 1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
Grade 3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living (ADL)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

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

Complicated diarrhea is severe and defined as any CTCAE Grade 3 or 4 diarrhea, or Grade 1 or 2 with one or more of the following signs or symptoms:

- Moderate to severe abdominal cramping
- Nausea/vomiting ≥Grade2
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding (red blood in stool)
- Dehydration

Management:

A. Uncomplicated Diarrhea

I. CTCAE Grade 1

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

1. Administer loperamide*

a. Initial dose 4mg followed by 2mg after every unformed stool. Re-evaluate after 24 hours, if:

i. Diarrhea is resolving:
- Continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
  - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns

ii. Diarrhea is not resolving:
- Administer loperamide at 2mg every 4 hours for the next 24 hours. Re-evaluate after 24 hours. If diarrhea is resolving, administer loperamide at 2mg after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours. If diarrhea is not resolving continue loperamide treatment at 2mg every 4 hours and re-evaluate every 24 hours.

b. If Grade 1 diarrhea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (i.e., octreotide, budesonide or tincture of opium).

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):

a. Stop all lactose containing products and eat small meals

b. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber
- Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)

c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility

d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
- Avoid acidic drinks such as tomato juice and fizzy soft drinks

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

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

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

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

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

II. CTCAE Grade 2

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

1. Administer loperamide*
   a. Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:

      i. Diarrhea is resolving, continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns

      ii. Diarrhea is not resolving, consider loperamide dose of 2mg every 2 hours for 24 hours. If Grade 2 diarrhea persists after total of 48 hours of loperamide treatment, start second-line agents (i.e.,octreotide, budesonide or tincture of opium).
         - Consider performing stool work-up, CBC, electrolytes and other tests as appropriate

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):

   a. Stop all lactose containing products and eat small meals

   b. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber
      - Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)

c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility

d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
   - Avoid acidic drinks such as tomato juice and fizzy soft drinks

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

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

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

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

III. **Persistent (≥ 3days/72 hours) Grade 2 Diarrhea**: hold lapatinib and chemotherapy until diarrhea resolves (<Grade 1/return to baseline bowel pattern).

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

   a. After diarrhea resolves (<Grade 1/return to baseline bowel pattern), resume treatment with lapatinib and chemotherapy.

IV. **Recurrent Diarrhea (more than 1 occurrence of Grade 2 diarrhea):** once the 2nd occurrence of Grade 2 diarrhea resolves to ≤Grade 1, consider reducing the dose of lapatinib by one dose level.

1. Consider a dose reduction for chemotherapy.

B Complicated Diarrhea

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

1. Participant **must** call physician immediately for any complicated severe diarrhea event
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool*
3. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhea
4. For dehydration use intravenous fluids as appropriate, if participant presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolytes and other tests as appropriate
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia
   Hold lapatinib and chemotherapy until symptoms resolve to ≤Grade 1 (without complicating features) and reintroduce lapatinib at a reduced dose
   a. Consider a dose reduction for chemotherapy
7. Supportive care and other interventions should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
8. Intervention may require hospitalization for participants most at risk for life threatening complications

