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PROTOCOL: An open label, pilot study of Veliparb (ABT-888) and Lapatinib (Tykerb) in patients with metastatic, triple negative (ER, PR, and HER-2 Negative) Breast Cancer

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Study documents included in this submission:

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COMPREHENSIVE CANCER CENTER
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UAB 1372: An Open Label, Pilot Study of Veliparib (ABT-888) and Lapatinib (Tykerb) in Patients with Metastatic, Triple Negative (ER, PR, and HER-2 Negative) Breast Cancer

Table of Contents:

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1.0 OBJECTIVES OF STUDY

1.1 Primary Objective

In patients with metastatic, estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER-2-Neu) negative breast cancer (called triple negative breast cancer or TNBC), we will:

- Characterize the safety profile and treatment tolerance of Veliparib (ABT-888) in combination with Lapatinib (Tykerb).

1.2 Secondary Objectives

In patients with metastatic TNBC, who will be treated with the combination of Veliparib and Lapatinib, we will:

- Estimate the objective response rate (ORR) (complete responses [CRs] plus partial responses [PRs]);
- Determine progression free survival (PFS);
- Correlate pre-treatment tumor gene expression profile, biomarkers of DNA repair (H2AX, BRCA localization), EGFR location and signaling, and apoptosis markers with the ORR and PFS;
- Correlate serial measures of circulating tumor cells (CTCs) and serum levels of M30 with the ORR and PFS.
- Determine the pharmacokinetics of Veliparib and Lapatinib when given in combination.

2.0 BACKGROUND AND RATIONALE

2.1 "Triple Negative" Breast Cancer Has a Poor Prognosis

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths in American women. Despite recent advances in breast cancer therapy, metastatic disease remains incurable. One of the reasons for the lack of cure has been the inability to select subsets of patients most likely to benefit from specific therapies.

The use of modern genomic techniques has significantly enhanced our understanding of breast cancer biology. Thus, five distinct breast cancer tumor subsets have been recognized, including hormone receptor (HR) positive luminal A and B, human epidermal growth receptor 2 (HER-2-Neu) positive, "normal"-like, and basal-like.[1,2] Basal-like breast cancer (BBC) is typically TNBC, often demonstrates overexpression of the epidermal growth factor receptor-1 (EGFR1), is positive for cytokeratins 5/6/17, and is typically high grade.[3-5] TNBC is a "special clinical interest" cancer because it represents a significant proportion of breast cancer patients (10-20%), has a very poor prognosis in a significant proportion of patients, and as yet, no targeted approach to therapy has been found.

Conforti and colleagues characterized the use of immunohistochemical analysis in the identification of BBC; in 800 breast cancer specimens from a single institution, triple-negative staining had positive and negative predictive values of 67% and 99%. This finding suggests that while not all TNBC are BBC, non-TNBC are almost never BBC.[6,7] Thus, BBC comprise the majority of the tumors that fit the triple negative phenotype. These cancers are more commonly found in African American women, particularly pre-menopausal, as well as in individuals who harbor a deleterious mutation in the BRCA1 gene.[8]

In addition, Pietenpol and her team have recently found that TNBC is a highly diverse group of cancers, and that subtyping may be necessary to better identify molecular-based therapies.[9] In her study, they analyzed gene expression profiles from 21 breast cancer data sets and identified 587 TNBC cases. Cluster analysis clearly identified 6 TNBC subtypes displaying unique gene expression and ontologies, including 2 basal-like (BL1 and BL2), an immune-modulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype. Further, genomic expression analysis allowed them to identify TNBC cell line models representative of these subtypes. Predicted "driver" signaling pathways were pharmacologically targeted in these cell line models as proof of concept that analysis of distinct gene expression signatures can inform therapy selection. Thus, if validated, these data may be useful in biomarker selection, drug discovery, and clinical trial design that will enable alignment of TNBC patients to appropriate targeted therapies.

Harris et al. retrospectively evaluated 474 patients with advanced breast cancer enrolled in the CALGB trial 9342 who received paclitaxel in three different schedules.[10] Of the 136 patients in this study for whom complete biomarker data were available, 44 patients had tumors that were triple negative. They found that the majority of these patients had overexpression of p53, and the majority of them were African-American. The response rate to chemotherapy observed in these patients was 26% (compared to 23% in other breast cancer subtypes), but the time to progression (TTP) was 2.8 months (compared to 4.5 months for other breast cancer subtypes), and the overall survival (OS) was 8.6 months (compared to 12.8 months for other breast cancer subtypes).

A similar retrospective analyses has been published including patients enrolled in different neoadjuvant clinical trials at the MDACC.[11] In this retrospective evaluation they found that 258 out of 1143 (23%) were triple negative. Interestingly, the TNBC patients had a higher pathological complete response (pCR) (25%) compared with other breast cancer subtypes (11%). However, the 5-year OS was lower for those patients with TNBC (66%) as compared with other subtypes of breast cancer (83%); clearly the best 5-year OS was observed in those patients that had a pCR. The authors concluded that triple negative expression constitutes an independent unfavorable prognostic factor with regard to overall survival unless achieving pCR after neo-adjuvant therapy.

Carey et al. retrospectively examined the relationship of neoadjuvant chemotherapy response to outcome among breast cancer subtypes.[12] They also found that triple negative tumors are more sensitive to anthracycline-based neoadjuvant chemotherapy than other types of breast cancers. Patients that had pCR to chemotherapy (27%) had a good prognosis regardless the subtype (including the triple negative subtype). However, the overall poorer prognosis of triple negative

was due to the higher likelihood of relapse (73%) in those patients in whom pathologic CR was not achieved.

Nam et al. from the National Cancer Center in Korea reported that women with TNBC have a higher risk of brain metastases than other breast cancer types.[13] The study included 805 patients with advanced breast cancer who were treated between 2001 and 2006. Patients with TNBC had the highest rate of brain metastases (37%), the lowest survival following brain metastasis, and the lowest OS.

Thus, given the lack of effective therapy (especially targeted therapy) in patients diagnosed with TNBC and the poor prognosis associated with it, new therapies for these patients are needed. As described, therapeutic strategies based on functional molecular abnormalities in tumor cells are warranted.

2.2 PARP Inhibition in Triple Negative Breast Cancer

Poly (ADP-ribose)-polymerase (PARP) is a nuclear enzyme that recognizes deoxyribonucleic acid (DNA) damage and facilitates DNA repair.[14, 15] Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP then poly (ADP-ribosyl)ates many nuclear target proteins, including those that facilitate DNA repair of both single-stranded or double-stranded DNA breaks. Thus, PARP inhibition will result in less efficient DNA repair following a DNA damage insult. DNA-damaging agents, chemotherapy and radiation therapy, remain as the main treatment for patients with cancer. Since cancer cells are genetically unstable, often exhibiting complex karyotypes (deletions, insertions, and unbalanced translocations of chromosomal fragment), these cells are more susceptible than normal tissues to cytotoxicity induced by DNA-damaging agents.[16] Of these, deficiencies in mismatch repair and homologous recombination are associated with the largest number of malignancies. These deficiencies render cells more dependent on PARP for DNA repair and, hence, are more prone to cytotoxicity induced by PARP inhibition.[17] In particular, tumor cells with BRCA1 or BRCA2 deficiencies are exquisitely sensitive to PARP inhibition, even in the absence of any other insults.[18, 19] Recently, a new class of compounds, the PARP inhibitors, has gained attention for their ability to induce synthetic lethality in BRCA-associated tumors. PARP inhibitors induce synthetic lethality by targeting homologous recombination (HR)-mediated DNA repair deficient tumors while maintaining minimal normal tissue toxicity.[20]

The proof-of-principle study was presented by Tutt and his team at the 2009 ASCO annual meeting; the study was a phase 2 single-arm study of Olaparib (a PARP inhibitor) in patients with metastatic breast cancer who also harbored a deleterious mutation in BRCA1 or BRCA2;[21] A total of 54 patients were included in the trial. The first 27 patients received olaparib on a continuous daily schedule at a dose of 400 mg twice daily. The second 27 patients received olaparib at 100 mg twice daily. The entire patient population included 33 patients with mutations in BRCA1, 20 patients with BRCA2 mutations, and 1 patient who had a mutation in both genes. More than half of the patients had triple-negative disease and had received a median of 3 prior chemotherapy regimens. The ORR was 41% among patients treated at 400 mg twice daily and 22% in the population treated with the lower dose. The median PFS in the cohort treated at 400 mg twice daily was 5.7 (range, 4.6-7.4) months. In general, the treatment was well tolerated, although side effects were somewhat more prominent in women treated with the higher dose. Although the higher dose appeared to be somewhat more active, a formal comparison is not possible in this small, nonrandomized experience. Interestingly, the extent of prior treatment did not influence the likelihood of obtaining a response.

However, this approach is only applicable to the 5-10% of all cancers with hereditary mutations in key proteins in the homologous recombination mediated DNA repair pathway. Thus, much effort has been undertaken to expand the utility of PARP inhibitors beyond the current realms of BRCA-associated tumors by combining with agents that alter the DNA damage/repair pathways. Specifically, in TNBC, which often demonstrates a "BRCAness" phenotype, PARP inhibitors showed initial promise when combined with DNA damaging chemotherapy (Iniparib in combination with gemcitabine and carboplatin) ,[22, 23] but ultimately failed to improve outcomes over chemotherapy alone in a randomized phase III clinical trial.[24] Thus, although the PARP inhibitor data looks promising in TNBC associated with BRCA mutations, new agents or combination of agents (especially targeting agents) or new combinations of agents are needed for all triple negative breast cancer patients in order to improve their prognosis.

2.3 EGFR Inhibition in Triple Negative Breast Cancer

The EGFR/HER family of transmembrane type I receptor tyrosine kinases are enzymes that play an important role in cell proliferation, differentiation and survival. These receptor tyrosine kinases, which include HER1 (epidermal growth factor receptor, EGFR), HER2 (HER2/neu, c-erbB2), HER3 and HER4 contain an extracellular domain and intracellular protein tyrosine kinase core. The ectodomain of HER1, HER3, and HER4 interacts with a specific set of ligands, whereas no natural ligand has been identified for HER2 which can be activated by heterodimerization with other ligand activated HER co-receptors. Upon ligand binding to the active domain of HER1, HER3, or HER4, these receptors preferentially recruit HER2 into a heterodimeric complex in which the HER2 kinase can modulate receptor internalization and prolong signal transduction. Upon dimerization, conformational changes lead to autophosphorylation and initiation of divergent signal transduction cascades.[25] The type I receptors signal through Ras/Raf/MAPK/ERK pathway, stimulating cell division.[26] Cell line evidence also suggests that the type I receptors modulate cell survival through activation of Akt/phosphoinositol 3-kinase (PI3-kinase) pathway.[27]

HER1 is expressed or over-expressed in many human solid tumors including breast cancer, and plays an important role in progression to invasion and metastases.[28] The HER1 tyrosine kinase is activated by binding of a variety of ligands to the external domain. In particular, HER1 overexpression is correlated with high metastatic rate, short survival time, and poor prognosis.[29] Autophosphorylation by the HER1 tyrosine kinase initiates a signaling cascade that feeds downstream cell cycle control machinery regulating cell proliferation, and these reactions are a major component in growth factor–induced proliferation of cancer cells.[28] EGFR is often overexpressed or amplified in 45-70% of TNBC and is associated with aggressive disease phenotype.[4, 30-32] For example, overexpression of EGFR is correlated with increased tumor size, lymph node involvement, and decreased survival in invasive breast cancers.[33]

Based on the preclinical observations described before, anti-EGFR therapies (monoclonal antibodies against the receptor or small molecules inhibiting tyrosine kinases) have been evaluated in patients with metastatic TNBC. However, targeted therapy against EGFR using the anti-EGFR monoclonal antibody cetuximab had limited activity as a single agent in TNBC or in combination with different chemotherapy agents. The first trial was a randomized phase II study of cetuximab as a single-agent and in combination with carboplatin; in this trial, Carey et al. found that EGFR targeting alone is insufficient in the majority of TNBC patients (response rate of 6%) and combination with carboplatin produced responses in fewer than 20% of metastatic TNBC patients. Pathway analysis in tumor biopsies found that after one week of treatment with cetuximab, the EGFR pathway was inhibited in

only 5 of 13 patients.[34] Another clinical trial evaluated again cetuximab but in combination with irinotecan and carboplatin; in this second randomized trial, O'Shaughnessy et al. observed a similar improvement in the response rate, but there were no improvement in PFS or OS.[35] Most recently, a third randomized phase II trial (BALI II Trial) evaluating the addition of cetuximab to cisplatin in patients with TNBC demonstrated a modest benefit in PFS but a non-significant response rate.[36]]

Additionally, trials evaluating EGFR tyrosine kinase inhibitors have been disappointing. As an example, Baselga et al. evaluated the antitumor activity of gefitinib (an oral nonpeptide anilinoquinazoline compound that inhibits the tyrosine kinase activity of EGFR) in patients with previously treated, advanced breast cancer.[37] Of 31 assessable patients, 12 (38.7%) had stable disease, including 3 (9.7%) with recurrent breast cancer that stabilized for 6 months. No complete or partial responses were observed. Sequential immunohistochemical studies in skin and tumor biopsies demonstrated complete inhibition of EGFR phosphorylation in both healthy and malignant tissues. The downstream consequences of receptor blockade were distinct in skin and tumor samples: while phosphorylation of mitogen-activated protein kinase was inhibited in both tissues, gefitinib treatment induced p27 and a decrease in Ki67 in skin but not in tumors. Furthermore, gefitinib did not inhibit the activated form of Akt in the tumors. This study demonstrated a good correlation between the degree of inhibition of EGFR in skin and in breast tumors. The lack of significant clinical activity of gefitinib is not due to lack of receptor inhibition in these tumors but rather to lack of EGFR dependence in the tested population Another example was a clinical trial in which erlotinib, an EGFR tyrosine kinase inhibitor, and bevacizumab were combined. In this trial, the combination was well-tolerated by metastatic breast cancer patients, but had limited survival benefit and EGFR expression levels were not indicative of response.[38]

Targeting EGFR is problematic due to many TNBC harboring RAS and PTEN (30%) mutations,[39, 40] which activate signaling downstream of EGFR. Alternatively, compensatory up-regulation of other receptor tyrosine kinases, such as HER2, could account for resistance to targeting EGFR.[41-43] **Together these studies demonstrate that targeting EGFR alone is problematic, thus necessitating new therapeutic approaches.**

2.4 EGFR and PARP inhibition in triple negative breast cancer

2.4.1 EGFR/HER2 Inhibition and DNA Repair

One important consideration of the EGFR signaling is its role in regulating the DNA damage response; this mechanism does not depend on wild-type p53 or ras status. In particular, the effects of EGFR inhibition on the DNA repair pathways have been shown to occur in tumor cells independent of p53 or ras status.[44-47] As shown in Figure 1a-c, EGFR/HER2 inhibition with lapatinib, the oral dual EGFR/HER2 tyrosine kinase inhibitor, attenuated homologous recombination (HR) repair in the TNBC cell lines MDA-MB231, MDA-MB468, and MDA-MB-453 as measured by radiation induced rad51 foci, a marker for HR repair.[48] Furthermore, our laboratory has found that the mechanism by which EGFR/HER2 inhibition with lapatinib attenuates DNA repair may be through altering protein-protein interactions between EGFR and BRCA1 (Figure 2a-b). Additionally, the nuclear localization of EGFR is reduced by lapatinib (Figure 3a-b).