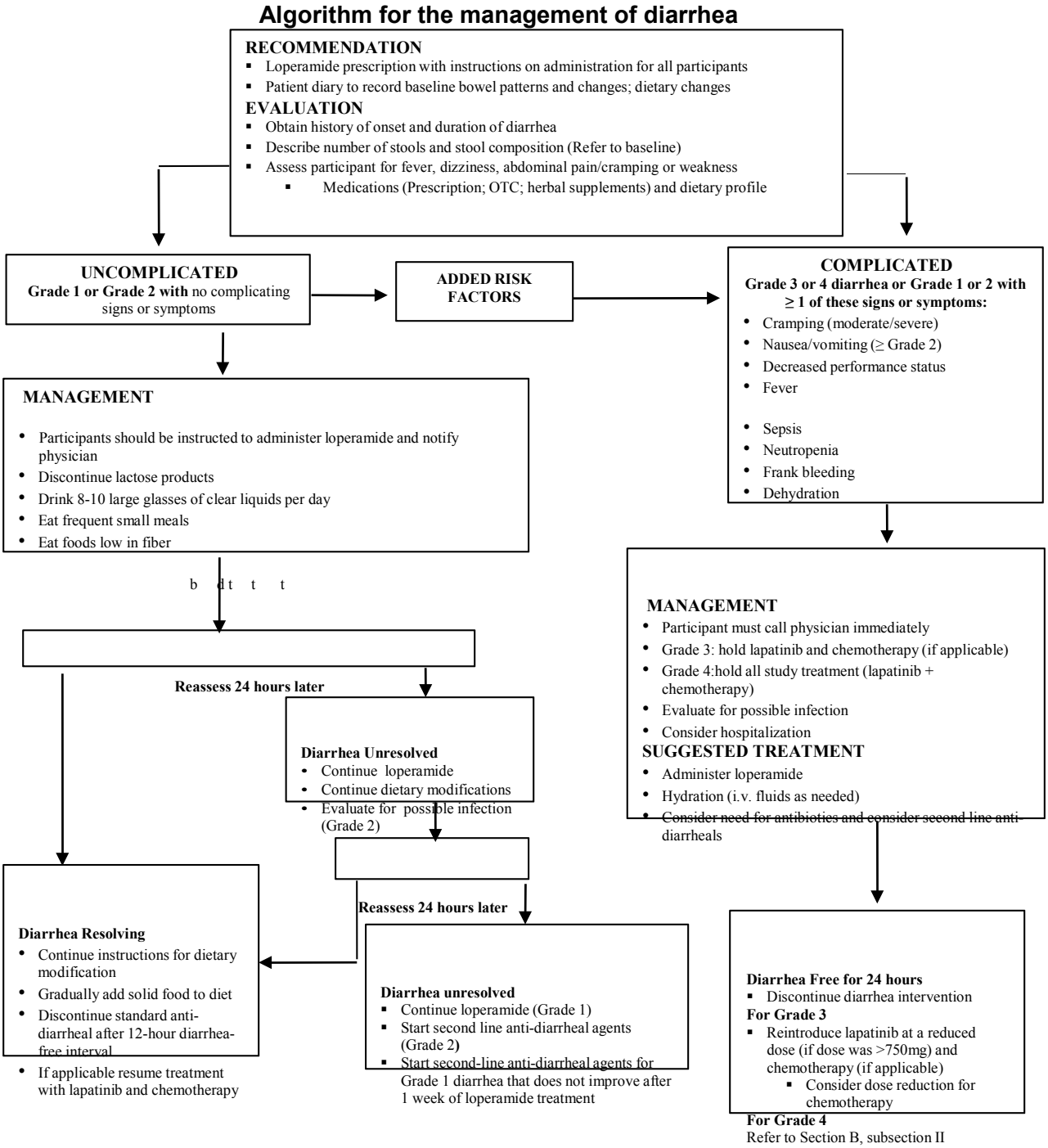
II. CTCAE Grade 4

1. Participant must call physician immediately for any Grade 4 diarrhea event
2. Hold treatment with lapatinib and chemotherapy
   - Evaluate the patient case history when deciding on the re-initiation of study treatment, including dose modifications, following resolution of diarrhea (≤Grade 1)
3. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool*
4. For dehydration use intravenous fluids as appropriate, if participant presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolyte and other tests as appropriate
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
7. Supportive care and other intervention should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours

8. Intervention may require hospitalization for participants most at risk for life threatening complications

* Refer to and follow the recommended supportive care guidelines in the previous sections

TABLE 5: ALGORITHM FOR THE MANAGEMENT OF DIARRHEA



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

4.2.4 SPECIFIC MANAGEMENT GUIDANCE – HEPATOTOXICITY

If a participant 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 study treatment;
- Complete the SAE data collection tool, the liver event CRF, and the liver imaging and/or liver biopsy CRFs, if these tests are performed;
- Promptly report the event to Novartis within 24 hours of learning its occurrence (refer to Section 7.3.1.6 for guidance on prompt reporting to NOVARTIS);
- Make every reasonable attempt to have participants return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments, and close monitoring
- Monitor every week until liver chemistries resolve, or return to within baseline values;
- Do not re-challenge with study treatment.
- A specialist or hepatology consultation is recommended

***NOTE**: Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a participant meets the criterion of total bilirubin >2.0 × ULN, then the actions detailed 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 participant 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 study treatment for 2 weeks, make every reasonable attempt to have participants return to clinic within 24-72 hrs for repeat liver chemistries and liver event follow up assessments. Repeat liver chemistry testing in 2 weeks. If ALT <3 x ULN discuss the possibility of re-challenging with study treatment with investigator.

If the treatment is exhibiting efficacy **and** the participant wants to continue for potential benefit of lapatinib therapy after being informed of the results of liver chemistry testing, then the study treatment may be re-started at the reduced dose agreed upon by the investigator and the provider. The liver event CRF should be completed and 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 participant 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 ALT >3 and < 5 × ULN for > 4 weeks, discontinue the treatment and complete liver safety testing and case report forms;
- if at any time the participant meets any of the liver chemistry stopping criteria, then proceed as described above.

Liver Chemistry Follow up

For all participants who meet any of the liver chemistry criteria described, complete the following liver event assessments:

- 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;
- Blood sample for pharmacokinetic (PK) analysis, obtained within one week of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the study procedures manual (SPM).
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Fractionate bilirubin if total bilirubin ≥2xULN.
- 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 the AE form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications form;
- Record alcohol use on the liver event alcohol intake form.

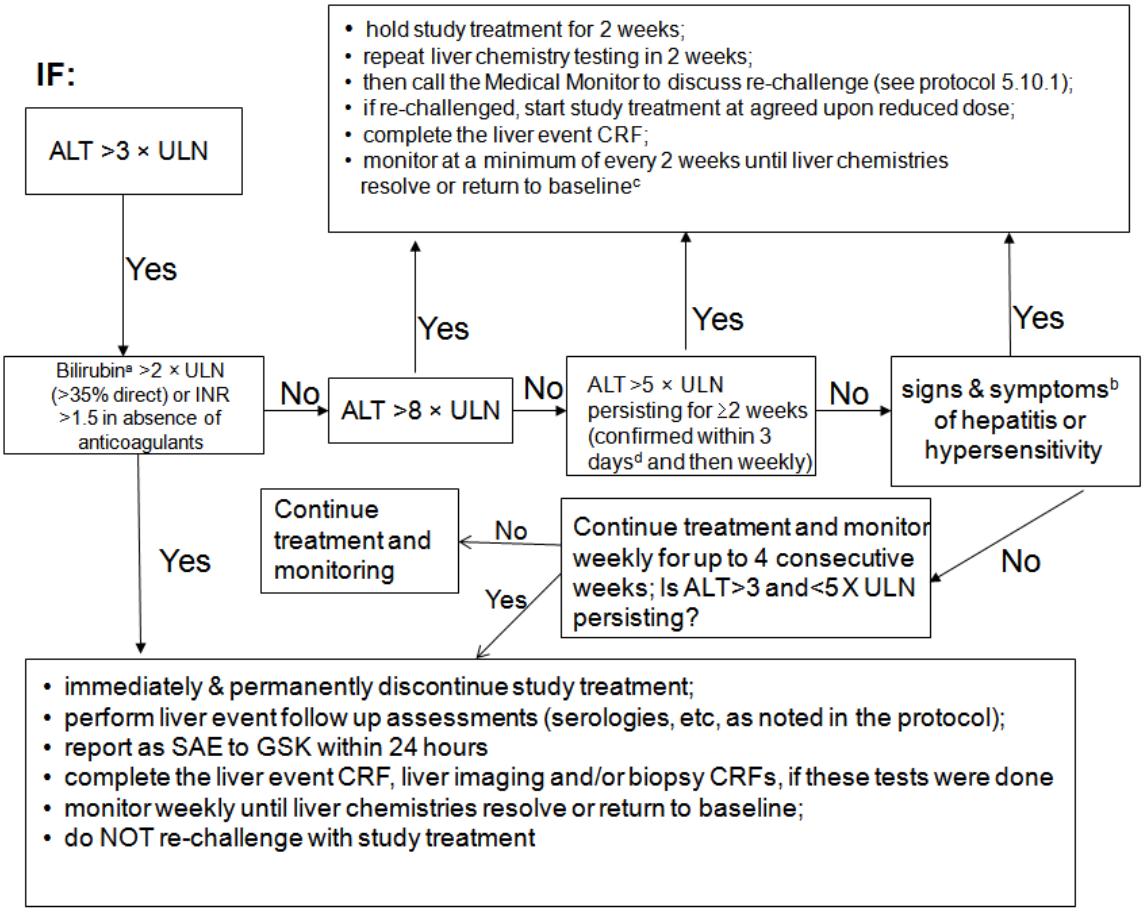
The following assessments are required for participants with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

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

- Liver imaging (ultrasound, magnetic resonance, or computerized tomography), and/or liver biopsy to evaluate liver disease.

TABLE 6: LIVER CHEMISTRY STOPPING RULES AND FOLLOW-UP CRITERIA

Liver Chemistry Stopping Rules and Follow up Criteria



a. bilirubin fractionation should be performed if testing is available. If testing is unavailable and a participant meets the criterion of total bilirubin >2.0 × ULN, then the event should still be reported as an SAE and actions taken as described. If bilirubin fractionation is unavailable, record presence of detectable urinary bilirubin on dipstick (indicating direct bilirubin elevations and suggesting liver injury).
b. the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
c. once liver chemistries resolve, or return to baseline, then continue monitoring per the protocol assessment schedule
d. retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists

4.2.5 SPECIFIC MANAGEMENT GUIDANCE – SKIN DISORDERS

Evaluation and Grading Guide

The Most Commonly Reported Dermatological Reactions

Papulopustular rash affecting especially the upper body, including face and scalp. Association with pruritus, burning or tenderness may occur; Maculopapular rash affecting the upper body. Pruritus may also occur; Nail or hair changes – any hair changes or loss, or paronychia; Dry skin, pruritus, and photosensitivity

Severe Skin Events

Lapatinib-related severe dermatological events are infrequent (1-3%). NCI-CTCAE (version 4.0) $\geq$ Grade 3 skin events 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 participants treated with lapatinib, it is recommended that participants 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.

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 participants were able to resume lapatinib therapy at the same dose after resolution of skin event; these participants 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 participants who present with NCI-CTCAE Grade 3 skin events which recover briskly to NCI-CTCAE Grade 1 (within 14 days) after holding lapatinib.

Stopping rules

Lapatinib should be permanently discontinued if an NCI-CTCAE Grade 3 dermatological reaction is intolerable to the patient <u>despite recommended treatment interventions</u>, 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.

Treatment
It is strongly recommended that participants who develop dermatological reactions receive evaluations for management on the specific side effect.

Participants should be encouraged to avoid exposure to sunlight. Broad spectrum sunscreens (containing titanium dioxide or zinc oxide) with an SPF of at least 30 should be applied.
A variety of agents can be used to manage skin reactions. These include mild-to-moderate strength steroid creams (fluticasone prioprionate 0.5%), topical or systemic antibiotics, topical or systemic antihistamines and immunomodulators, and hypoallergenic moisturizers and emolliens for dry skin (5-10% urea in cetomacrogel cream or soft paraffin).

There is no standard treatment, known or established, that is proven effective for drug-related skin rashes or changes due to lapatinib. A **papulopustular** rash has been the most commonly observed skin adverse event, which frequently improves with an unchanged, uninterrupted dose of lapatinib therapy. The need for oral or topical antibiotics (minocycline, doxycicline, flucolaciclline or metronidazole cream) and topical steroids is a clinical decision of the investigator and, if indicated, a dermatology consultation. For **pruritic** lesions oral antihistamine agents were reported successful. For **paronychia** antiseptic bath and local potent corticosteroids in addition to tetracycline therapy is recommended. If no improvement, a dermatology or surgery consultation is recommended. For **infected** lesions appropriate, culture driven, systemic or topical antibiotics are indicated.

Oral retinoids are not recommended because of theoretical concerns about negatively affecting the lapatinib mechanism of action and topical steroids result in irritation/severe dryness. Oral steroids may be used for a short treatment course (maximum of 14 days) which may help participants to remain on study therapy.

For participants with extensive or symptomatic NCI-CTCAE Grade 3 or 4 dermatologic event, or chronic, persistent or recurring lower grade skin events, dermatology consultation is encouraged. Upon consultation with a dermatologist, other treatment options (including immunomodulators such as topical tacrolimis or pimecrolimus) may be recommended for difficult to treat/unresponsive skin toxicities.

4.3 TOXICITY RELATED DOSE REDUCTION GUIDELINES

Guidelines for dose reduction of hematologic and non-hematologic toxicities are provided in the following tables.

4.3.1 HEMATOLOGIC TOXICITIES

TABLE 7: DOSE REDUCTION GUIDELINES (HEMATOLOGIC TOXICITIES)

CTCAE v4 grade	Intervention
Grade 1-2	No dose adjustments
Grade 3	Follow Guidance below based on occurance:
1st occurance	Interrupt capecitabine and cyclophosphamide treatment until resolution to Grade ≤2, and resume capecitabine treatment at one dose reduction and cyclophosphamide treatment at the same dose level
2nd occurance	Interrupt capecitabine and cyclophosphamide treatment until resolution to Grade ≤2, and resume capecitabine treatment at the same dose level cyclophosphamide treatment at one dose reduction
3rd occurance	Interrupt capecitabine and cyclophosphamide treatment until resolution to Grade ≤2, and resume capecitabine treatment at one dose reduction and cyclophosphamide treatment at one dose reduction
4th occurance	Discontinue treatment permanently
Grade 4	Follow Guidance below based on occurance:
1st occurance	Interrupt capecitabine and cyclophosphamide treatment until resolution to Grade ≤2, and resume capecitabine treatment at one dose reduction and cyclophosphamide treatment at one dose reduction
2nd occurance	Discontinue treatment permanently

4.3.2 NON-HEMATOLOGIC TOXICITIES

TABLE 8: DOSE REDUCTIONS (NON-HEMATOLOGIC TOXICITIES)

CTCAE v4 grade	Intervention
Grade 1	No dose adjustments
Grade 2	Follow Guidance below:
(per investigator's determination)	No dose adjustments. Interrupt study treatment until resolution to Grade ≤1, and resume at same dose, or reduce dose of study drug most likely to have caused the AE by one dose level. If the dose of the likely causative drug is not reduced after the first occurrence, a dose reduction must be implemented after a second recurrence.
Grade 3	Interrupt study treatment until resolution to Grade ≤1, and reduce dose(s) of study drug(s) most likely to have caused the AE by one dose level.
Grade 4	Discontinue treatment permanently, unless determined by the investigator that the participant is deriving clinical benefit. In this case, interrupt study treatment until resolution to Grade ≤1, and resume treatment at a dose to be determined individually.