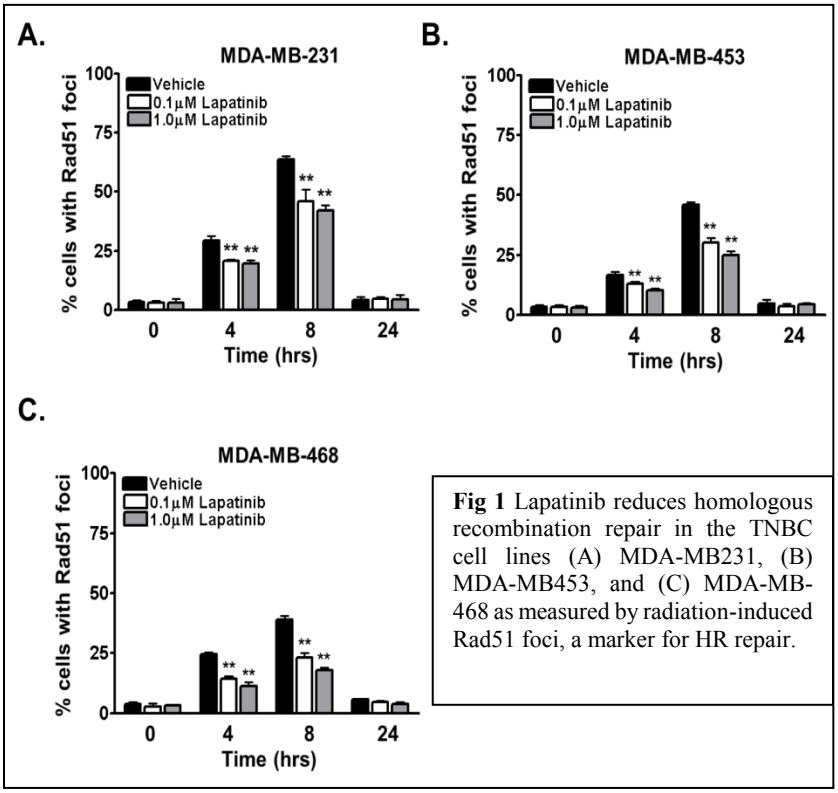

Fig 1 Lapatinib reduces homologous recombination repair in the TNBC cell lines (A) MDA-MB231, (B) MDA-MB453, and (C) MDA-MB-468 as measured by radiation-induced Rad51 foci, a marker for HR repair.

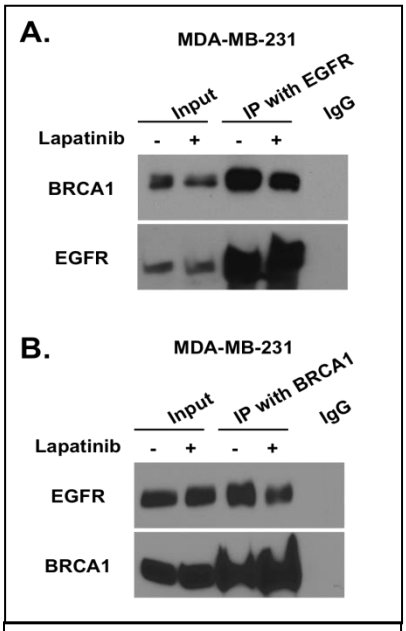

Fig 2 Lapatinib reduces EGFR-BRCA1 interaction in MDA-MB231 TNBC cells. (A) BRCA1 is found in immunoprecipitates with EGFR. (B) Reciprocally, EGFR is found in immunoprecipitates with BRCA1.

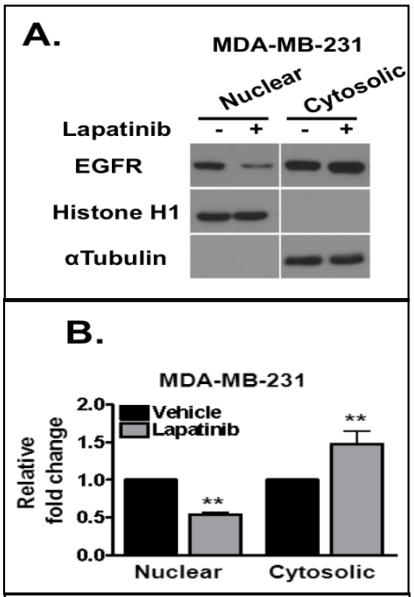

Fig 3 Lapatinib reduces nuclear EGFR while increasing cytosolic EGFR in MDA-MB231 TNBC cells. (A) sub-cellular fractionation (B) Quantification.

2.4.2 Induction of cytotoxicity by combining lapatinib and veliparib in triple negative breast cancer cell lines.

Importantly, because EGFR inhibition attenuated homologous recombination repair, we hypothesized that lapatinib could induce a synthetic lethal interaction with the PARP inhibitor veliparib, which targets HR defective cells. Indeed, we recently reported a contextual synthetic lethality in vitro with combined EGFR and PARP inhibition with lapatinib and veliparib, respectively, in multiple TNBC cell lines (Figure 4a-c and [46, 48]). The mechanism of cytotoxicity involves persistent DNA damage and activation of the intrinsic pathway of apoptosis (Figure 5a-b). Further dissection of the mechanism reveals that EGFR and BRCA1 can be found in the same protein complex, which is reduced by lapatinib (Figure 2 a-b). Interestingly, lapatinib also increases cytosolic BRCA1 and EGFR, away from their nuclear DNA repair substrates (Figure 3a-b, and data not shown[48]). These results were observed in triple negative breast cancers that possessed p53, ras, PI3K, or PTEN mutations. Taken together, these results reveal a novel regulation of homologous recombination repair involving EGFR and BRCA1 interaction and alteration of subcellular localization. Additionally, a contextual synthetic lethality may exist between combined EGFR and PARP inhibition that can be investigated in TNBC patients.

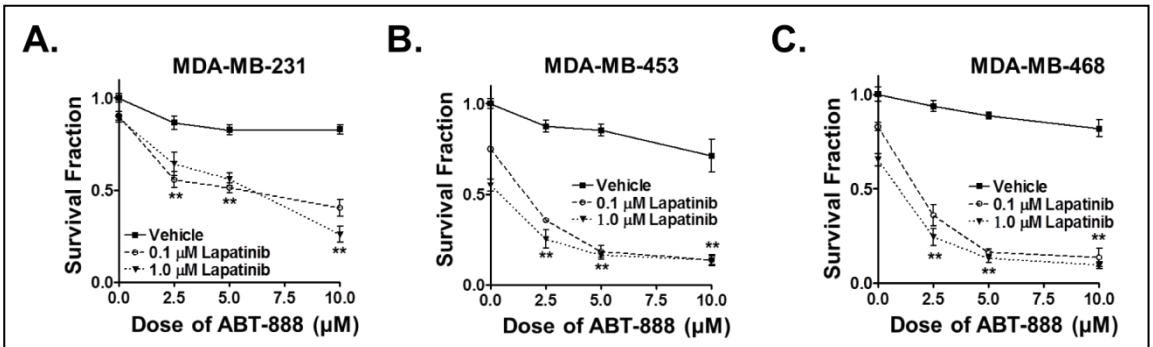

Fig 4. Lapatinib induces synthetic lethality in TNBC cell lines (A) MDA-MB231, (B) MDA-MB453, and (C) MDA-MB-468 as measured by colony formation assays

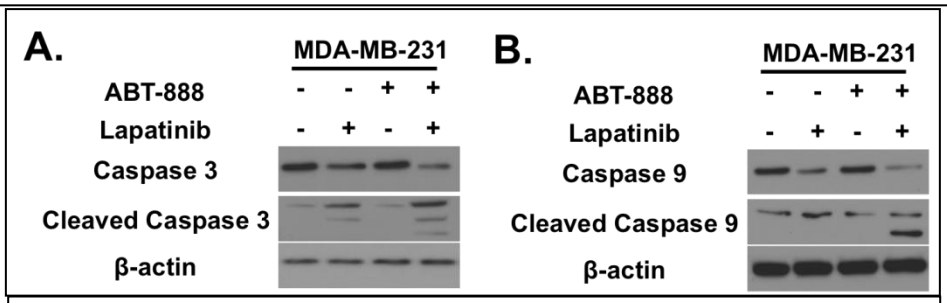

Fig 5. Combination lapatinib and veliparib induces apoptosis in the TNBC cell line MDA-MB231 as measured by cleaved (A) caspase 3 or (B) caspase 9

2.4.3 *In vivo* anti-tumor efficacy of combining EGFR and PARP inhibition (lapatinib/veliparib) in orthotopic breast cancer xenografts

To further validate our intriguing results in vivo, we tested the combination of lapatinib and veliparib in mice bearing orthotopic xenografts of TNBC cell line MDA-MB231 cells. As shown in Figure 6, a significant tumor growth delay was observed in combination treated mice versus no response in mice given either agent alone.

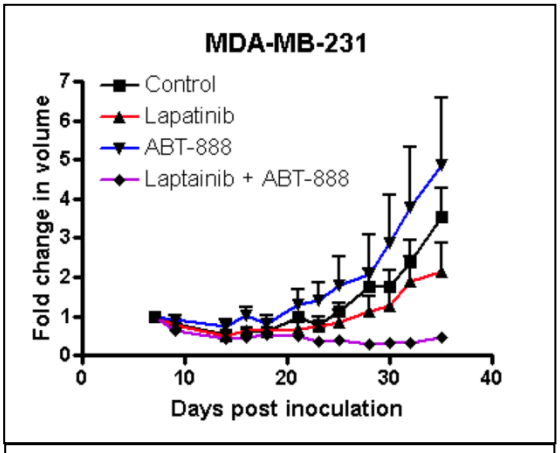

Fig 6. Combination lapatinib and veliparib induces synthetic lethality in orthotopic MDA-MB-231 xenografts

2.4.4 DNA damage and repair proteins may be a putative biomarker for sensitivity to combination EGFR/PARP inhibition.

Recent evidence suggests that nuclear EGFR participates in development of resistance to cancer therapeutics, like gefitinb,[49] radiation[50] and even cetuximab.[51] The first link between nuclear EGFR and cancer was proposed in 1994, two independent studies demonstrated that nuclear EGFR was significantly associated with tumor grade, mitotic frequency, and proliferation.[52, 53] Breast cancer patients with elevated nuclear EGFR were found to have decreased overall survival[54] and also related to tumor size, lymph node involvement, and Nottingham prognostic index.[33] Our laboratory has recently reported that EGFR inhibition, and subsequent reduction in EGFR phosphorylation, decreases EGFR nuclear fraction while simultaneous increasing cytosolic fraction. Interestingly, we also observed reduced BRCA1 nuclear localization following Lapatinib. Thus, we believe assessing EGFR and BRCA1 staining and subcellular localization may be a biomarker for sensitivity to response to combination lapatinib/veliparib. Additionally, as combining EGFR and PARP inhibition resulted in persistent DNA double strand break damage, we can be readily measure by immunofluorescence persistent □-H2AX foci, a well-characterized marker for DNA double strand breaks, as another marker to correlate with response.

2.4.5 Summary of EGFR and PARP inhibition

Based on these exciting preclinical results showing induced synthetic lethal interactions between EGFR and PARP inhibition with lapatinib and veliparib, respectively, in human triple negative breast cancer, we propose to evaluate the combination of lapatinib and veliparib in patients with metastatic TNBC who have failed no more than 2 chemotherapy regimens in an open label, pilot study. The trial will evaluate the safety and efficacy of the combination of (Lapatinib and Veliparib).

2.5 Veliparib

Veliparib Pre-Clinical Data Veliparib (ABT-888) is a novel, orally bioavailable, small molecule that is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutic agents.[14, 15, 55] Veliparib increases sensitivity of tumor cells to DNA-damaging agents in vitro and in vivo and inhibits PARP in murine tumors in vivo and human peripheral blood mononuclear cells and human tumors ex vivo. Veliparib inhibits both, PARP-1 and PARP-2. *In vitro*, veliparib increases sensitivity of tumor cells to DNA-damaging agents including chemotherapy agents (such as TMZ, irinotecan, cyclophosphamide, BCNU, cisplatin, and carboplatin), and radiation therapy. In addition, the combination of veliparib and chemotherapy agents (such as TMZ, carboplatin, paclitaxel) has demonstrated significant efficacy in a variety of preclinical tumor models, including settings where chemotherapy alone is ineffective and in both BRCA1- or BRCA2-competent and BRCA1- or BRCA2-mutated backgrounds.

Veliparib Pharmacokinetics In rats and dogs, veliparib is primarily cleared in the urine as intact parent drug, with a small fraction of clearance from metabolism.[55] The renal clearance and minimal metabolism observed in rats and dogs and the minimal metabolism observed *in vitro* in all species evaluated are consistent with the low molecular weight and good solubility of veliparib.[55]

Preliminary clinical pharmacokinetic (PK) data available from 6 human studies indicate that exposure of veliparib is approximately dose-proportional over 10 through 150 mg BID dose range.[55] The absorption of veliparib after oral dosing is relatively fast where veliparib plasma concentrations peak at approximately 1 to 2 hours after dosing across dose levels. The terminal half-life of veliparib is about 6 hours, with minimal accumulation following multiple BID dosing. Food does not have a significant effect on veliparib bioavailability. The mean total urinary recovery of veliparib is 86%, which indicates that renal excretion is an important pathway in veliparib elimination. Potential drug-drug interactions (DDI) of veliparib are being evaluated in veliparib combination studies. Veliparib is not a potent inhibitor, nor an inducer, of the major human cytochrome P450s (CYPs), suggesting a minimal potential for DDIs at the anticipated therapeutic concentrations. A Phase 0 Study A10-161 of Veliparib in patients with advanced cancer demonstrated that Veliparib is orally bioavailable and primarily cleared through renal excretion, with a half-life of 4 to 5 hours.[56] Substantial inhibition of PARP activity (>90%) was observed in tumor biopsies collected 3 to 6 hours after dosing with either 25 mg or 50 mg of veliparib. Complete inhibition of PARP activity in PBMCs, maintained through 24 hours after dosing, was achieved in 3 of the patients who received 50 mg veliparib. Interestingly, no serious adverse events, dose-limiting toxicities, or deaths were reported for this study.[56]

Veliparib Toxicology The toxicological profile of veliparib has been characterized in animal models (6 and 9 months duration in rats and dogs respectively), in genotoxic studies and in embryo-fetal development studies.[55] The primary target organs of veliparib are the central nervous system (convulsions and other CNS-related signs), the hematologic system (decreased red and white blood cells), the bone marrow (hypocellularity), the lymphoid tissues (lymphocyte depletion), and the male (germ cell depletion) and the female (corpora lutea decrease and minimal degeneration of granulosa cells in follicles) reproductive tissues, with lesser effects on the cardiovascular system (10% QTc prolongation) and the gastrointestinal tract (single cell necrosis). Convulsions and other CNS-related signs were considered exposure-dependent and were generally self-limiting, ameliorated by dose reduction or cessation of dosing, or respondent to treatment. All other findings were dose-dependent and reversible upon discontinuation of veliparib administration. Veliparib was genotoxic (induced chromosomal aberrations in vitro and increased micronuclei formation in vivo) and was toxic to the

developing fetus (increased incidence of fetal, visceral, skeletal malformations and/or variations). Veliparib also absorbs ultraviolet light and is distributed to both the skin and the eyes following systemic exposure, which poses a potential photo-toxicity risk.[55]

Veliparib Safety Multiple clinical studies have been conducted at this time using Veliparib as a single agent and in combination with chemotherapy and radiation therapy; safety profile has been defined in these studies.[55] At present, there have been more than 800 patients exposed to Veliparib. From the single agent studies conducted in patients with cancer, the most common reported side effects with veliparib as a single agent were: nausea, fatigue, anemia, lymphopenia, hyperglycemia, diarrhea, decrease appetite and headache. As described before, in the Phase 0 Study A10-161 of Veliparib in patients with advanced cancer no serious adverse events, dose-limiting toxicities, or deaths were reported for this study.34 In the Phase 1 Study M10-128, patients received Veliparib (10 to 300 mg) in combination with whole-brain radiation therapy; again, Veliparib was well tolerated and the most commonly reported adverse events were fatigue, headache, and nausea.[56]

Safety data is also available using the combination of Veliparib and chemotherapy regimens including TMZ as a single agent, carboplatin and paclitaxel, and FOLFIRI.[55, 57] Study M06-862 was a dose-escalating phase I trial of Veliparib in combination with TMZ; doses ranged from 10 mg veliparib BID/150 mg/m2 TMZ once daily to 80 mg veliparib BID/200 mg/m2 TMZ once daily; in addition to neutropenia and thrombocytopenia, the other most commonly reported adverse events were nausea, fatigue, vomiting, constipation, decreased appetite, and headache. A follow-up trial, study M10-440, was conducted; this trial was a Phase 2 randomized, double-blind, placebo-controlled study of veliparib (20 or 40 mg BID) in combination with TMZ and showed that the most common treatment-emergent adverse events were nausea, fatigue, constipation, thrombocytopenia, and vomiting. In the Phase 1 Study M11-070, a trial that evaluated subjects with metastatic castration-resistant prostate cancer treated with veliparib in combination with TMZ, the most frequent secondary effects were fatigue, nausea, platelet thrombocytopenia, and constipation. In the Phase 1 dose-escalation Study M10-758, veliparib, starting at a dose of 30 mg twice a day, was administered in combination with carboplatin/gemcitabine; the most commonly reported adverse events were thrombocytopenia, anemia, nausea, neutropenia, constipation, fatigue, and headache. In the Phase 1 Study M10-977, subjects with advanced solid tumors were treated with veliparib in combination with FOLFIRI; the most common treatment-emergent adverse events were diarrhea, nausea, fatigue, alopecia, vomiting, and constipation. In the Phase 1/2 Study M10-190, veliparib was administered in combination with radiation therapy with concurrent and adjuvant TMZ; the most commonly reported adverse events were fatigue, thrombocytopenia, nausea, headache, and insomnia. Lastly, in the Phase 1 Study M11-846, a trial evaluating the bioavailability and food effect of 3 formulations of veliparib on pharmacokinetics in subjects with solid tumors, the most common secondary effects were anemia, fatigue, dyspnea, abdominal distension, constipation, diarrhea, nausea, pain, and cough.

Thus, Veliparib has been well tolerated as a single agent and in combination with chemotherapy and radiation therapy; interestingly, Veliparib does not add additional toxicity to the one seen with chemotherapy or radiation therapy.

Veliparib Activity in Breast Cancer The therapeutic potential of PARP inhibitors in breast cancer was suggested by two clinical trials. In the first trial, patients with metastatic breast cancer were treated with Veliparib and TMZ; an ORR of 50% was seen in patients with BRCA1/2 mutations.[57] Interestingly, a single-arm trial evaluating a different PARP inhibitor (Olaparib) in metastatic breast cancer patients with BRCA1/2 mutations demonstrated single-agent activity, with an ORR of 38% in heavily pretreated patients.[58] A similar trial in BRCA1/2 mutation carriers with metastatic ovarian

cancer showed a response rate of 33%.38 Notably, both single-agent studies demonstrated increased response rates with higher doses of PARP inhibitor (olaparib 100 mg BID and 400 mg BID), where both doses are considered biologically active. Together, these results validate the proof of concept that PARP inhibition is an attractive therapeutic target in breast and other cancers. In the ongoing Phase 2 trial in metastatic breast cancer, a 50% CBR (14/28; 1 CR, 6 PR, 7 SD) has occurred to date in patients with deleterious BRCA mutations; this is in contrast to historical clinical data that suggest that TMZ monotherapy has low activity in breast cancer (two Phase 2 studies with a dose-dense TMZ regimen demonstrated no responses in patients with metastatic breast cancer and 2 responses (2/51) in patients with brain metastases from histologically confirmed breast cancer[59, 60]).

2.6 Lapatinib

Lapatinib Pre-Clinical Data Lapatinib (Tykerb, GW572016) is an orally active dual HER1/HER2 kinase inhibitor that blocks signal transduction pathways.[61] This dual inhibition is an attractive therapeutic strategy for epithelial cancers, as ligand-induced HER1/HER2 dimerization triggers off potent proliferative and survival signals. In vitro studies with Lapatinib have shown marked activity, leading to growth arrest and apoptosis in HER1 and HER2 overexpressing cell lines. Lapatinib markedly reduced tyrosine phosphorylation of HER1 and HER2; in addition, lapatinib also reduced the activation of MAP kinase and Akt, the downstream effectors of proliferation and survival, respectively.[61] Lapatinib has demonstrated activity against human breast cancer xenografts in animal models.[62-64]

Lapatinib Toxicology A range of toxicology studies has been conducted to support the oral administration of lapatinib to humans.[65] Repeat oral dose toxicity studies have been completed in rats and dogs for up to 6 and 9 months, respectively. The effects of lapatinib on fertility in the rat and embryo-fetal development in the rat and rabbit have been investigated. A range of genetic toxicity studies has been performed in vitro and in vivo. The significant findings from the toxicology studies are summarized below.

Following single oral administration, lapatinib was well-tolerated by both CD-1 mice and Wistar Han rats at doses up to 2000 mg/kg.[65] Treatment-related findings consisted of reversible changes in body weight and body weight gain as well as reversible GI effects. A 13-week oral dose ranging pilot carcinogenicity study in mice showed that treatment with lapatinib at doses up to 200 mg/kg/day was generally well tolerated. Microscopic changes attributable to treatment with lapatinib were noted in the liver and preputial gland of males and large intestines (cecum and colon) of males and females.

Administration of lapatinib to rats and dogs for up to 6 months or 9 months resulted primarily in exaggerated pharmacologic effects and organ toxicities generally associated with degenerative and/or inflammatory epithelial changes (GI tract and accessory digestive organs, skin, mammary gland, liver and prostate).[65] Other treatment-related effects included clinical signs, decreased body weight and food consumption, organ weight changes and alterations in clinical pathology parameters. Following the recovery period, treatment-related changes were either significantly improved or completely reversed. There were no effects on male or female rat gonadal function, mating, fertility or pregnancy nor were there any increases in the number or incidence of any malformations when rats or rabbits were given lapatinib during the period of major organogenesis. At maternally toxic doses (□60 mg/kg/day in rats and rabbits), lapatinib treatment was associated with growth retardation and developmental variations. In genetic toxicity studies, lapatinib was demonstrated to be non-mutagenic and nonclastogenic.

Lapatinib Pharmacokinetics The pharmacokinetics of lapatinib are similar in healthy volunteers and patients, demonstrating oral absorption that is incomplete, highly variable, and sometimes delayed.[65] After dosing, plasma concentrations rise to a peak at approximately 4 h and thereafter decline with measured half-lives averaging up to 14 h. However, accumulation with daily dosing achieves steady state in 6-7 days, which suggests a true elimination half-life on the order of 24 h. Administration of the same daily dose in a BID schedule results in 2-fold greater systemic exposure than a QD schedule. Despite this inconsistency, systemic exposure generally increases with increasing dose. Absorption is increased by ingestion with food. Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with negligible renal excretion. Significant changes in systemic exposure to lapatinib result from co-administration of drugs that are potent inhibitors or inducers of CYP3A.

Lapatinib Safety Safety results from Phase I monotherapy studies in cancer patients indicate that lapatinib administered on a QD schedule was generally well tolerated at doses of lapatinib ranging from 175 mg to 1800 mg QD. Doses of 500 and 750 BID were better tolerated than 900 mg BID.[65] The majority of AEs were Grade 1 or 2 gastrointestinal and/or skin toxicities. The incidence of diarrhea increased with increasing dose, whereas the incidence of rash was not related to dose. The Phase II/Phase III program had enrolled a total of 1581 subjects. Of these, 1001 subjects were enrolled in Phase II monotherapy studies. Data suggest that lapatinib administered as monotherapy at doses of 1250 mg QD, 1500 mg QD, and 500 mg BID is generally well tolerated. For the completed and ongoing Phase II and Phase III studies, the preliminary safety data was similar to what has been observed in the Phase I monotherapy studies and combination studies. The most common AEs considered related by the investigator were gastrointestinal (diarrhea, nausea, vomiting), rash, fatigue, and anorexia. The majority of all AEs were Grade 1 and Grade 2.

SAE data from ongoing lapatinib studies (all phases) are from 2312 subjects treated with lapatinib.[65] For the ongoing studies, a total of 831 SAEs were reported from 405 individual subjects. The most frequently reported SAE was diarrhea, with a total of 47 reports, 37 of which were assessed as related to investigational product. Dyspnea, vomiting, dehydration, and nausea were also among the most frequently reported SAEs regardless of relatedness. Overall, 24.6% of the SAEs reported were assessed as related to investigational product by the investigator. The most frequently reported drug-related events were: diarrhea, neutropenia, vomiting, nausea, dehydration, and decreased ejection fraction. Diarrhea which may lead to dehydration, nausea, and vomiting are all included in the development core safety information for lapatinib. Interstitial pneumonitis and two cases of interstitial pneumonia have been reported in the lapatinib program. Subjects on the lapatinib program have experienced a decrease in LVEF, giving an approximate incidence for this event of 1.4%.

Lapatinib Activity in Breast Cancer In clinical trials, lapatinib has demonstrated activity in heavily pre-treated women with trastuzumab- and chemotherapy-resistant breast cancer.[66, 67] In the first-line setting, lapatinib appears to have substantial activity in women with HER2-positive breast cancer, based on an ongoing phase 2 study.[68] Results from this study indicate an objective response rate of approximately 30% in patients not previously treated with chemotherapy for metastatic disease.

A pivotal study, comparing the efficacy of capecitabine with or without lapatinib, randomized patients with metastatic breast cancer to receive either lapatinib in combination with capecitabine or single agent capecitabine.[69, 70] All patients had metastatic disease that had progressed following treatment with an anthracycline, a taxane, and a trastuzumab-containing regimen. Time to progression in patients receiving the combination of lapatinib and capecitabine was nearly double

that of patients receiving capecitabine alone. The combination arm showed a median time to disease progression of 8.5 months, compared with 4.5 months for those treated with single-agent capecitabine. Moreover, fewer patients in the combination arm had disease recurrence in the brain. Side effects associated with lapatinib were found to be relatively minimal, with the most frequently reported toxicities being mild-moderate diarrhea and hand and foot syndrome. Given the theoretical risk of cardiotoxicity in patients receiving HER2-targeted therapy, all patients were closely monitored for the development of cardiac events. Of the 161 patients in the combination arm, four developed minor heart problems that reversed upon lapatinib discontinuation. No patients were withdrawn from study due to cardiotoxicity.[70]

2.7 Rationale

TNBC represents a significant proportion of breast cancer patients, has poor prognosis in a considerable number of patients and, no targeted approach to therapy is available at this time. The luminal breast cancer type category derive major clinical benefit from agents target ER; this therapy improved cure rates in the adjuvant setting and prolonged disease control in the metastatic setting. Similarly, the HER-2-neu category have had substantial clinical benefit from targeting the HER-2 receptor plus chemotherapy including dramatic reduction in disease recurrence rate in the adjuvant setting and enhanced response rate and duration of response in the metastatic setting. Thus, new targeting agents in TNBC are needed!

As presented in the background, there is **strong provocative preclinical data** demonstrating the activity of the combination of an EGFR inhibitor (lapatinib) and a PARP inhibitor (veliparib) in basal-like breast cancer. These preclinical data provide a strong rationale for the testing of this combination in patients with metastatic or recurrent triple negative breast cancer in whom taxane and anthracycline therapy has failed.

In addition, the clinical data supports the hypothesis that the combination of lapatinib plus veliparib will be safe and have efficacy in patients with metastatic triple negative breast cancer. Because there is no suggestion in the published literature that the toxicities of the two targeted agents will overlap, the known active and non-toxic doses of both agents will be used. For lapatinib, the dose was chosen at 1250 mg daily as this is the current recommended dose used for breast cancer in combination with capecitabine.[69] We believe that combining this dose of lapatinib with veliparib will be better tolerated than capecitabine. The data obtained in this pilot study will be used to design a phase II clinical trial that will be conducted by the Translational Breast Cancer Research Consortium.
The dose of veliparib at 200 mg BID is based on our preclinical studies where veliparib was given 100mg/kg twice a day orally with lapatinib 30mg/kg twice a day orally. No toxicity was observed in mice with this combination, and per AbbVie Oncology, the 100mg/kg twice a day dose is equivalent to the 200mg PO twice a day dose in humans. Single agent dosing of veliparib is currently at 400mg BID. Additionally, the 200mg twice a day dose is well tolerated in combination with radiotherapy concurrently.[56] Importantly, we have built in this trial a cohort with lower doses of both agents if toxicity is observed in the initial cohort using the standard doses described above.

3.0 STUDY DESIGN (Table 1 and Figure 7)

The study is an open-label, single arm, single institution, pilot clinical trial of Veliparib (a PARP inhibitor) in combination with Lapatinib (an EGFR inhibitor) in patients with pathologically confirmed TNBC (ER negative, PR negative, HER-2-Neu negative by IHC [0, 1] or FISH) who have not received prior therapy in the metastatic setting (but failed anthracyclines and taxanes in the

neoadjuvant or adjuvant setting) or who have failed prior chemotherapy in the metastatic setting (including anthracyclines and taxanes and no more than two prior regimens for metastatic disease as long as patients have adequate performance status – see Appendix B). The data obtained in this pilot study will be used to design a phase II clinical trial that will be conducted by the Translation Breast Cancer Research Consortium.

As described in **Figure 7,** patients will receive Lapatinib (1250 mg PO daily continuously) in combination with Veliparib (200 mg PO every 12 hours continuously). A cycle of therapy is defined as 28 days of PO therapy. Lapatinib will start Day 1 cycle 1 and Veliparib will start on Day 2 Cycle 1 (for better understanding of the PK of the drugs as well as to induce a DSB repair defect first with Lapatinib). Dose reductions of Lapatinib and Veliparib will be allowed. Patients developing grade 1 and 2 toxicities will be permitted to take a drug holiday of up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drugs may be resumed at the same level. In the event of recurrent toxicity, there will be two dose reductions permitted (dose reduction minus one will be Lapatinib 1000 mg PO daily continuously and Veliparib 150 mg PO every 12 hours continuously); dose reduction minus two will be Lapatinib 750 mg PO daily and Veliparib 100 mg PO every 12 hours continuously. If the adverse event recurs after dose reduction two, the patient will be taken off the study. Patients developing grade 3 and 4 toxicities will be interrupted for up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drugs may be resumed at a reduced dose (Lapatinib 1000 mg PO daily continuously and Veliparib 150 mg PO every 12 hours continuously). If the adverse event recurs, the patient will be taken off the study.

The primary endpoint of the trial is safety of the combination of Lapatinib and Veliparib. Objective response rate (ORR) and progression free survival (PFS) will be secondary endpoint. Patients will be evaluated for response every 2 cycles (8 weeks) using the RECIST 1.1 criteria (see Appendix D); patients with stable disease, PR or CR may continue therapy until disease progression or intolerance to the combination. Patients with progressive disease (PD) at any time will go off the study. The total enrollment goal is 20 patients; patients will be enrolled in a single site (University of Alabama at Birmingham) over a projected 12-18 months accrual interval. A biopsy of an accessible metastatic lesion will be obtained in appropriate patients (see inclusion criteria). Tissue obtained in this trial will be analyzed for global gene array analysis or other comprehensive genomic analysis ("Next-Gen" genomic analysis) at UAB and HudsonAlpha Institute for Biotechnology, and immunohistochemistry (ER, PR, HER2, Ki67), biomarkers of DNA repair such as H2AX and BRCA localization, EGFR location and signaling, and apoptosis markers; data obtained from the biopsies will be correlated with ORR and PFS. Plasma DNA and serum levels of M30 will be obtained and correlated with the efficacy data. Adverse events (toxicity) will be assessed continuously while the patient is in active therapy with appropriate adjustments of Lapatinib and Veliparib doses as described above. The protocol will be approved by the UAB Institutional Review Board (IRB).