4.4 DOSE ADJUSTMENT

The following tables show the dose adjustment levels for the study drugs in relation to the Hematologic Toxicities (Section 5.4.1) and Non-Hematologic Toxicities (Section 5.4.2) discussed above.

4.5.1 DOSE ADJUSTMENT LEVELS FOR CAPECITABINE

TABLE 9: CAPECITABINE DOSE ADJUSTMENT LEVELS

Dose Level	Capecitabine
0	500mg tid
-1	500mg tid alternating with 500mg bid
-2	500mg bid

4.4.2 DOSE ADJUSTMENT LEVELS FOR CYCLOPHOSPHAMIDE

TABLE 10: CYCLOPHOSPHAMIDE DOSE ADJUSTMENT LEVELS

Dose Level	Cyclophosphamide
0	50mg daily
-1	50mg daily alternating with 25mg daily
-2	25mg daily

4.4.3 DOSE ADJUSTMENT LEVELS FOR LAPATINIB

TABLE 11: LAPATINIB DOSE ADJUSTMENT LEVELS

Dose Level	Lapatinib
0	1000mg daily
-1	750mg daily
-2	500mg daily

4.4.4 DOSE ADJUSTMENT GUIDELINES FOR TRASTUZUMAB

Trastuzumab dose modifications are not permitted. Trastuzumab doses may be delayed as a result of adverse events.

4.4.5 OFF-TREATMENT

In cases where the Hematologic Toxicities do not resolve to a Grade ≤2 Adverse Events or Non-Hematologic Toxicities do not resolve to a Grade ≤1 Adverse Event after two subsequent dose adjustments, and / or the investigator determines no clinical benefit is being derived; patients will have their treatment interrupted. If after three weeks of no improvement, the patient will be permenantely taken off treatment.

4.4.6 MISSED DOSE OF ORAL MEDICATIONS

Patients will be instructed on how and when to take the medications at home. They will be provided with a Daily Dose Diary[1] and instructed on how to complete the form. They will also be informed to bring the completed diary and pill bottles with them to their next study visits, until discontinuation.

In the event a patient misses one day of dose (all three oral medications) or a single medication with a daily dose, they will be instructed to:

1. Record the missed medication(s) on the Daily Dose Diary
2. Resume normal medication dose(s) on the following day

If a patient misses >2 consecutive days of dose (all three oral medications) or a single medication within the daily dose >2 consecutive times, they will be instructed to:

[1] This study will utilize the CRIC / CISO standard Daily Dose Diary form.

1. Record the missed medication(s) on the Daily Dose Diary
2. Contact the study team for instructions

4.5 CONCOMITANT MEDICATIONS

The following table shows potential drug interactions with lapatinib:

TABLE 12: POTENTIAL DRUG INTERACTIONS WITH LAPATINIB

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	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

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) aprepitant may require a concurrent dose reduction of 1-2 lapatinib tablets.
4. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact a NOVARTIS 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.

An additional list of medications can be found in Appendix I.

4.6 DURATION OF THERAPY

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator".

4.7 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Investigators, co-investigators, or clinical personnel associated with the study have the discression to withdraw participants from the whole study or portions of this study based on safety concerns that would add additional and untoward risks to the participant. Study participants may withdraw from the study. Participants who wish to withdraw consent must do so in writing. They may choose to continue follow-up and to have their data used for current and future projects. They may also choose to withdraw consent and to have any associated research data discarded. However, in the event of participant withdrawal of consent, any prior work done with their data will remain in the data set and will be unable to be removed. Participant withdrawal of consent will not affect any clinical data that have already been utilized in analysis.

4.8 DURATION OF FOLLOW-UP

Patients will be followed for one year after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. The follow-up period will consist of either two telephone calls and / or two clinic visits occurring at three month intervals.

5.0 STUDY PROCEDURES

A summary of required evaluations is presented on the following study calendar.

TABLE 13: STUDY VISIT SCHEDULE

Study Procedure	***Visit Schedule***					
	Screening [1]	***Each cycle*** [2]	***Every 2 cycles***	***Every 3 cycles***	***End of treatment***	***Follow Up***
Eligibility Review	X					
Informed Consent[3]	X					
Demographic Information	X					
Medical History	X					
Toxicity Assessment	X	X			X	
Performance Status	X	X			X	
Physical Examination	X	X			X	
CBC with differential	X	X[4]			X	
Electrolytes, BUN, Creatinine, Mg	X	X			X	
LFT (AST, ALT, alkaline phosphatase, bilirubin)	X	X[4]			X	

Study Procedure	*Visit Schedule*					
	Screening [1]	*Each cycle*[2]	*Every 2 cycles*	*Every 3 cycles*	*End of treatment*	*Follow Up*
Pregnancy test[5]	X	X			X	
Ejection Fraction (MUGA/Echo)[6]	X			X	X	
Imaging studies (CT/MRI)[7]	X		X		X	
Treatment (detailed in Section 4.1)		X	X	X		
Daily Dose Diary (Patient Completed)		X	X	X		
Death						X

[1]= Within 28 days before the first dose of study treatment.
[2]= Within 1 day of treatment.
[3]= Informed consent may be obtained >28 days before the first dose of study treatment but must have been signed before any study-specific screening procedures or evaluations are performed.
[4]= During cycle 1 CBC and LFT will be evaluated weekly.
[5]= For participants of childbearing potential. Test will be serum and / or blood (at the discression of the ordering physician).
[6]= The same method of assessment and radiographic center should be used throughout the study.
[7]= Imaging studies include a chest CT and contrast-enhanced CT or MRI of the abdomen and pelvis.