Figure 7: Treatment Plan

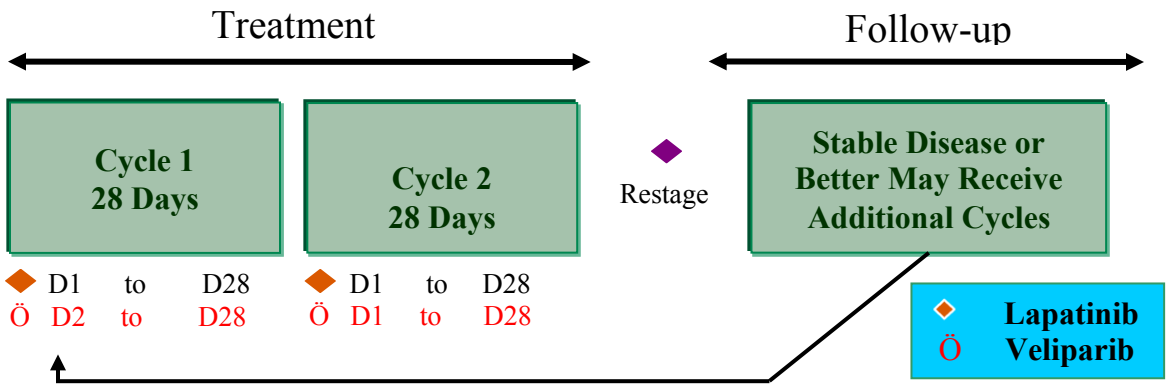

Table 1

Pre-study Evaluation (Section 4)	Therapy (Section 6)	Follow-up
Eligibility • Pathologically confirmed ER/PR negative, HER-2-Neu negative (by IHC [0,1] or FISH) breast carcinoma – metastatic stage • Measurable disease by RECIST 1.1 criteria (see Appendix D) • Patients who have not been treated for metastatic disease or who have progressed on chemotherapy regimens in the metastatic setting are eligible • Prior use of anthracyclines and taxanes in the adjuvant/neoadjuvant settings or metastatic disease is required. • Adequate organ function • PS: ECOG 0-2 (see Appendix B) • Life expectancy > than 12 weeks • At least 19 years of age • Biopsy of metastatic lesion is mandatory, if appropriate	**Lapatinib:** 1250 mg PO daily continuously in combination with **Veliparib:** 200 mg PO twice a day continuously. Veliparib starts Day 2 Cycle 1 A cycle is defined as a 28 day period. Initial evaluation for response will occur after 2 cycles of therapy; patients with stable disease, PR or CR may continue until disease progression or intolerance to the combination. Re-evaluation of tumor status (response) will occur every 2 cycles of therapy. Patients with PD at any time will be taken off study.	• Assessment of response every 2 cycles (clinical and imaging). • Standard therapy toxicity monitoring. • Lapatinib and Veliparib pharmacokinetics.

This trial includes a continuous assessment stopping rule in order to have a high probably of stopping early if the toxicity rate is unacceptably high, say 60%, while having low probability of stopping early if the toxicity rate is acceptable, say 30%. This rule is based on a Pocock-type boundary as described by Ivanova et al (Anastasia Ivanova, Bahjat F. Qaqish, and Michael J. Schell. Continuous Toxicity Monitoring in Phase II Trials in Oncology. Biometrics 61, 540–545, 2005). This stopping rule is considered a guideline with the final decision of termination of the study to be made by the data safety committee

Table 2: Minimum number of toxicities (X) required to consider stopping the study after N subjects, for 20 patients

X	3	4	4	5	5	6	6	7	7	7	8	8	9	9	9	10	10	11
N	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

This rule will provide a probability of 0.10 of stopping early if the true toxicity rate is 30%. In that case the expected number of subjects on the trial will be 18.87 and the expected number of toxicities will be 5.7. If, on the other hand, the true toxicity rate is 60%, then the probability of stopping early is 0.87 with an expected sample size of 9.8 and 5.9 expected toxicities. Table 2 is the stopping guideline if 'X' out of 'N' has a pre-defined toxicity. As an example, if we enroll 3 patients and all have toxicity, then we will consider stopping the trial; if we enroll 6 patients and 5 patients have toxicity then the trial will be stopped.

Drug related toxicities for the safety analysis described above are defined as: a) any grade 3 or 4 non-hematologic toxicity except anorexia, alopecia, nausea, fatigue, fever without neutropenia; b) failure to recover to baseline (except alopecia) after delaying the next dose by more than 14 days; c) grade 3 or 4 neutropenia complicated by fever $\geq 38.5^0$ C or infection, or grade 4 neutropenia of a least 7 days duration; or d) grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by hemorrhage. Toxicity evaluation of the patients enrolled in the trial will be done using the NCI Common Toxicity Criteria, Version 4.0, and will be presented to the Clinical Protocol Monitoring Committee (UAB Safety and Monitoring Plan).

If toxicity meets the stopping rule at any time during the first 5 patients enrolled in the pilot study (see table 2), the protocol will allow the investigators to open a new 20 patient cohort using Lapatinib 1000 mg PO a day and Veliparib 150 mg PO twice a day. The new cohort will follow the same rules used in the original cohort (Cohort -1). Patients developing grade 1 and 2 toxicities will be permitted to take a drug holiday of up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drugs may be resumed at the same level. In the event of recurrent toxicity, there will be one dose reduction permitted (dose reduction minus one will be Lapatinib 750 mg PO daily continuously and Veliparib 100 mg PO every 12 hours continuously). If the adverse event recurs after dose reduction two, the patient will be taken off the study.

Patient Selection Criteria

4.1 Inclusion Criteria

- Patients must have pathologically documented breast cancer which is stage IV.
- Tumor must be HER-2-neu negative (defined as 0 or 1+ staining by immunohistochemistry or gene amplification ratio ≤ 2.0, by FISH), estrogen and progesterone receptors negative (< 1%). Patients with BRCA 1 or 2 mutations will NOT be included.
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) (RECIST criteria 1.1 – see Appendix D).
- Biopsy of a metastatic lesion is not required for protocol entry but all patients with reasonably accessible lesions (chest wall, breast, skin, subcutaneous, superficial lymph nodes, bones and liver metastases) must agree to biopsy (lung and brain metastasis will not be biopsied):

  - Biopsies may be done with local anesthesia or intravenous conscious sedation, according to standard institutional guidelines.
  - If a biopsy requires general anesthesia, then it is only allowed if acquisition of tissue is necessary for clinical reasons (i.e. is clinically indicated), and excess tissue that would otherwise have been discarded is then used for research purposes. If a biopsy requires general anesthesia, then a biopsy of that site for research purposes only, *without* a coexisting clinical indication is not allowed on this protocol.
  - Patients with reasonably accessible lesions as described above, who will not agree with the biopsy, will not be enrolled in the trial.
  - Patients with **NO** reasonably accessible lesions as described above can be enrolled in the trial.
- Prior Therapy:
  - No more than two regimens in the metastatic setting as long as patients have adequate performance status. Patients with no prior chemotherapy for metastatic disease may be included in the trial if they received anthracyclines and taxanes in the adjuvant or neoadjuvant settings. Chemotherapy naïve patients with metastatic disease must have failed anthracyclines and taxanes.
  - Chemotherapy treatment prior to enrollment must be discontinued for at least 3 weeks prior to study entry.
  - Patients must have completed radiation therapy at least 21 days prior to beginning protocol treatment.
- Patients must have recovered from all reversible toxicities related to prior therapy before beginning protocol treatment, and may not have any pre-existing treatment-related toxicities greater than grade 2. Patients must have < grade 2 pre-existing peripheral neuropathy.
- Patients may receive bisphosphonates; however, if used, bone lesions may not be used for progression or response.
- At least 19 years of age.
- Life expectancy of greater than 12 weeks.
- ECOG performance status ≤ 2 (See Appendix B).
- Patients must have normal organ and marrow function as defined below:
  - Absolute neutrophil count: ≥ 1,000/μL,
  - Hemoglobin: ≥ 9 mg/dL,
  - Platelets: ≥ 100,000/μL,
  - Total bilirubin: ≤ 1.5 X institutional upper limit of normal,
  - AST(SGOT)/ALT(SGPT): ≤ 2.5 X institutional upper limit of normal without liver metastases, OR, ≤ 5 X institutional upper limit of normal if documented liver metastases,
  - Creatinine: ≤ 1.5 mg/dL, OR calculated creatinine clearance ≥ 40 mL/min (calculated by the modified Cockcroft and Gault method).
- Ability to understand and the willingness to sign a written informed consent document.
- Use of an effective means of contraception in subjects of child-bearing potential.
- Negative serum or urine beta-HCG pregnancy test at screening for patients with childbearing potential.
- Ejection fraction must be ≥ 50%

4.2 Exclusion Criteria

- Patients may not be receiving any other investigational agents.
- No prior use of anthracyclines and taxanes for metastatic disease or in the adjuvant or

neoadjuvant setting.
- Metastatic lesions identifiable only by PET.
- QTc > 470 msec. Excluded are patients who may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.
- Patients may not be receiving concurrent chemotherapy for treatment of metastatic disease.
- Active brain metastases: evidence of progression ≤ 3 months after local therapy (patients should be asymptomatic and off corticosteroids and anticonvulsants for at least 3 months prior to study entry).
- Patients with brain metastases must have at least one site of measurable disease outside of the central nervous system.
- Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, history of recent myocardial infarction, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease or psychiatric illness/social situations that would limit compliance with study requirements.
- Uncontrolled seizure disorder.
- Pregnant or lactating women are excluded. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated. These potential risks may also apply to other agents used in this study.
- A prior invasive malignant disease within five years except for skin cancer (squamous cell or basal cell carcinoma).
- Patients with known history of HIV or Hepatitis B because of potential for added toxicity from treatment regimen.
- Dementia or altered mental status that would prohibit the understanding of informed consent.

4.3 Withdrawal of Patients

A patient should be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Patients should be removed from therapy if any of the following occurs:
- Disease progression in patients receiving the combination of Lapatinib and Veliparib. Every effort should be made to document objective evidence of tumor progression radiographically and not solely based on clinical and/or tumor marker suggestions of progression.
- The occurrence of unacceptable toxicity indicating the need for cessation of treatment. Patients will be followed until stabilization or resolution of the toxicity.
- The physician feels it is in the best interest of the patient to stop treatment.
- Patient refusal to continue with therapy.
- Non-compliance by the patient with protocol requirements.
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome, if possible.
- Patient becomes pregnant.
- Termination of the study by investigator industry partners.

Treatment may be delayed for up to 2 weeks beyond planned resumption of the next cycle. If a patient does not fulfill re-treatment criteria by that time, they will be removed from the trial; if unacceptable toxicity to one of the agents used in this combination occurs in a patient enrolled in the study, then patient will NOT continue on a single agent.

4.4 Pregnancy

Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation, the potential risks of an unintentional pregnancy and should practice an effective method of birth control. Women of childbearing potential must have a negative pregnancy test within 7 days of initial dosing. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study. In addition, all women of childbearing potential must be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The Investigator must immediately notify our industry partners (AbbVie and Novartis Pharmaceuticals Corporation) in the event of a confirmed pregnancy in a patient participating in the study.

5.0 DRUG INFORMATION

5.1 Veliparib or ABT-888

Veliparib is an oral potent inhibitor of PARP which is a nuclear enzyme that recognizes DNA damage and facilitates DNA repair. PARP activity is essential for the repair of single-stranded DNA breaks through the base-excision repair pathways and is important modulator of the non-homologous end-joining and homologous recombination double-stranded break repair pathways. The patient's weight will NOT be used to determine the dose of Veliparib to be used for the study.

5.1.1 Pharmaceutical Formulation

The chemical name of Veliparib is 1H-Benzimidazole-7-carboxamide,2-[(2R)-2-methyl-2-pyrrolidiny]-, and it molecular weight is 244.29. Veliparib will be provided by AbbVie as immediate release capsules (strengths: 10, 20, 40, 50, and 100 mg). The components of the capsules are microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide (may contain FD&C blue#1, FD&C yellow#6, or FD&C yellow#5.

5.1.2 Labeling and Packaging

Veliparib will be provided by AbbVie free of charge for this study. Veliparib will be packaged in bottles containing the capsules. Each bottle label will include all the information, as required by local regulations and must remain affixed to the bottle. The site staff must complete all blank spaces on the label prior to dispensing drug to the patient. AbbVie will provide the study site with detailed instructions and training for the handling of study supplies.

5.1.3 Dispensing Procedures and Storage Conditions

All clinical supplies provided by AbbVie must be stored in a secure place at the proper storage conditions until they are dispensed for patient use or are returned to AbbVie. Upon receipt of a shipment, the pharmacist will open and inspect the shipment, verify that the Veliparib has been

received intact/in the correct amounts/at the correct address, sign/date the proof of receipt, and register the shipment.

The investigational product is for investigational use only and is to be used only within the context of the study. Capsules must be stored in the original container at 15º to 25ºC (59º to 77ºF). Patients will receive enough capsules every 28 days (every cycle); patients must keep a diary indicating time and date of each dose. Patient diary will be reviewed by the study coordinator every 28 days and the diary will be kept within the study records at the end of the active therapy of the patient. Patients will be instructed to bring their used bottles of Lapatinib to each return visit, along with any unused tablets. The site will record the bottle number and dose of Veliparib given to each patient in the source documents.

Accountability for investigational clinical supplies at the site rests with the Investigator at the participating site. The investigational product will be shipped to a designated person at the study site and must be stored in a pharmacy, or other locked and secured in a storage facility, accessible only to those individuals authorized by the site's Principal Investigator. The study product will be administered in accordance with the protocol, only to patients participating in the clinical trial. It is a violation of the regulations to use unapproved study products for purposes other than those described in the protocol.

The site will complete the required documentation, provided by UAB to account for investigational product dispensation. Each time the study product is dispensed to a patient; all information must be recorded immediately on a drug dispensation form(s).

Unused capsules will be destroyed on site at the conclusion of the study and suitably documented by the study team. Empty bottles and partially used bottles with capsules should be recorded and destroyed as per institutional SOP's after study drug administration. All returns of study product will be accurately recorded on the provided form(s).

5.1.4 Adverse Events Associated With Veliparib

At present, there have been more than 800 patients exposed to ABT-888, however only one study tested this drug as a single agent. From this single agent study, conducted in subjects with cancer, the most common reported side effects (≥10%) with veliparib as a single agent were: nausea (50), fatigue (43), anemia (32), hyperglycemia (27), lymphopenia (24), hypoalbuminemia (22), abdominal pain (22), diarrhea (22), decreased appetite (22), headache (20), low sodium (19), increases in liver enzymes (17), back pain (15), ascites (15), constipation (15), thrombocytopenia(12), leukopenia (12), dizziness (12), increased creatinine (10), dyspnea (12), insomnia (10), and dry mouth (10), hot flushes (10). Less frequent, but potentially severe events include dehydration (6.9). Based upon events of seizures in preclinical studies using high doses (much higher of what it will be used in this study) seizures are a potential risk; however, in ongoing clinical studies, uncommon events of seizure have been observed. In preclinical studies also it has been demonstrated that Veliparib absorbs ultraviolet light; therefore, the potential exists that Veliparib may contribute to a risk of reddening or tanning of the skin when exposed to direct sunlight. In addition, as with any drug, allergic reactions are a possibility from a simple rash to anaphylactic shock. Side effects on an unborn or nursing infant are not known; however, in preclinical studies harmful effects on fetal development have been noted in experimental pregnant animals.

5.1.5 Veliparib Dosing

The daily dose of Veliparib will be 200 mg PO every 12 hours continuously for 28 days (a cycle), starting on Day 2 Cycle 1. Patients developing grade 1 and 2 toxicities will be permitted to take a drug holiday of up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drug may be resumed at the same level. In the vent of recurrent toxicity, there will be two dose reductions permitted (Veliparib 150 mg PO every 12 hours continuously and Veliparib 100 mg PO every 12 hours continuously). If the adverse event recurs, the patient will be taken off the study. Patients developing grade 3 and 4 toxicities will be interrupted for permitted for up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drugs may be resumed at a reduced dose (Veliparib 150 mg PO every 12 hours continuously). If the adverse event recurs, the patient will be taken off the study. **Veliparib will start on day 2.**

5.2 Lapatinib (GW572016 or Tykerb®) (See also Lapatinib Package Insert)

Lapatinib is an orally active dual HER1/HER2 kinase inhibitor that blocks signal transduction pathways. This dual inhibition is an attractive therapeutic strategy for epithelial cancers, as ligand-induced HER1/HER2 dimerization triggers off potent proliferative and survival signals. Lapatinib will be provided free of charge by Novartis Pharmaceuticals Corporation for this pilot study.

5.2.1 Packaging, Labeling, and Storage of Study Drug

Lapatinib will be supplied by Novartis Pharmaceuticals Corporation as lapatinib ditosylate monohydrate tablets. The tablets contain 250 of the active drug, and they are oval, biconvex, orange, film-coated, and are debossed on one side with FL HLS. The tablets contain 400 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet. Lapatinib must be stored at room temperature, in accordance with manufacturer guidelines.

All clinical supplies provided by Novartis Pharmaceuticals Corporation must be stored in a secure place at the proper storage conditions until they are dispensed for patient use or are returned to them. Upon receipt of a shipment, the pharmacist will open and inspect the shipment, verify that the lapatinib has been received intact/in the correct amounts/at the correct address, sign/date the proof of receipt, and register the shipment.

The investigational product is for investigational use only and is to be used only within the context of the study. Capsules must be stored in the original container at 15º to 25ºC (59º to 77ºF). Patients will receive enough capsules every 28 days (every cycle); patients must keep a diary indicating time and date of each dose. Patient diary will be reviewed by the study coordinator every 28 days and the diary will be kept within the study records at the end of the active therapy of the patient. The site will record the package number and dose of Lapatinib given to each patient in the source documents.

Accountability for investigational clinical supplies at the site rests with the Investigator at each participating site. The investigational product will be shipped to a designated person at the study site and must be stored in a pharmacy, or other locked and secured in a storage facility, accessible only to those individuals authorized by the site's Principal Investigator. The study product will be administered in accordance with the protocol, only to patients participating in the clinical trial. It is a violation of the regulations to use unapproved study products for purposes other than those described in the protocol.

The site will complete the required documentation, provided by UAB to account for investigational product dispensation. Each time the study product is dispensed to a patient; all information must be recorded immediately on a drug dispensation form(s).

Unused capsules will be destroyed on site at the conclusion of the study and suitably documented by the study team. Empty bottles and partially used bottles with capsules should be recorded and destroyed as per institutional SOP's after study drug administration. All returns of study product will be accurately recorded on the provided form(s).

5.2.2 Adverse Events Associated With Lapatinib

Expected non-hematologic toxicities for the use of Lapatinib include diarrhea, rash, mucositis, dry skin, elevation of the liver enzymes (especially in patients with prolonged use) and nausea. The majority of these events have been grade 1 and 2 and very rarely grade 3 or 4. Hematological toxicity has not been associated with this agent.

Diarrhea, including severe diarrhea, has been reported during treatment with Lapatinib. Diarrhea generally occurs early during treatment, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4 to 5 days. Lapatinib-induced diarrhea is usually low-grade, with severe diarrhea of NCI CTCAE Grades 3 and 4 occurring in <10% and <1% of patients, respectively. Early identification and intervention is critical for the optimal management of diarrhea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhea with anti-diarrheal agents (such as loperamide) after the first unformed stool is recommended. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids,use of antibiotics such as fluoroquinolones (especially if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4 neutropenia), and interruption or discontinuation of therapy (see Appendix I for diarrhea management guidelines).

Lapatinib has been reported to decrease LVEF; in clinical trials, the majority (>57%) of LVEF decreases occurred within the first 12 weeks of treatment; however, data on long-term exposure are limited. Caution should be taken if Lapatinib is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment to ensure that the patient has a baseline LVEF that is within the institution's normal limits. LVEF should continue to be evaluated during treatment with Lapatinib to ensure that LVEF does not decline below the institution's normal limits.

Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and post-marketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. If changes in liver function are severe, therapy with lapatinib should be discontinued and patients should not be retreated.

No pulmonary toxicity has been noted with lapatinib. However, interstitial lung disease (ILD) has been described in mainly lung cancer patients receiving tyrosine kinase inhibitors against HER1, like gefitinib. Interstitial lung disease, which may be acute in onset, has been observed uncommonly in patients treated with gefitinib. These patients usually present with a fairly acute onset of dyspnea,

sometimes associated with cough or low-grade fever. This may become quite severe within a short period of time and usually results in hospitalization. Radiological investigations, often including CT scan, frequently show pulmonary infiltrates or interstitial shadowing with ground-glass appearance. There is often respiratory distress with arterial oxygen desaturation. Cultures are frequently negative for bacterial growth. If patients present with an acute worsening of respiratory symptoms such as dyspnea, cough, and fever, lapatinib will be interrupted and the patient promptly investigated for ILD. If ILD is confirmed, lapatinib will be discontinued and the patient treated appropriately.

QT prolongation was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypocalcemia, hypokalemia, and hypomagnesemia should be corrected prior to lapatinib administration.

5.2.3 Lapatinib Dosing

The daily dose of Lapatinib will be 1250 mg PO every 24 hours continuously for 28 days (a cycle). Patients developing grade 1 and 2 toxicities will be permitted to take a drug holiday of up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drug may be resumed at the same level. In the vent of recurrent toxicity, there will be two dose reductions permitted (Lapatinib 1000 mg PO every 24 hours continuously and Lapatinib 750 mg PO daily). If the adverse event recurs, the patient will be taken off the study. Patients developing grade 3 and 4 toxicities will be permitted to take a drug holiday of up to 14 days; after the drug holiday, if the adverse event has resolved to the satisfaction of the investigator, the study drugs may be resumed at a reduced dose (Lapatinib 1000 mg PO every 12 hours continuously). If the adverse event recurs, the patient will be taken off the study. Lapatinib will start on day 1.

Patients should be carefully instructed by study personnel on how to take lapatinib. Patients will be instructed to take lapatinib, 1250 mg (5 tablets) PO on a daily basis, at approximately the same time each day. Lapatinib must be taken on an empty stomach—either 1 hour (or more) before a meal or 1 hour (or more) after a meal. Patients may not use anything but water to help them swallow their lapatinib. Medications that modify gastric pH, while not prohibited, are restricted and further described in the table of prohibited medications. Histamine H2 antagonists and proton pump inhibitors are allowed. NOTE: Lapatinib is not to be taken with grapefruit or grapefruit juice. Grapefruit and grapefruit juice should not be taken at any time during the study. If the patient vomits after their lapatinib dose, the patient should be instructed not to retake the dose. Patients should take the next regularly scheduled dose of lapatinib. If vomiting persists, the patient should contact their study doctor.

In vitro data suggest the possibility of drug-drug interactions with lapatinib involving metabolic enzymes and transporter proteins. Because lapatinib is predominantly eliminated by metabolism through CYP3A4/5, drugs that inhibit or induce these enzymes may alter systemic exposure. Ketoconazole, a CYP3A4 inhibitor, has been shown to elevate lapatinib plasma concentrations 3.5-fold. Carbamazepine, a CYP3A4 inducer, has been shown to reduce lapatinib plasma concentrations by 72%. Therefore, use of lapatinib with drugs that alter CYP3A4/5 activity should be undertaken with caution. Lapatinib has been shown to modestly inhibit CYP3A4 and Pgp, and potently inhibit BCRP at in vitro concentrations near the high end of those expected clinically. In the absence of clinical data, use of lapatinib with drugs that are substrates for CYP3A4, Pgp, and BCRP should

proceed with caution. For a comprehensive list of prohibited medications, please refer to Appendix H.

In August 2011, the lapatinib prescribing information was revised to include information regarding potential interactions with midazolam and digoxin. Following co-administration of lapatinib and midazolam, 24-hour systemic exposure of orally administered midazolam increased by 45%, while 24-hour systemic exposure of intravenously administered midazolam increased by 22%. The use of midazolam for a procedure (e.g. port placement) is permitted; however, investigators and patients should be aware of the potential interaction. Following co-administration of lapatinib and digoxin, systemic concentration of oral digoxin increased approximately 2.8-fold. Concomitant use of digoxin is not prohibited; however, every effort should be made to switch the patient to a suitable alternative. In the event that an alternative to digoxin is not available, serum digoxin concentrations should be monitored prior to the initiation of lapatinib therapy, and throughout co-administration. If the digoxin serum concentration is greater than 1.2 ng/mL, the digoxin dose should be reduced by half.

5.3 Compliance

Compliance with Lapatinib and Veliparib will be evaluated by a physical pill count at the scheduled clinic visits on Weeks 4, 8, 12, 16, 20, and 24. Patients will be instructed to bring their used bottles of Lapatinib and Veliparib to each return visit, along with any unused tablets. The investigator/designee will count the number of remaining tablets at each visit to assess compliance. In the event that the patient forgets to bring their used study meds to their clinic visit, compliance will be assessed by direct questioning of the subject. In this case, patients should be counseled to bring their used drug bottles to their next scheduled appointment so that compliance may be confirmed by pill count. Patients should be instructed to report any missed doses of either Lapatinib or Veliparib to the study coordinator.

Compliance with Lapatinib and Veliparib will be calculated by the ratio of number of pills actually taken to the number of pills that should have been taken. Compliance will be defined as a ratio $\geq$ 0.75. Subjects with ratios between 1.00 and 0.75 will be allowed to continue on study. Study staff should ensure patient understanding of dosing instructions for patients whose compliance is less than 100%. In addition, the importance of compliance with anticancer therapy should be reinforced. Patients found to be in less than 75% compliance on more than one occasion will be taken off study for non-compliance. Subjects who miss doses as a result of physician prescribed drug holidays will not be considered non-compliant. Calculation of the compliance ratio should thus be adjusted such that the "number of pills that should have been taken" reflects the drug holiday.

6.0 TREATMENT PLAN

6.1 Introduction

Patients with pathologically confirmed TNBC (estrogen receptor negative, progesterone receptor negative, HER-2-Neu negative – see definitions in section 4.2) who have metastatic disease and have not been treated previously for metastatic disease (but received anthracyclines and taxanes in the adjuvant or neoadjuvant settings) or have failed one or more chemotherapy regimens in the metastatic setting (anthracyclines and taxanes) will be offered participation in this trial with appropriate informed consent. It is mandatory for the patients enrolled in the trial to have a biopsy of one of the metastatic lesions before they will be treated with the research schema (see eligibility

criteria) if biopsy sites are appropriate; patient advocates will play a very important role in this task of the protocol. Patients with **NO** reasonably accessible lesions as described above can be enrolled in the trial.

6.2 Pilot Trial

Twenty patients evaluable for response will be entered into this phase pilot trial; they will receive Lapatinib (1250 mg a day continuously for 28 days) in combination with Veliparib 200 mg every 12 hours for 28 consecutive days, starting on Day 2 Cycle 1). No blinding will be used in this study. Patients will be evaluated for response every 2 courses (every 8 weeks) according to the RECIST criteria version 1.1 (see Appendix D). Treatment will be administered on an outpatient basis. Treatment may continue without interruption in patients with CR, PR or SD until progression of the disease or unacceptable toxicity. Patients cannot receive any other concomitant therapy: chemotherapy, targeted therapy, radiation therapy, or other investigational agent while participating in the study. There are some restrictions on concomitant medications which must be recorded (see Appendix H). Patients may receive bisphosphonates; however, if used, bone lesions may not be used for progression or response. Patient with PD at any time will be taken off the study.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information about the patients (initials, sex, age), date, and outcome of screening process: enrolled in the study, reason for ineligibility or refused to participate. Investigators will be expected to maintain an enrollment log for all patients enrolled in the study indicating their assigned study number. A patient will be considered enrolled upon assignment of a patient number. Each patient will sign an informed consent provided by the site.

6.2.1 Study Entry

Principal investigator will hold the IND for the trial. All patients must be registered with the Clinical Trials Network and Monitoring Office of the UAB Comprehensive Cancer Center (Pam Dixon, O.C.N.) before enrollment in study. Prior to initiation of therapy eligibility criteria must be confirmed. At the time of registration, a study identification number will be generated. All subsequent case report forms will use this study identification number.

6.2.2 Pre-study Assessments

Informed consent will be obtained before study-specific screening evaluations are performed. Screening evaluations must be performed within 4 weeks prior to day 0.

Within the 4 weeks prior to therapy initiation patients will undergo baseline clinical evaluation (including history, physical evaluation, vital signs, and performance status) and all enrolled patients will undergo biopsy of a selected lesion according to the guidelines described in eligibility criteria. Additional pre-study evaluations include: CBC with differential and platelets, CMP (fasting), CA27.29, pregnancy test (within 7 days if indicated), tumor measurements by images or staging studies which are defined as studies contributing to response evaluation, e.g. CTs (chest, abdomen, and pelvis), MRI, bone scan, PET, or plain x-rays, EKG and echocardiogram, and concomitant medication assessment. The ejection fraction will be confirmed as normal before proceeding with the first dose of lapatinib.

Patients with reasonably accessible lesions as described above, who will not agree with the biopsy, will not be enrolled in the trial. Patients with **NO** reasonably accessible lesions as described above can be enrolled in the trial.

6.2.3 Treatment and Assessments

Patients will not be randomized; patients will be treated as described before. For this pilot study, a course of therapy is 28 day. We are allowing a treatment window of ± 1-3 days. Lapatinib will be administered before Veliparib. Patients will be restaged with the same images or staging studies used in the baseline evaluation (staging studies are defined as studies contributing to response evaluation, e.g. CTs (chest, abdomen, pelvis), MRI, bone scan, PET, or plain x-rays every 8 weeks (as an example, before course 3, 5, 7, 9, ..), and tumor response defined by RECIST criteria version 1.1. Patients with SD, PR or CR may continue therapy until disease progression or intolerance to therapy. An EKG will be obtained on day 2 and 3 of cycle one. Also, an EKG will be obtained on day one of each subsequent cycle. Echocardiogram will be obtained every 3 months.

In addition, patients will undergo performance status, CBC with differential and platelets, CMP, concomitant medication assessment; and assessment of adverse events on day 1 of each cycle. Hypocalcemia, hypokalemia, and hypomagnesemia will be corrected prior to lapatinib administration. Physical evaluation, vital signs, and weight will be performed day 1 of each cycle. CA27.29 will be obtained every 8 weeks. Pharmacokinetic samples are described in section 6.3.

Patients 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 investigational product.
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 should be temporarily discontinued. If the left ventricular ejection fraction recovers during the next 3 weeks, the patient may be restarted on investigational product at a reduced dose. For such patients, 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 subject should be withdrawn from investigational product. Patients with an NCI CTCAE grade 3 or 4 LVEF relative decrease must be withdrawn from study medications. Patients will be monitored closely for pulmonary toxicity. Patients with an NCI CTCAE Grade 3 or 4 interstitial pneumonitis must be withdrawn from study medications.

6.2.4 Post-treatment/Follow-up Assessments

Patients will be taken off study treatment following progression; patients will also be taken off treatment for treatment delay of more than 2 weeks, or concurrent illness that in the opinion of the investigator would affect clinical assessment or endanger the patient. In the event of refusal of further therapy, the patient will continue to be followed for outcome. Only if the patient withdraws consent will outcome data cease to be collected.