6.0 MEASUREMENT OF EFFECT

The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients will be reported. All eligible patients who begin treatment will be included in the analysis of response, survival and time-to-failure.

Response will be evaluated according to the RECIST criteria v1.1:

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥10 mm and 2x slice thickness on CT scan. Lymph nodes must be ≥15 mm in **short axis.** Bone lesions may be measurable if there is a lytic/soft tissue component that meets minimum size criteria. CXR lesions must be ≥20 mm.

Non-measurable lesions - all other lesions, including small lesions (i.e. longest diameter <10mm or pathologic lymph nodes with 10-15mm short axis) or lesions not conventionally measurable (i.e. leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed).

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

6.1 METHODS OF MEASUREMENT

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

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

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

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

6.1.1 BASELINE DOCUMENTATION OF "TARGET" AND "NON-TARGET" LESIONS

All measurable lesions up to a maximum of five lesions total (2 per organ), representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

Lymph node measurements should reflect the **short diameter.**

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

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

Non-measurable and non-target lesions are included in determination of progression if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician.

6.2 RESPONSE CRITERIA

6.2.1 EVALUATION OF TARGET LESIONS

TABLE 14: TARGET LESION EVALUATION TABLE

**** Complete Response (CR):***	Disappearance of all target lesions
**** Partial Response (PR):***	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
**** Progressive Disease (PD):***	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
**** Stable Disease (SD):***	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

6.2.2 EVALUATION OF NON-TARGET LESIONS

TABLE 15: NON-TARGET LESION EVALUATION TABLE

**** Complete Response (CR):***	Disappearance of all non-target lesions and normalization of tumor marker level
**** Incomplete Response / Stable Disease (SD):***	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
**** Progressive Disease (PD):***	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

6.2.3 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria:

TABLE 16: EVALUATION OF BEST OVERALL RESPONSE TABLE

Target lesions	***Non-Target lesions***	***New Lesions***	***Overall response***
CR	CR	No	CR

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

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

6.3 CONFIRMATION

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

6.3.1 DURATION OF OVERALL RESPONSE

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

6.3.2 DURATION OF STABLE DISEASE

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

6.3.3 PROGRESSION-FREE SURVIVAL

From the date of registration to date of first documentation of progression or symptomatic deterioration (as defined in above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

6.3.4 OVERALL SURVIVAL

From the date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

7.0 ADVERSE EVENTS

7.1 ADVERSE EVENT MONITORING

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Participants enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or death.

7.2 DEFINITIONS

7.2.1 DEFINITION OF ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 SEVERITY OF ADVERSE EVENTS

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:
Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 SERIOUS ADVERSE EVENTS

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

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

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

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

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

- after the patient has provided informed consent and until atleast 30 days after the patient has stopped study treatment/participation

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

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

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

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

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

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

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

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

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

Addition to SAE definition
Cardiovascular events have been seen in participants taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines, and interstitial pneumonitis has been reported in participants 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 relative to baseline which is below the institution's lower limit of normal. Refer to NCI CTCAE grading of left ventricular cardiac function.
- Any signs or symptoms of pneumonitis that are Grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen). Refer to NCI CTCAE grading of pneumonitis/pulmonary infiltrates.

Hepatobiliary events have been seen in participants 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) ***or*** ALT>3xULN and INR>1.5, if INR measured (INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants).

NOTE: bilirubin fractionation should be performed if testing is available. If testing is unavailable and a participant meets the criterion of total bilirubin >2.0 × ULN, then record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. The event should still be reported as an SAE.

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

7.3 STEPS TO DETERMINE IF AN ADVERSE EVENT REQUIRES EXPEDITED REPORTING

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely—The AE is *unlikely related* to the study treatment.
- Unrelated – The AE is *clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the Drug Information Section (section 4.0) of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.4 REPORTING REQUIREMENTS FOR ADVERSE EVENTS

7.4.1 EXPEDITED REPORTING

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- SAEs will be reported to NOVARTIS and the FDA within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
  - To facilitate submission, the Prinicipal Investigator can submit to NOVARTIS and FDA via the MedWatch Form 3500A to the FDA, which can be accessed at: http://www.accessdata.fda.gov/scripts/MedWatch/

- ***FDA Reporting***
  MedWatch forms will be sent to the FDA online at the above internet address or to the following:
  MEDWATCH
  5600 Fishers Lane
  Rockville, MD 20852-9787
  (F) - 1-800-FDA-0178 (1-800-332-0178)

- ***NOVARTIS Reporting***
  Fax: 877-778-9739

- The Institutional IRB must be notified of "any unanticipated problems involving risk to participants or others" in accordance with the Institutional policy. Such policies will be provided to the CISO QA prior to enrolling 1st patient. (for USC refer to HSPP Policies and Procedures chapter 14 available at http://www.usc.edu/admin/oprs/policies/hspp.html UPR/UPIRSO).

  The following events meet the definition of UPR:
  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to participants or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the participant or others.
  6. Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

- The USC NCCC Data and Safety Monitoring Committee (DSMC) must be notified within 24 hours of submission of such reportable event to the IRB. The patient ID and the study number as well as identifier of the SAE report should be submitted to the DSMC Coordinator via email or Fax to the attention of the DSMC Coordinator at 323-865-0089.

7.4.2 ROUTINE REPORTING

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission. For studies requiring USC DSMC review, this report should also be forwarded to the DSMC Coordinator.

8.0 DRUG INFORMATION

Patients who enroll in this study will follow the treatment and dosage schedule (Section 4.1). There are four study drugs – 3 are commercially available, 1 will be provided by the Sponsor.

8.1 STUDY DRUGS – COMMERCIALLY AVAILABLE

These drugs are commercially available and FDA approved for treatment of breast cancer.