The following evaluations and procedures will be performed at **early termination** (discontinuation for any reason before documentation of disease progression): clinical evaluations (weight, physical examination, vital signs and performance status); there must be a complete and clear documentation

of objective response or disease progression (staging studies are defined as studies contributing to response evaluation, e.g. CTs (chest, abdomen, pelvis), MRI, bone scan, PET, or plain x-rays using the RECIST criteria version 1.1 (reason(s) for discontinuation must be documented); laboratory assessment (CBC with differential and platelet count, and CMP); concomitant medication assessment; and assessment of adverse events (if the patient has an ongoing toxicity, the patient should be followed until resolution or stabilization. Serious and non-serious adverse events occurring within 30 days of day 0 of the last treatment should be reported on the appropriate adverse event CRF).

6.3 Ancillary Studies

Pharmacokinetics for Lapatinib and Veliparib In this pilot trial, pharmacokinetics will be done in all patients enrolled in the trial. Pharmacokinetics will be carried out during the first course of therapy. Samples for the first day will be collected 5 minutes before start of the therapy, 30 and 60 minutes after the first dose of Lapatinib and then 2, 4, 6, 8, and 24 hours after the start of the therapy with Lapatinib, On day 2, patients will take the dose of Lapatinib and Veliparib at the same time of day 1 and samples will be taken 30 and 60 minutes after the first dose of Lapatinib and Veliparib, then 2, 4, 6, 8, and 24 hours. Additional samples will be taken on day 3, before the third day dose of Lapatinib and Veliparib. Same schema will be followed on days 8, 9 and 10 as on days 1, 2, and 3. A total of 3-5 mL of blood will be collected in red top tubes at each of the described time points. The actual time of administration of each agent and sample collection should be recorded. See section 7.6 of the protocol for statistical analysis of pharmacokinetics. PK analysis will be conducted at UAB: PK/PD Shared Facility of the UAB Comprehensive Cancer Center.

MicroRNA Profiling Serum (serum separator tubes) will be sent to Dr. Anton Wellstein's lab at Georgetown University to establish microRNA profiles in serum that can predict treatment response or resistance. A genome wide analysis of the microRNA's that are detectable in serum to derive a subset of informative microRNA's will be run. A genomic wide analysis will be run on a subset of 5 patients before and after treatment to find the most informative microRNA's (Before initiation of therapy and then on day 8, 15 and 29). Informative microRNA's are defined by: the effect of treatment (longitudinal=before/after treatment); and disease status or inter-individual differences among the patients (horizontal comparison). From the serum samples sent for this analysis, only a small amount of serum is needed for this analysis. Serum that is left over after this analysis is completed will be sent back to UAB to facilitate the other correlative work for this protocol. No funding is necessary to conduct the evaluation in the laboratory; funds are needed only for shipping.

Biopsies –
A tumor biopsy of one of the metastatic lesions (see eligibility criteria for biopsy guidelines) will be obtained before initiation of therapy. Biopsy samples will preferably be obtained using a 14-18 gauge core needle; **at least** two core biopsies will be obtained and snap frozen individually for gene expression; a **third** core will be used for the preparation of paraffin-embedded blocks or formalin fixed tissue.

Biopsy of a metastatic lesion is not required for protocol entry but all patients with reasonably accessible lesions (chest wall, breast, skin, subcutaneous, superficial lymph nodes, bones and liver metastases) must agree to biopsy. Lung biopsies are not acceptable for research only. Biopsies may be done with local anesthesia or intravenous conscious sedation, according to standard institutional guidelines. If a biopsy requires general anesthesia, then it is only allowed if acquisition of tissue is necessary for clinical reasons (i.e. is clinically indicated), and excess tissue that would otherwise

have been discarded is then used for research purposes. If a biopsy requires general anesthesia, then a biopsy of that site for research purposes only, *without* a coexisting clinical indication is not allowed on this protocol. Patients with reasonably accessible lesions as described above, who will not agree to the biopsy, will not be enrolled in the trial. Patients with **NO** reasonably accessible lesions as described above can be enrolled in the trial.

Two of the snap frozen research biopsies will be sent to Dr. Yang's laboratory located at the Hazelrig Salter Radiation Oncology Center (176F, Suite 2222G, phone 975-2881, lab pager 2677#) where biopsies will be stored for batching. All samples will be indelibly labeled with the appropriate study number, and date of acquisition; these data will be correlated with clinical efficacy including complete response and objective response. One of the frozen research biopsies will be processed for targeted gene expression analysis, tumor microRNA profiling, and copy number variation of commonly amplified or deleted genes in cancer using the Nanostring nCounter DX system with FLEX configuration (Yang Lab). This system will also allow for the analysis of the Prosigna Breast Cancer Prognostic Gene Signature Assay (based on the PAM50 gene set established by Charles Perou et al., Nature 2000) that provides intrinsic subtyping information as well as prognostic information as it relates to drug response. Targeted gene expression will be performed using prebuilt gene panels by Nanostring including the Human Kinase (519 kinases), Human Immunology (594 immunology genes), Human Cancer Reference (236 cancer related genes), and Human Inflammation (184 inflammation gene) kits. Tumor microRNA profiles will also be analyzed using total RNA from tumor biopsies (800 human miRNAs). Lastly, copy number variation of commonly altered genes in cancer will be investigated from DNA harvested from the tumor. For each analysis, as little as 100ng of total RNA or 300ng of genomic DNA is needed for highly reproducible results. Additionally, if available, formalin-fixed paraffin-embedded tissues from the original primary tumor will also be subjected to this analysis to investigate the evolution of the tumor from primary to metastatic.

Fifteen slides will also be prepared from the formalin-fixed paraffin embedded tissue for analysis by conventional IHC of ER, PR, Her-2, EGFR, PARP, Ki67, apoptotic markers, and biomarkers of DNA repair such as H2AX, PARP, and BRCA localization. All samples will be indelibly labeled with the appropriate study number, and date of acquisition; these data will be correlated with clinical efficacy including complete response and objective response.

The second frozen core research biopsy will be sent to Hudson Alpha Institute at a later designated time point to be used for comprehensive genomic analysis such as Next-GEN genomic analysis.[71] "Next-GEN genomic analysis will be done at HudsonAlpha Institute for Biotechnology in Huntsville, Alabama (Shared Facility of the UAB Comprehensive Cancer Center) by Dr. Richard Myers' group. No funding is necessary to conduct the evaluation in the laboratory at this time or macro-dissection; funds are needed only for shipping.

Researchers at HudsonAlpha Institute for Biotechnology led by Dr. Richard M. Myers will obtain tissues from Dr. Erica M. Stringer-Reasor and colleagues at UAB from patients with TNBC enrolled in the pilot Study. HudsonAlpha Institute for Biotechnology will analyze the tissues for several functional genomics features on a genome-wide scale, as well as whole exome DNA sequencing, to identify genetic variants. The functional genomics readout and genetic variation measurements will be assessed to help identify differences associated with TNBC itself, subtypes of TNBC and/or responses to drug treatments. The researchers at Hudson will utilize their expertise in applying six different genome-wide functional genomics measurements, as well as whole exome sequencing, whole genome sequencing and specialized array-based genotyping to measure genomic and genetic variants for cancers, brain diseases, autoimmune diseases and drug responses.

The functional genomics measurements will include the use of ultrahigh throughput sequencing to measure mRNAs and long non-coding RNAs (RNA-seq), microRNAs (miRNA-seq), DNA methylation (a combination of two approaches, RRBS and Methyl1450 arrays), protein:DNA interations (ChIP-seq), chromatin markers (also ChIP-seq) and chromatin accessibility measurements (DNase-seq).

To measure DNA sequence variation, two types of ultrahigh throughput DNA sequencing will be performed: whole exome sequencing, where all the exons and exon:intron boundaries in the human genome are sequenced deeply; and whole genome sequencing, to be used on a modest number of samples due to expense. A combination of exome and whole genome sequencing with inexpensive genotyping of 1 million or more polymorphic DNA markers around the genome may be used to supplement the DNA sequencing and to improve the ability to identify large DNA sequence variants known as copy number variants.

Fifteen slides will be prepared from the paraffin blocks or formalin fixed tissue by a designated pathologist at UAB for analysis by conventional IHC of ER, PR, Her-2, EGFR, Ki67, apoptotic markers, and biomarkers of DNA repair such as H2AX and BRCA localization. All samples will be indelibly labeled with the appropriate study number, and date of acquisition; these data will be correlated with clinical efficacy including complete response and objective response.
Any leftover study blood and tissue samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. Any samples will only be released for use in future studies after approval by the Principal Investigator and other regulatory bodies, as appropriate.

Pharmacogenomic Analyses – Blood samples for pharmacogenomic analyses will be collected on a first day before initiation of research agents. Blood will be collected into one 6 ml K_2EDTA polypropylene blood collection tube (Becton-Dickinson) and into one PAX gene tube. The 6 mL polypropylene K_2EDTA tube will be placed in an ice bath immediately following collection and stored upright in a freezer set at -20ºC (+/- 10ºC) until sending to the laboratory. It is important to collect a full tube of whole blood. The PAX gene tube should be stored upright at room temperature for a minimum of 2 hours or a maximum of 4 hours before processing or transferring to a freezer. They should be stored upright in a wire rack and stored at -20 degrees Celsius or colder until sending to the laboratory. Blood samples should be sent to The University of Alabama (Attention: The University of Alabama at Birmingham; Center for Clinical Translation Science (CCTS) Laboratory, Jefferson Tower, Room 1531, 625 19th Street south, ; Birmingham, AL 35233) as soon as logistically possible following blood draws. The University of Alabama will store the samples until assays are to be performed. Samples will be shipped to The HudsonAlpha Institute for Biotechnology. The Hudson Alpha Institute may conduct pharmacogenomic assays possibly including, but not limited to, DNA sequencing of exons as well as DNA sequencing from RNA transcripts, DNA methylation screens, and tests for specific single nucleotide polymorphisms. These tests on normal tissue may provide reference values for comparison against similar tests previously approved for the patients' tumor tissue. The protocol will provide the tubes (EDTA and PAX gene tubes).

Plasma Tumor DNA (ptDNA)-

Successful treatment depends on the ability to monitor disease burden and response to therapies. Recently, a proof of principle study has shown that plasma tumor DNA (ptDNA) can be used as a reliable breast cancer biomarker in metastatic disease, due to its sensitivity and wide dynamic range. ptDNA more accurately reflects changes in response to therapies, and absolute levels of ptDNA

demonstrate prognostic significance. Thus, ptDNA as a liquid biopsy shows great promise in the clinical management of metastatic breast cancer. The key is to maximize removal of contaminating cells and genomic DNA form these cells as large genomic DNA fragments hinder plasma DNA analysis.

It is now well-established that cells naturally secrete or shed small DNA fragments into the circulation with most of this DNA being compartmentalized in the plasma component of whole blood. Small amounts of cell-free circulating DNA can be detected in plasma from healthy individuals,[79,80] is often highly elevated in metastatic cancer patients [79,81] and correlates with disease burden.[78,82,83] Interestingly, how ctDNA enters the plasma is not precisely known. While the fragment size of circulating DNA in healthy individuals suggests that it originates from apoptotic cells,[80] circulating DNA is also shed from non-apoptotic cells and in this instance it is often larger and more variable in size.[84,85,86] For clarity, we prefer and will henceforth use the term plasma tumor DNA (ptDNA) over ctDNA since there is confusion regarding ctDNA versus DNA derived from CTCs, which are distinctly different. In addition, ptDNA is more specific as it is a subset of ctDNA, since ctDNA also includes urine tumor DNA (utDNA) as well as ctDNA in other bodily fluids. Recent work, including that from our own group, supports the utility of ptDNA as a facile means for liquid biopsy. [78,81,87]Ben Park's group and others have shown that cancer specific somatic mutations can be detected in ptDNA from metastatic breast cancer patients with up to a 100% concordance when blood is taken concurrently with tissue biopsy. [78,81,87] In contrast, Dr. Park's group also demonstrated that mutational discordance can occur between ptDNA and primary breast cancer tissues when there is a prolonged period (greater than 3 years) between initial diagnosis and recurrence.[87] This speaks to the now proven concept of tumor heterogeneity and clonal evolution. ptPtDNA has also been used to identify treatment associated mutational changes . [77,81]Thus, assessment of ptDNA can relay the mutational status of a patient's cancer with the ability for serial testing.

Blood will be collected in three cell-free DNA BCT tubes (Streck) per time point: at baseline before drug administration, on days 15 and 29 (day 1 of cycle 2 pre-treatment). Samples collected in the DNA BCT tubes are stable for up to 14 days at temperatures between 6-37^{O} C. Once tubes are filled completely the tube should be mixed by gently inverting 8 to 10 times. The tubes will be transferred to Dr. Yang's lab for processing and freezing of the samples which will be batched and sent at a later date for analysis to Ben Park's lab at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University.

Serum Marker of Apoptosis - Serum levels of M30 will be drawn pre-dose, Day 8, and Day 15of cycle one only. The changes of the serum levels of M30 at each time point will be correlated with levels of M30 in CTCs as well as with efficacy parameters. M30 serum evaluations will be conducted at the Mayo Clinic by Dr. Paul Haluska. Activation of the intrinsic apoptotic pathway involves release of cytochrome c to the cytosol, activation of caspases (specifically caspase 9 followed by caspase 3), and cleavage of hundreds of substrates by caspase 3.[72, 73] Among the caspase 3 substrates is cytokeratin 18, which yields a fragment that is uniquely detectable using the monoclonal antibody M30 upon caspase cleavage.[74] When apoptotic cells lyse, all of these proteins (cytochrome c, cleaved/activated caspase 3 and cleaved cytokeratin 18) are released to the circulation, where they can be detected by ELISA to provide an assessment of the degree of epithelial cell apoptosis. Samples will be sent to Mayo Clinic for later analysis. No funding is necessary to conduct the evaluation in the laboratory; funds are needed only for shipping.

6.4 Subject Discontinuation/Early Termination

Patients may withdraw from this study at any time. Any patient who withdraws will be encouraged to return to the study center for the post-dose evaluations. The termination visit consists of all evaluations scheduled for the termination visit. The primary reason(s) for discontinuation must be recorded on the appropriate CRF page. The PI may discontinue a patient from treatment. Reasons may include, but are not limited to, the following: clinically significant deterioration, noncompliance, persistent grade 3 or 4 adverse event or any significant adverse event that compromises the patient's ability to participate in the study, requirement of a significant surgical procedure or radiation therapy during the treatment period of the study, investigator's determination that it is not in the patient's best interest to continue participation, development of brain metastases, or pregnancy. Patients will be monitored for 30 days following the end of treatment and will be removed from the study at the end of this follow-up period Patients who have an ongoing research-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

6.5 Study Discontinuation

The principal investigator and/or UAB CCC and/or Novartis Pharmaceuticals Corporation and/or AbbVie have the right to terminate the study for any reason, including: the incidence or severity of adverse events indicates potential health hazard for patients, subject enrollment is unsatisfactory; data recording is inaccurate or incomplete, or other reasons discussed with the principal investigator and the UAB CCC.