8.1.1 CAPECITABINE (XELODA®)

Capecitabine is an oral prodrug of 5'-deoxy-5-fluorouridine (5'DFUR) that is converted to 5'fluorouracil (5-FU). 5-FU is metabolized to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) which cause cell injury in two ways. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bine to thymidylate synthase to form a covalently bound ternary complex which inhibits the formation of thymidylate from uracil. Thymidylate is essential for the synthesis of DNA so a deficiency inhibits cell division. Secondly, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate during RNA synthesis; this interferes with RNA processing and protein synthesis. Capecitabine is commercially available (Xeloda®) and supplied in 150mg (light peach colored) and 500mg (film coated) tablets. Additional guidance and information regarding the marketed product capecitabine (Xeloda) can be found in the current capecitabine product labeling information.

8.1.2 CYCLOPHOSPHAMIDE (CYTOXAN®)

Cyclophosphamide is an alkylating agent that is biotransformed principally in the liver to its primary active metabolite, phosphoramide mustard. Phosphoramide mustard forms inter-strand and intra-strand DNA crosslinks by covalently binding to N7 guanines, and also causes single-strand DNA breaks. Cyclophosphamide is commercially available (Cytoxan®) and supplied in 25mg and 50mg tablets. Additional guidance and information regarding the marketed product cyclophosphamide (Cytoxan®) can be found in the current cyclophosphamide product labeling information.

8.1.3 TRASTUZUMAB (HERCEPTIN®)

Trastuzumab is a HER2/neu receptor antagonist indicated for the treatment of HER2-overexpressing breast cancer. Trastuzumab is commercially available (Herceptin®) and provided as a sterile, white to pale yellow, preservative free lyophilized powder for intravenous (IV) administration. Each vial of trastuzumab contains 440mg of trastuzumab, 9.9mg of L-histidine HCl, 6.4mg of L-histidine, 400mg of α,α-trehalose dihidrate, and 1.8mg of polysorbate 20, USP. Reconstitution with 20ml of the supplied Bacteriostatic Water for Injection (BWFI) USP, containing 1.1% benzyl alcohol as a preservative, yields 21mL of a multidose solution containing 21mg/mL trastuzumab, at a pH of ~6. Additional guidance and information regarding the marketed product trastuzumab (Herceptin®) can be found in the current trastuzumab product labeling information.

8.2 STUDY DRUG – SPONSOR PROVIDED

This drug is being provided by the Sponsor, GlaxoSmithKline. This drug is also approved by the FDA for treatment of breast cancer.

8.2.1 LAPATINIB (TYKERB®)

Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both epidermal growth factor receptor (EGFR) and human epidermal receptor type 2 (HER2). Lapatinib is commercially available (Tykerb®) and provided as a 250mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. Each 250mg tablet of lapatinib contains 405mg of lapatinib ditosylate monohydrate, equivalent to 250mg lapatinib free base per tablet. Additional guidance and information regarding the marketed product lapatinib (Tykerb®) can be found in the current lapatinib product labeling information.

9.0 STATISTICAL CONSIDERATIONS

9.1 PATIENT ACCRUAL

The study will enroll a total of 40 patients with HER-2 positive metastatic breast cancer. We expect the study to be open to accrual for approximately 24 months.

9.2 STATISTICAL ANALYSES AND POWER CALCULATIONS FOR THE PRIMARY OBJECTIVES

9.2.1 STATISTICAL ANALYSIS FOR THE PRIMARY OBJECTIVE

In the reported literature, when capecitabine and lapatinib were used to treat patients with HER-2 positive metastatic breast cancer, a median PFS of 8.4 months was reported [23]. In our study, we propose a treatment regimen which adds well-tolerated metronomic cyclophosphamide and trastuzumab to capecitabine plus lapatinib, hence it is expected that this 4-drug regimen would result in a better PFS. One-sided one-sample logrank test will be used to evaluate the improvement in PFS compared to the reported historical PFS rate.

9.2.2 POWER OF THE STATISTICAL ANALYSIS FOR THE PRIMARY OBJECTIVE

In the calculation of power, the PFS function of HER-2 positive metastatic breast cancer patients treated with capecitabine and lapatinib was approximated using the Kaplan-Meier PFS curves shown in Figure 2A of the published literature[23]. From Figure 2A of that paper, patients with HER-2 positive breast cancer treated with capecitabine and lapatinib had a 0.5-year PFS of approximately 54% and a 1-year PFS of approximately 18%. The median PFS for those patients was 8.4 months.

As stated above, this study will be open to enrollment for approximately 2 years at a rate of 20 patients per year. A total of 40 patients will be enrolled. Given that most patients would progress within a year, the study will have one additional year for follow-up. The power for the comparison between PFS among this study cohort and that of the historical data was estimated for a detection of a difference in hazard ratio of 0.67, i.e., 1/3 decrease in hazard for disease progression. That corresponds to a PFS rate of approximately 66% at 0.5-year and 32% at 1-year in our patients, comparing to 54% and 18% at 0.5-year and 1-year in the historical data. With 10% type I error, a one-sided logrank test will have at least 80% power for detecting a hazard ratio of 0.67 with a sample size of 40 patients. This sample size and power are sufficient.

9.3 FUTILITY ANALYSIS

One futility analysis will be performed during the trial, after first 20 patients are enrolled, by testing the following at the level of 0.005:

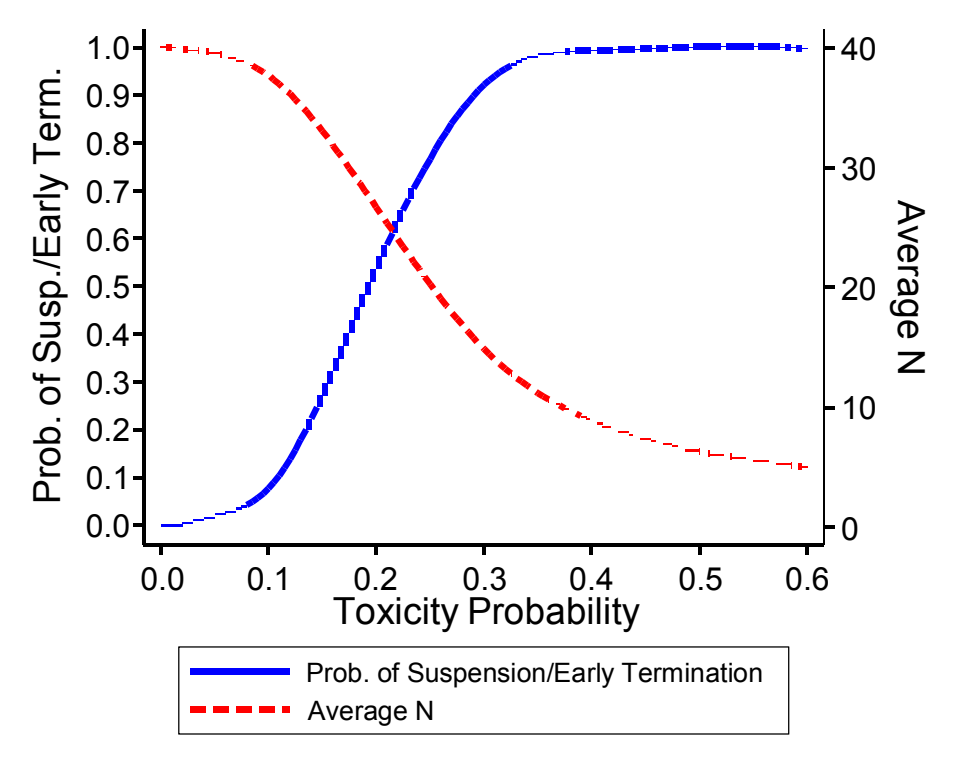
$$\frac{\ln(Haza\square\square d\ \square\square atio\ a\square\square\ 1}{\square\square\square\square\square\square\square\square\square) - \ln(0.67)}$$

$$\square\frac{1}{\#E\square\square\square\square\square}$$

In the formula, the number 0.67 is the Hazard Ratio for progression (compared to the historical data[23]) under the alternative hypothesis for the design of this trial. Based on the assumed model, at the end of the 1st year after the trial starts, approximately 6 events are expected to have occurred under the alternative hypothesis. With 6 events, it will be very unlikely to terminate the trial due to futility at the end of the 1st year.

9.4 INTERIM MONITORING OF TOXICITIES

Toxicities monitoring will be adopting a Bayesian approach. We assume that the number of patients experiencing unacceptable toxicities (as listed in Section 4.2.1) among patients who are enrolled follows a binomial distribution, and that the prior distribution of the probability of toxicity follows a uniform distribution. A safety analysis will be undertaken after an initial 6 patients are enrolled and have received at least 1 cycle of treatment. In addition, interim monitoring analysis of toxicities will be performed after every 3 occurrences of unacceptable toxicities that are listed in Section 4.2.1. At each interim analysis of toxicities, the posterior distribution of the probability for a patient to experience any unacceptable toxicity (p_{tox}) will be calculated. If it is >92.7% likely that $p_{tox} \geq 0.15$, the study will be suspended pending DSMC and study committee review. Otherwise the trial will continue as planned. A simulation study showed that using this toxicity monitoring rule, there will be 27% probability to suspend/terminate the trial if the true toxicity rate is 15%. The probability for suspending/terminating the trial is 53% if the true toxicity rate is 20%, and the probability is 80% if the true toxicity rate is 26%. Suspension/early termination probability is around 5% when the true toxicity rate is 8%. Expected sample size is 39, 34, 27, and 20, respectively, for the toxicity rate of 8%, 15%, 20% or 26%. Please refer to the figure below for the probability of suspension/termination and expected sample size for different toxicity rates.



9.5 MONITORING OF TOXIC DEATHS

There will not be a formal statistical rule for the monitoring of toxic deaths. However, for any occurrence of toxic deaths, we will immediately notify the Data Safety and Monitoring Committee (DSMC – see Section 10.7) of USC Norris Comprehensive Cancer Center and the study committee and it will be reviewed within 24 hours.

10.0 STUDY MANAGEMENT

10.1 CONFLICT OF INTEREST

All investigators will follow the University conflict of interest policy. Any USC investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must complete a "Statement of Outside Interests Related to Research" Form. The application is reviewed and approved by the Conflict of Interest Review Committee (CIRC) USC conflict of interest policy is available at http://ooc.usc.edu/conflict-interest-research

10.2 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL AND CONSENT PROCESS

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol and all study related documents used in the study (e.g. pill diary, brochure, advertisement etc).

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing a dated IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person authorized to obtain the informed consent

10.3 REGISTRATION PROCEDURES

For patients enrolled at USC, the Research Coordinator must complete the protocol eligibility form to ensure that the patient is eligible. The PI will review the patient eligibility (with assistance from the Research Coordinator- who will assemble the required source documents, and do an initial review) prior to registering the patient on study.

The Research Coordinator or data manager will then register the patient into the Cancer Center database, CAFÉ, by accessing the Registration forms. Likewise, after the patient has completed the study, the Off Study forms in cafe will need to be completed, for Off Treatment and Off Study.

10.4 RECORDS AND DATA SUBMISSION

A. Confidentiality of Records

The original data collection forms will be kept in secure file cabinets, for USC patients forms will be kept in the Clinical Investigations Support Office (CISO).

B. Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent with the Human Rights and the HIPAA authorization must be given to the patient. Institutional policy regarding distribution and location of original consent documents should be followed. When a study is opened at two or more institutions, a copy of the signed consent and HIPAA should be sent to USC CISO QA team as soon as possible, and not later than within 5 business days of obtaining consent. For patients consented at USC/LAC, institutional policy should be followed: a copy of ICF and HIPAA should be uploaded through True to USC CRO and to CISO QA Team. The original will be kept in the patient research chart maintained by the study assigned Data Manager.

C. Registration Eligibility Worksheet

At the time of registration, the completed Eligibility Worksheet will be submitted to the QA Monitor at CISO for review of eligibility compliance.

D. Data Collection Forms and Submission Schedule

Protocol data will be entered into eCRFs in CAFÉ.

Within two weeks of registration, the data manager will complete the initial set of On-Study forms and baseline Toxicities.

Within two weeks of completion of each course of treatment, the data manager must complete the Course Assessment, Toxicities, and if appropriate Response data.