6.6 Study Parameters

	Pre-Treatment (within 4 weeks of initiation) +/-	Day 1 of each cycle	Day 8 of cycle 1	Day 15 of cycle 1		Every 8 weeks +/-	At Progression +/-	End of Treatment/ Early Termination
Informed Consent	X							
History/Height	X							
Physical Exam/Vital Signs/Weight	X	X					X	X
Performance Status	X	X					X	X
Toxicity Assessment[10]		X					X	X
CBC/Differential/Platelets[11]	X	X					X	X
CMP (fasting)[11]	X	X					X	X
Magnesium		X						
Concomitant Medications	X	X					X	X
Pregnancy Test[1]	X							
Staging Studies[2]	X					X	X	X
Biopsy of a Metastatic Lesion[3]	X							
Serum CA27.29 Level	X					X	X	X
Lapatinib Administration[7]								
Veliparib Administration [7]								
Pharmacokinetics[4]		X	X					
ptDNA[5,6] and serum[5]		X	X	X				
Echocardiogram and EKG[8]	X	X						
Pharmacogenomics [9]		X						

1 Must be obtained within 7 days of initial dosing. Only for patients with childbearing potential.
2 Staging studies are defined as studies contributing to response evaluation, e.g. CTs (chest, abdomen, and pelvis), MRI, bone scan, PET, or plain x-rays.
3 Mandatory if metastatic site is accessible (see inclusion criteria), i.e. chest wall, breast, skin subcutaneous, superficial lymph node, bone or liver metastases (not lung or brain). Biopsy samples will preferably be obtained using a 14-18 gauge core needle; **at least** two core samples will be obtained and snap frozen and a third sample for the preparation of the paraffin-embedded blocks.
4 Samples for the first day will be collected 5 minutes before start of the therapy, 30 and 60 minutes after the first dose of Lapatinib and then 2, 4, 6, 8, and 24 hours after the start of the therapy with Lapatinib, On day 2, patients will take the dose of Lapatinib and Veliparib at the same time of day 1 and samples will be taken 30 and 60 minutes after the first dose of Lapatinib and Veliparib, then 2, 4, 6, 8, and 24 hours. Additional samples will be taken on day 3, before the third day dose of Lapatinib and Veliparib. Same schema will be followed on days 8, 9 and 10. A total of 3-5 mL of blood will be taken at each of the described time points. The actual time of administration of each agent and sample collection should be recorded.
5 Blood samples (see Appendix E for ptDNA sampling details) will be obtained from each patient at days 1 (baseline; before the initiation of the research medications), on days 15 and 29 (day 1 of 2nd cycle pre-treatment) of the first cycle. Serum will obtained (5 ml blood sample) from each patient at days 1 (baseline; before the initiation of research medications), on days 8, 15, and 29 (day 1 of 2nd cycle pretreatment) of the first cycle (serum will be used for evaluation of micro RNA profiling and M30-protein).
6 Because shipments of ptDNA samples can only occur on Mondays through Thursdays, initiation of treatment cannot occur on Fridays.
7 Patients will receive Lapatinib (1250 mg PO daily continuously) in combination with Veliparib (200 mg PO every 12 hours continuously). A cycle of therapy is defined as 28 days of PO therapy. Lapatinib starts on Day 1 and Veliparib on Day 2.
8 Echocardiogram will be obtained every 3 months while on active therapy. EKG will be obtained at baseline, day 2 and 3 of cycle one, and day one of each subsequent cycle. Patients 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 investigational product. 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 should be temporarily discontinued. If the left ventricular ejection fraction recovers during the next 3 weeks, the patient may be restarted on investigational product at a reduced dose. For such patients, 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 subject should be withdrawn from investigational product. Patients with an NCI CTCAE grade 3 or 4 LVEF relative decrease must be withdrawn from study medications.
9 Blood samples for pharmacogenomic analyses will be collected Cycle 1 Day 1 only before initiation of research agents. Blood will be collected into one 6 ml K2EDTA polypropylene blood collection tube (Becton-Dickinson) and into one PAX gene tube.
10 Patients with an NCI CTCAE Grade 3 or 4 interstitial pneumonitis must be withdrawn from study medications.
11 Cycle 1, Day1 CBC and CMP only need to be obtained if prior labs are greater than 4 weeks.

6.7 Efficacy and Safety Assessments

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee; version 1.1 (see Appendix D).[75] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

6.7.1 Definitions

Measurable Disease – Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥ 10mm with CT scan, or ≥ 10mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Definitions proved for normal: short axis < 10 mm, Measurable (Target): short axis ≥ 15mm, Non-measurable: short axis 10 to <15 mm, Target nodes measured in the short axis (perpendicular to longest diameter) more reproducible and predictive of malignancy. Short axes of target nodes to be added to the sum of longest diameters.

Non-Measurable Disease – All other lesions (or sites of disease), including small lesions (longest diameter <10mm or pathological lymph nodes with ≥ 10 to <15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable

Target Lesions – All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lends themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum. If lymph nodes are to be included in the sum, then only the short axis is added to the sum. The baseline sum LD will be used as referenced by which to characterize the objective tumor response.

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

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline.

Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout the follow-up.

6.7.2 Guidelines for Evaluation of Measurable Disease

General Aspects of Tumor Measurement - 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. Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Specific Methods of Tumor Measurement:

- Clinical lesions – Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Chest x-ray – Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Conventional CT and MRI – This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. If CT scans have slice thickness greater than 5mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-holding scanning techniques, if possible.

- PET-CT – At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- Ultrasound (US) – Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of C in selected instances.

- Endoscopy, Laparoscopy – The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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

- Cytology, Histology – These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

-FDG-PET – While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease. New lesions on the basis PF FDG-PER imaging can be identified according to the following:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to pre-existing site of disease on CT that is not progressing on the basis of the anatomic images this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A "positive" FDG-PET scan lesion means one which is FDG avid with uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.7.3 Response Criteria

6.7.3.1 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or not) must have reduction in short axis to < 10mm.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. (Note: the appearance of one or more new lesions is also considered progression.)

- Stable Disease (SD): Neither sufficient shrinkage to qualify or PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.7.3.2 Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis). Note: If serum CA27.29 levels are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
-Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

6.7.4 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)				
Target Lesions	**Non Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease

(i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when non-lesions can be measured is not advised.

6.7.5 Duration of Response

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

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

6.7.6 Definitions Related to Evaluation Unrelated to Objective Response

Overall Survival is the observed length of life from entry into the study to death or the date of last contact.

Progression-Free Survival is the period from study entry until disease progression, or death, whichever occurs first.

Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.

Subjective Parameters including performance status, specific symptoms, and side effects.

Side effects are graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (see Appendix A). Any patient who receives treatment on this protocol will be evaluated for toxicity. Each patient will be assessed periodically according to the study parameters table for the development of any toxicity. Dose modifications will be made based on toxicities as described earlier.

7.0 STATISTICAL CONSIDERATIONS

This is an open-label, single arm, single institution, pilot clinical trial. The primary objective is to characterize the safety profile and treatment tolerance of Veliparib (ABT-888) in combination with Lapatinib (Tykerb) in patients with metastatic, estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER-2-Neu) negative breast cancer. Secondary objectives will estimate the objective response rate (ORR) (complete responses [CRs] plus partial responses [PRs]); Determine progression free survival (PFS); correlate pre-treatment tumor gene expression profile, biomarkers of DNA repair (H2AX, BRCA localization), EGFR location and signaling, and apoptosis markers with the ORR and PFS; Correlate serial measures of CTCs and serum levels of M30 with the ORR and PFS and determine the pharmacokinetics of Veliparib and Lapatinib when given in combination. A total of 20 (maybe 25 if an additional cohort is added) patients will be enrolled in a single site (University of Alabama at Birmingham) over a projected 12-18 months accrual interval.

7.1 Primary Endpoint

We will characterize the safety profile and treatment tolerance of Veliparib (ABT-888) in combination with Lapatinib (Tykerb). Drug related toxicities for the safety analysis are defined as (see section 3.0 also): a) any grade 3 or 4 non-hematologic toxicity except alopecia, and nausea which is not refractory to anti-emetics; b) failure to recover to baseline (except alopecia) after delaying the next dose by more than 14 days; c) grade 3 or 4 neutropenia complicated by fever $\geq$ 38.5^0 C or infection, or grade 4 neutropenia of a least 7 days duration; or d) grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by hemorrhage. Toxicity evaluation of the patients enrolled in the trial will be done using the NCI Common Toxicity Criteria, Version 4.0).

7.2 Secondary Endpoint

In patients with metastatic TNBC, who will be treated with the combination of Veliparib and Lapatinib, we will estimate the ORR (CRs plus PRs); determine PFS; correlate pre-treatment tumor gene expression profile, biomarkers of DNA repair (H2AX, BRCA localization), EGFR location and signaling, and apoptosis markers with the ORR and PFS; correlate serial measures of CTCs and serum levels of M30 with the ORR and PFS; determine the pharmacokinetics of Veliparib and Lapatinib when given in combination.

7.3 Stratification

No Stratification will be incorporated in this pilot study.

7.4 Sample Size and Power Justification

This is a single arm pilot study to evaluate the safety of combination of Veliparib and Lapatinib in patients with metastatic TNBC. A total of 20 patients will be enrolled to evaluate the safety as treatment related toxicity rate and the objective response rate. The sample size is NOT determined by the statistical power but the feasibility and relative precision of estimate, e.g. standards error of the estimation is <=10%. Assuming the acceptable toxicity rate with combination therapy is no more than 30%; then, we will be able to have two sided 95% exact confidence intervals (Clopper-Pearson intervals) of toxicity estimate from 11.8% to 54.3%. Meantime, this sample size will provide two-sided 95% exact confidence intervals (Clopper-Pearson intervals) of objective response rate estimation as follow:

Table 2 Exact 95% Confidence Interval for Response Rate Estimation

Response rate %	Confidence interval (lower) %	Confidence interval (Upper) %
20	5.73	43.66
25	8.66	49.10
30	11.89	54.28

If the response rate is equal or greater than 30%, we will propose a phase II trial to be conducted in the Translational Breast Cancer Research Consortium (TBCRC).

7.5 Analysis plan

We will consider that any subjects enrolled to the study as intent-to -treat (ITT) population; patients must at least start therapy or they will be replaced. The ITT patients will be included for all efficacy analysis. We will consider any patients who received at least one dose of Lapatinib and/or Veliparib as safety analysis population. The safety analysis population will be used for safety evaluation. The final statistical analysis will be conducted after all patients that have completed treatment with documentation of toxicity, response and progression free survival.

7.5.1 Analysis of Safety

The primary analysis is of safety that will include any patients who receive at least one dose of Lapatinib and/or Veliparib. The treatment related toxicity rate will be estimated at the end of the study along with two sided 95% exact confidence intervals (Clopper-Pearson intervals). Analysis of safety data will be descriptive. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Adverse event and serious adverse event (AE/SAE) (AE/SAE definition is in 9.1.1) reporting during the study will be summarized by relationship to study drug and intensity. Number and proportion of adverse event, serious adverse event and grade 3 or 4 lab toxicity will be reported by body system and by each study arm. Patient's baseline lab data and its change during treatment at each visit will be presented. Graphic statistics tool such as box plot will be used when it is appropriate.

7.5.2 Analysis of Efficacy endpoints

At the completion of the study, the secondary endpoint of ORR rate will be estimated along with two-sided 95% confidential intervals for Lapatinib and Veliparib combination group with exact method of Clopper-Pearson intervals. Secondary endpoint analysis will be descriptive. Mean, median, and range will be used to describe continuous demographic variables. Frequency and proportion will be used to describe categorical variables. The K-M estimator will be used to estimate median progression free survival along with 95% confidence intervals.

Exploratory analysis will be conducted on the correlations between clinical outcomes and biomarkers or gene expression profiles. Gene expression profile, proliferation/apoptosis markers, and circulating level of tumor cells will be analyzed between responders and non-responders using two-sample t-test test assuming normal distribution for gene expression level. An appropriate normal transformation will be conducted prior analysis when it is necessary. Alternatively, one way analysis of variance (ANOVA) can be used to evaluate gene expression and biomarkers by responders. Logistic regression analysis will be used to predict response with these genes or biomarkers with or without adjustment for covariate, e.g. age. Two-sample log rank test will be used to compare PFS curves classified by biomarkers or gene expression profiles so that potential prognostic biomarkers or genes will be identified. Multivariate Cox proportional hazards model will be used to identify a set of biomarkers for prediction of time to disease progression between responders and non-responders. Hazards ratios with 95% confidence intervals will be calculated for each significant biomarker in terms of predicting time to disease progression. Since this is an exploratory pilot study which will be used as a hypothesis generator. We will include EGFR expression and location, and markers of apoptosis and DNA repair as covariate in all above

exploratory analysis.

7.5.3 Analysis of Pharmacokinetics

Non-compartmental pharmacokinetic parameters, including maximal plasma or serum concentration (C_{max}),, area under the curve to the last collection point (AUC_{last}), area under the curve for dose interval (AUC_{0-t}), area under the curve extrapolated to infinity (AUC_{inf}), time of maximal concentration (T_{max}), elimination rate constant (k_{el}), terminal half-life ($t_{1/2}$), total clearance (CL), and a volume of distribution (V_{ss}), will be determined using computer software such as SAS for Lapatinib and Veliparib. Compartmental and population pharmacokinetic analysis will also be conducted using different models such as one- or two- compartmental model with zero-order input, if warranted. Descriptive statistics including mean, standard deviation, coefficient of variation, geometric mean, median, minimum and maximum will be computed for each pharmacokinetic variable by dose group; descriptive statistics for natural-log transformed $AUC_{(last)}$, $AUC_{(0-inf)}$, C_{max}, T_{max}, C_{eoi}, k_{el}, $t_{1/2}$, CL and V_{ss} for Lapatinib and Veliparib will also be provided for each dose group. In addition, mean and median concentrations of research agents versus time graphs will be provided for each dose group and Cycle. The linearity of pharmacokinetic parameters will be explored. Descriptive statistics of the non-compartmental parameters will be calculated for Cycle 1 and cycle 2. The pre-dose-concentrations at Weeks 1-5 for first 2 cycles may be plotted to explore the accumulation.

7.6. Interim analysis

There is no interim analysis for efficacy. This trial includes a continuous assessment stopping rule to limit the exposure of subjects to a potentially unacceptable toxic dose. Drug related toxicities for the safety analysis are defined as: a) any grade 3 or 4 non-hematologic toxicity except anorexia, alopecia, nausea, fatigue, fever without neutropenia; b) failure to recover to baseline (except alopecia) after delaying the next dose by more than 14 days; c) grade 3 or 4 neutropenia complicated by fever > 38.50 C or infection, or grade 4 neutropenia of a least 7 days duration; or d) grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by hemorrhage. Toxicity evaluation of the patients enrolled in the trial will be done using the NCI Common Toxicity Criteria, Version 4.0.

This trial includes a continuous assessment stopping rule in order to have a high probably of stopping early if the toxicity rate is unacceptably high, say 60%, while having low probability of stopping early if the toxicity rate is acceptable, say 30%. This rule is based on a Pocock-type boundary as described by Ivanova et al (Anastasia Ivanova, Bahjat F. Qaqish, and Michael J. Schell. Continuous Toxicity Monitoring in Phase II Trials in Oncology. Biometrics 61, 540–545, 2005). This stopping rule is considered a guideline with the final decision of termination of the study to be made by the data safety committee

Table 3: Minimum number of toxicities (X) required to consider stopping the study after N subjects, for 20 patients

X	3	4	4	5	5	6	6	7	7	7	8	8	9	9	9	10	10	11
N	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

This rule will provide a probability of 0.10 of stopping early if the true toxicity rate is 30%. In that case the expected number of subjects on the trial will be 18.87 and the expected number of toxicities will be 5.7. If, on the other hand, the true toxicity rate is 60%, then the probability of stopping early is 0.87 with an expected sample size of 9.8 and 5.9 expected toxicities.

Table 3 is the stopping guideline if 'X' out of 'N' has a pre-defined toxicity. As an example, if we enroll 3 patients and all have toxicity, then we will consider stopping the trial; if we enroll 6 patients and 5 patients have toxicity then the trial will be stopped.

7.7 Study Accrual

We plan to enroll a total of 20 subjects from a single institution (University of Alabama at Birmingham). We expect that the enrollment will be completed in 12-18 months. The study will be stopped 3 months after the last patient completes the therapy.

7.8 Data safety Monitoring

This study will utilize the UAB Cancer Center Data and Safety Monitoring Plan with monthly reviews of adverse events, accrual and protocol problems by the Clinical Protocol Monitoring Committee (CPMC) in addition to the stopping guidelines described in 7.6. The CPMC will continue to review all serious adverse events that occur during the course of the study on a monthly basis in addition to cumulative toxicity reports. It will provide recommendations regarding any safety or tolerability concerns that are discovered in the reviews. Final decision for stopping of the study due to safety is the responsibility of the CPMC and our industry partners, AbbVie and Novartis Pharmaceuticals Corporation.