- After Off Treatment, within two weeks of each follow up, complete the Follow Up forms.

10.5 DATA MANAGEMENT AND MONITORING / AUDITING

A. **Adherence to Protocol/Per Patient**: It is the responsibility of the USC Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at USC are all performed as specified in the protocol. When a study is opened at two or more institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

B. **Day-to-Day Monitoring – Eligibility:** At USC, the Study Coordinator will assist the Investigator in reviewing eligibility and will assemble the required source documents, and do a final review by completing an Eligibility Registration Worksheet. When a study is opened at two or more institutions, the PI at each institution will review the patient eligibility in accordance with that institution's policy.. For all institutions, the Eligibility Registration Worksheet with a copy of Informed Consent and supporting source documents will be submitted to CISO QA via email or Fax for verification prior to registering the patient on study.

C. **Day-to-Day Monitoring – Informed Consent:** Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. A copy of the ICF will also be provided to CISO QA for review. CISO SOP 3.3 will be followed.

D. **Day-to-Day Monitoring – Treatment:** The PI and co-investigators are responsible for ensuring that treatment is given per protocol. The Study Coordinator will review the treatment orders with the treating investigator. Regardless of who the treating physician is, there will be only one responsible Study Coordinator for each study at each of the hospitals affiliated with the USC Norris Cancer Center. The treating investigator will review the status of each patient on-study, with the Study Coordinator and treating physicians, on an on-going basis. When a study is opened at two or more institutions, CISO QA will periodically audit medical records for the participants on study at other institutions to ensure compliance and adherence to the protocol.

E. **Data Management – Patient Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, All written source documents not associated with the study research are maintained in the patient chart, which is stored in the Department of Medical Records at the appropriate hospital. At the Norris Hospital, the official medical record is the Electronic Patient File (EPF). Radiographical images are stored in the Department of Radiology and in an electronic system called Synapse. At Los Angeles County General Hospital the official medical record is called Affinity. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patients' hospital charts. It is the responsibility of the research staff to ensure that the patient chart contains the required documents and work closely with treating investigators to ensure all protocol-related assessments are carefully documented.

F. **Data Management – Research Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, to facilitate adherence to the protocol schedule and data management, research charts are created to collect copies of the relevant notes, orders and results, that are in the Patient Chart. In Addition, all source documents related to the research, such as original informed consent forms, HIPAA Forms, AE assessment worksheets, disease response worksheets and NTFs are maintained in the Research Charts. Protocol calendars, worksheets, and checklists, are also kept in the research chart. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site. It is the responsibility of the Data Manager to ensure that the research chart contains all the required documents.

G. **Data Management – Case Report Forms:** It is the responsibility of the Data Manager to complete the required case report forms. For in-house trials, case report forms are developed for each trial; these are used to finalize the data entry screens in the Cancer Center clinical trials database. It is the responsibility of the PI to review the Off-Study Summary form which summarizes pertinent toxicity, response and adherence information, once the patient has completed treatment.

10.6 QUALITY ASSURANCE MONITORING COMMITTEE (QAMC) OVERSIGHT

The Quality Assurance and Monitoring Committee (QAMC) of the NCCC has the responsibility for study auditing and monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual. QAMC procedures are detailed in the NCCC Data Safety and Monitoring Plan available on CISO Website.

10.6.1 QAMC ANNUAL PATIENT AUDITS

The QAMC is responsible for conducting audits and providing the initial review of the audits, for all open institutional (i.e. USC initiated), CCCP-sponsored trials, and any trials identified by the CIC. These trials are audited by the QAMC once a year. Faculty and staff at the Cancer Center involved in clinical research – but not directly involved in the research under evaluation – are asked to serve as auditors. Twenty percent of patients accrued during the past 12 months – and a minimum of 2 patients – are

selected at random; however, additional patients may be selected for audit if there is some indication that there might have been a problem or unusual circumstance (possibly related to compliance, toxicity, response or some indication of an irregularity). The audit involves a review of the research chart, hospital medical record (i.e., source documentation) and evaluates the following: documentation of eligibility (including failure to obtain appropriate informed consent) and baseline status of the patient; documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome. In addition, for investigative agents, a drug audit is also performed for these patients by the Research Pharmacist. In addition, for Institutional, Investigator Initiated Trials, Data in the CAFÉ database are compared to the information in the medical record.

10.6.2 QAMC ANNUAL PROTOCOL REVIEW

All open trials are reviewed at least once a year by the QAMC (or more often if stipulated by the CIC). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual; examination of gender and minority accrual; examination of all reported violations; review of past audits and correspondence with the PI; review of results of current audit (by an outside agency or by the NCCC QAMC); review of previous correspondence between the PI and the QAMC/DSMC. The QAMC review process is detailed in USC NCCC DSM Plan available on the CISO website.

10.7 DATA AND SAFETY MONITORING COMMITTEE (DSMC) OVERSIGHT

The Data and Safety Monitoring Committee (DSMC) is an independent body responsible for the safety of study participants through the review of new protocols to ensure an adequate adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials. DSMC procedures are detailed in USC NCCC DSM Plan available on the CISO website.

10.8 ADHERENCE TO THE PROTOCOL

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.8.1 EMERGENCY MODIFICATIONS

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

10.8.2 NON-EMERGENCY DEPARTURES FROM PROTOCOL

A protocol deviation is any variance from an IRB approved protocol.

If the deviation meets all of the following criteria, it is considered a minor protocol deviation that:

- Is generally noted or recognized only after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

If the deviation meets any of the following criteria, it is considered a protocol violation:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: All protocol violations will be entered in the clinical trial database by the Research Coordinator. In addition, Research Coordinator and Investigator should report all protocol violations within one (1) week of the knowledge of the event using iStar.

10.8.3 AMENDMENTS TO THE PROTOCOL

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB as well as to Novartis for review and for approval prior to implementation. It is the responsibility of the study PI to ensure that the appropriate agencies have been informed of the proposed amendments and that these have been reviewed and approved.

10.9 RECORD RETENTION

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.10 OBLIGATIONS OF THE INVESTIGATORS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDIX I: WORD LIST INHIBITORS INDUCERS

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