8.0 ADMINISTRATIVE RULES OF THE PROTOCOL

8.1 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in this approved protocol. Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UAB. The written amendment will be sent to the IRB at the investigator's site for approval. All revisions to the protocol will be provided to AbbVie and Novartis Pharmaceuticals Corporation by UAB. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to the UAB Clinical Protocols and Data manager Shared Facility Regulatory Office. If the revision is an Administrative Letter, Investigator must inform their IRB(s)/IEC(s).

8.2 Informed Consent

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility

of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

8.3 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

8.4 Study Management

8.4.1 Institutional Review Board (IRB) Approval and Consent

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB for the protocol, consent form, patient recruitment materials/process (e.g., advertisements), and any other written information to be provided to patients. The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, Amendments, and Administrative Letters) according to regulatory requirements or Institution procedures. Copies of the initial IRB approval as well as annual re-approvals must be submitted to UAB. UAB will provide copies of IRB approval to AbbVie and Novartis Pharmaceuticals Corporation

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. 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 an 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 or the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Documentation of IRB approval must be on file before any patient can be registered. All patients who sign informed consent, will be registered with UAB.

8.4.2 Study Monitoring

Data will be captured on electronic CRFs, and supporting documents will be faxed to the UAB Clinical Trials Network and Monitoring Office. Personnel from the Clinical Trials Network and Monitoring office of the University of Alabama at Birmingham will monitor the trial in real time and will periodically visit the investigative site to ensure proper conduct of the trial and proper collection of the data.

8.4.3 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. Any deviation from the protocol must have prior approval by the Principal Investigator and must be recorded and explained.

8.4.4 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 approved 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 conduction of the clinical research study. Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug pursuing 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. If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Records of the patient's participation in this study will be kept confidential so far as permitted by law. However, the patient's doctor and his/her staff, representatives of AbbVie, representatives of Novartis Pharmaceuticals Corporation, the U.S. Food and Drug Administration, and the IRB will be able to inspect patient records and have access to confidential information which identifies the patient by name. Any publication of data will not identify the patient by name. Should the patient's medical record need to be reviewed by a foreign regulatory agency, a member of the IRB staff will observe the review so that the record is not removed, copied, or identifiable information recorded in any manner.

8.4.5 Obligations of 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 ensure 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 ensuring 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 data entry. 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.

9.0 ASSESSMENT OF SAFETY

9.1 Adverse Event Reporting and Definitions

In the event of an adverse event the first concern will be for the safety of the subject. Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see http://ctep.cancer.gov/reporting/ctc.html - see Appendix A).

9.1.1 Adverse Events (AEs)

Adverse events should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate as it has been described throughout the protocol. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE should be completed.

The FDA has mandated that AbbVie be notified, at least one time per year, or at the agreed upon timeframe, of all non-serious adverse events that: (a) are grade 3-4 toxicity and (b) result in the subject's premature discontinuation of the study.

9.1.2 Serious Adverse Events (SAEs)

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).

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 at least 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.

SAEs require expeditious handling and reporting to UAB to comply with regulatory requirements. Investigators are required to report within 24 hours of investigator's knowledge (MedWatch Form 3500A) to the principal investigator (UAB – Erica M. Stringer-Reasor), who will report to the FDA, UAB IRB, AbbVie, and Novartis Pharmaceuticals Corporation in accordance with regulatory requirements or contractual agreement ANY serious treatment emergent (occurring at any time during treatment, not present at baseline and related to study drug) adverse event (SAE) as soon as possible. SAEs must be reported to local IRB according to their institutional guidelines. All SAEs must be collected and reported until 30 days following patient discontinuation of dosing; if only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

The following events will be reported as SAE:

- Cardiac dysfunction 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.
- Any signs or symptoms of pneumonitis that are Grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen).
- ALT ≥ 3XULN and total bilirubin ≥ 2XULN (>35% direct; bilirubin fractionation required) or ALT ≥ 3XULN and INR >1.5 (except patients receiving anticoagulants).

9.1.3 Reporting of Serious Treatment Emergent Adverse Events

All SAEs should be recorded on a MedWatch 3500A Form (can be accessed at: https://www.accessdata.fda.gov/scripts/MedWatch - see Appendix C) and faxed to:

Pam Dixon
Phone: 205-975-5387
Fax: 205-975-9875

and

Erica M. Stringer-Reasor
Phone: 205-934-3411
Fax: 205-995-9996

Once forms are reviewed, UAB will report to:

MedWatch
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)

and

AbbVie
Drug Safety
Fax: (847) 775-6706
Safetymanagement_oncology@abbvie.com

and
UAB IRB
and
Novartis Pharmaceuticals Corporation
Fax: (877) 778-9739
-mail:
MedWatch 3500A Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B., initials, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally the principal investigator and/or UAB may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that Lapatinib/Veliparib caused or contributed to an adverse event. The following general guidelines may be used.

Yes: if the temporal relationship of the clinical event to Lapatinib/Veliparib administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to Lapatinib/Veliparib administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

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APPENDIX A

NCI Common Toxicity Criteria, Version 4.03

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

APPENDIX B

ECOG Performance Status Scale

ECOG PERFORMANCE STATUS SCALE

GRADE	DESCRIPTION
0	Full activity, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX C

FDA MedWatch 3500A Form

http://www.accesdata.fda.gov/scripts/MedWatch

SAE Reporting

- SAE reporting period begins at the signing of informed consent.
- All SAEs, regardless of attribution must be reported by fax within 24 hrs of investigator's knowledge:
    - MedWatch Form 3500A must be submitted, regardless of completeness of information.
        - Fax to Pam Dixon at 205-975-9875.
    - If only limited information is available, follow-up reports are required.
- Affiliate SAEs must be reported to local IRB according to their institutional guidelines. **(Not Applicable for this trial)**
- UAB is responsible for submitting all SAE MedWatch forms to FDA.
- UAB is responsible for submitting all MedWatch forms to AbbVie and Novartis Pharmaceuticals Corporation
- All SAEs must be collected and reported until 30 days following patient discontinuation of dosing.
    - If only limited information is initially available, follow-up reports are required.
        - The original SAE form must be kept on file at the study site.

APPENDIX D
RECIST 1.1 Criteria

http://www.recist.com/recist-in-practice/01.html

APPENDIX E
Blood and Biopsy Procedures

UAB 1372 - Blood Draw and Biopsy Schedule
Paraffin blocks to UAB
Frozen biopsies to UAB

Blood for ptDNA to Dr. Park's Lab at Johns Hopkins
Blood for Pharmacokinetics to UAB
Serum Marker of Apoptosis to Mayo Clinic

A. Shipments to Johns Hopkins

Collect in Specified Tubes	Pre-Therapy Day 1	Post-Therapy Day 15	Post-Therapy Day 29
Three 10 ml – Streck tubes	X	X	X

Whole blood samples for pt DNA analysis will be obtained at: pre-therapy, and on Day 15 of the first cycle and day 1 of cycle 2. **The samples will be collected at each time point listed above:**

1. **<u>Pre-therapy</u>: into three Streck tubes (provided).**
2. **<u>At subsequent time points</u>: Three Streck tubes for each time point tubes (provided).**

Whole blood samples for ptDNA analysis will be obtained at pre-therapy Day 1, Day 15 and Day 29. These samples are to be sent at room temperature to Dr. Yang's Lab for processing.

Inspect the tube prior to use for cracks, debris or discolored fluid inside. Do not use the Streck tube if it is expired, broken or appears to be contaminated. Draw the Streck tubes first if multiple tube types are drawn for the protocol Perform venipuncture and fill the tube until blood flow stops. Mix the blood immediately by gently inverting the Streck tube 8- 10 times. Inadequate or delayed mixing may result in clotting and inaccurate test results. If blood is collected through an intravenous line, ensure that line has been cleared of I.V. solution before beginning to fill Streck tubes.

PROTECT FROM EXTREME TEMPERATURES. Store or transport samples at temperatures of 6-30^{o}C. DO NOT REFRIGERATE OR FREEZE.

The whole blood samples will be delivered to Dr. Yang's lab at UAB for processing. His lab will store these samples and batch until ready to ship to Dr. Park's lab.

Dr. Yang's lab should be notified of these samples. The lab pager number is 2677. The laboratory address is:

The Hazelrig Salter Radiation Oncology Center
176F
Suite 2222G
(Phone: 205-975-2881)

Notification that batched samples will be sent should occur on the day of shipping or

before if possible by email to: bpark2@jhmi.edu. Follow IATA Packaging Instructions (See below, section E). Blood should be shipped attention to:

Attention: Ben Park, M.D., Ph.D.
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
1650 Orleans Street
Room 151
Baltimore, Maryland 21287
TE: 443-287-4480
Fax: 410-614-4073

All sample tubes to be labeled with an indelible marker on the blue color label including

1. Study Number (UAB 1372)
2. Subject Study Number
3. Date of Collection
4. Time Point of Collection (pre-Rx; Day 15, or Day 29 (Day 1 of cycle 2; pre-Rx)

B. UAB - Paraffin blocks (all patients)

Pre-therapy paraffin blocks/Mandatory Research Block will be obtained:
As a mandatory biopsy (referred to subsequently as PTMB) if accessible tumor site (per protocol). If possible, this biopsy, when obtained, should be labeled with an indelible marker to include:

1. The clinical trial identification number (UAB 1372)
2. The subject's study number
3. The date of acquisition

These paraffin blocks are to be collected for sectioning. Approximately fifteen sections will be cut from each of these blocks by the designated pathologist.

C. To UAB – Snap-Frozen research biopsies (all patients with accessible tumor sites)

Prior to therapy, two tumor tissue core samples will be snap frozen for research studies. Biopsy samples, preferably obtained with a 14-18 gauge core needle, should be flash (snap) frozen (close cap tightly), ideally within 5 minutes but not greater than 30 minutes from the biopsy procedure, and stored in liquid nitrogen or at -80°C until shipping. One core sample will be placed in each vial.

All cryovials (NALGENE® Cryoware™ 5000-0000) will be labeled with an indelible marker to include:

1. The study identification number (UAB 1372);
2. The subject's study number;
3. The date of acquisition

Dr. Yang's lab should be notified of these samples. The lab pager number is 2677. The laboratory address is:

The Hazelrig Salter Radiation Oncology Center
176F
Suite 2222G
(Phone: 205-975-2881)

Preparing Tissue in Frozen Cryovials

Snap Freezing: Do not Cut the tissue and simply ship as is. Place each core of tissue into a labeled individual 2.0 ml NALGENE® Cryoware™ cryovials. The label should contain the UAB clinical trial number (UAB 1372) followed by the subject's study number, as well as the date the specimen was collected. Do not place the patient's name or medical record number on the label. The container will become very cold. Do not handle with unprotected hands. Safety goggles should be use throughout the procedure. Snap freeze samples in liquid nitrogen. If not available, you may use an alcohol/dry ice bath. Fill pan about 1-2 inches deep with methanol. The depth should be enough to cover the height of the vial. Slowly add crushed dry ice until the boiling stops. The bath is now ready for use. Drop the sealed vials directly into the liquid nitrogen (LN_2) carefully. Leave the vials in the liquid nitrogen for at least one minute. Once frozen, transfer the samples using tongs or a large spoon to remove the vials from the liquid nitrogen and transfer to a –80 °C freezer until shipped.

D. Serum (microRNA, PK, M30)

Blood samples for the assays will be taken at the times described in the protocol. Serum will be obtained in s serum separator tubes and will be sent to: Dr. Yang's Lab.

Dr. Yang's lab should be notified of these samples. The lab pager number is 2677. The laboratory address is:

The Hazelrig Salter Radiation Oncology Center
176F
Suite 2222G
(Phone: 205-975-2881)

E. Pharmacogenetic Sample Processing

Blood samples for pharmacogenomic analyses will be collected on a first day before initiation of research agents. Blood will be collected into one 6 ml K2EDTA polypropylene blood collection tube (Becton-Dickinson) and into one PAX gene tube. The 6 mL polypropylene K2EDTA tube will be placed in an ice bath immediately following collection and stored upright in a freezer set at -20ºC (+/- 10ºC) until sending to the laboratory. It is important to collect a full tube of whole blood. The PAX gene tube should be stored upright at room temperature for a minimum of 2 hours or a maximum of 4 hours before processing or transferring to a freezer. They should be stored upright in a wire rack and stored at -20 degrees Celsius or colder until sending to the laboratory.

Blood samples should be sent as soon as logistically possible following blood draws to:
The University of Alabama at Birmingham

Attention: Center for Clinical Translation Science (CCTS) Laboratory, Jefferson Tower, Room 1531, 625 19th Street south, Birmingham, AL 35233

F. IATA Packing Instructions

650 GENERAL REQUIREMENTS

Shippers of diagnostic specimens where a relatively low probability exists that infectious substances are present must comply with Packaging Instruction 650 of these regulations. Diagnostic specimens being transported for the purpose of initial diagnosis may be considered to fall under this category where a low probability exists that infectious substances are present. The shipper must also ensure that shipments are prepared in such a manner that they arrive at their destination in good condition and that they present no hazard to persons or animals during shipment.

Inner packaging contains:

- A watertight primary receptacle(s)- for diagnostic specimens the maximum quantity must not exceed 500mL
- A watertight secondary packaging -the maximum quantity per outer packaging for diagnostic specimens must not exceed 4L
- An absorbent material- must be placed between the primary receptacle and the secondary packaging. No absorbent material is required when shipping solid substances.

If multiple primary receptacles are placed in a single secondary packaging they must be wrapped individually or for those transported in liquid nitrogen, separated and supported to ensure that contact between them is prevented. The absorbing material, for example cotton or wool, must be sufficient to absorb the entire contents of all primary receptacles.

- An outer packaging of adequate strength for its capacity, weight and intended use.

The primary receptacle or the secondary packaging used for liquid diagnostic specimens must be capable of withstanding, without leakage, an internal pressure which produces a pressure differential of not less than 95 kPa (0.95 bar, 13.8lb/in2) in the range of -40.oC to + 55.oC(-40.oF to 130.oF). It is not necessary for the primary or secondary packaging to be capable of withstanding 95 kPa pressure differential when solid diagnostic specimens are being shipped.

Packages consigned as freight must be at least 100 mm (4 in) in the smallest overall external dimension.

An itemized list of contents must be enclosed between the secondary packaging and the outer packaging. Each package and the "Nature and Quantity of Goods" box of the airbill must show the text "DIAGNOSTIC SPECIMEN PACKED IN COMPLIANCE WITH IATA PACKING INSTRUCTION 650" (example below). A Shipper's Declaration for Dangerous Goods is not required.

650 SPECIFIC REQUIREMENTS

Substances shipped at ambient temperatures or higher- Primary receptacles include those of glass, metal or plastic. Positive means of ensuring a leak-proof seal, such as heat seal, skirted

stopper or metal crimp seal must be provided. If screw caps are used these must be reinforced with adhesive tape or parafilm.

Substances shipped on dry ice must be placed outside the secondary packaging(s) or alternatively in an overpack with one or more completed packaging. Interior support must be provided to secure the secondary packaging(s) in the original position after the dry ice has dissipated. The packaging must be leak-proof. The outer packaging must permit the release of carbon-dioxide gas. The primary receptacle must maintain its containment integrity at the temperature of the refrigerant as well as at the temperatures and pressure of air transport to which the receptacle could be subjected if refrigeration were to be lost. New shipping regulations effective January 1, 2005 (Package must have both the shipper and recipient's name, address and phone number)

Package must have the new UN3373 symbol and the words "Diagnostic Specimen" adjacent to that symbol; keep the biohazard sticker in place as well.

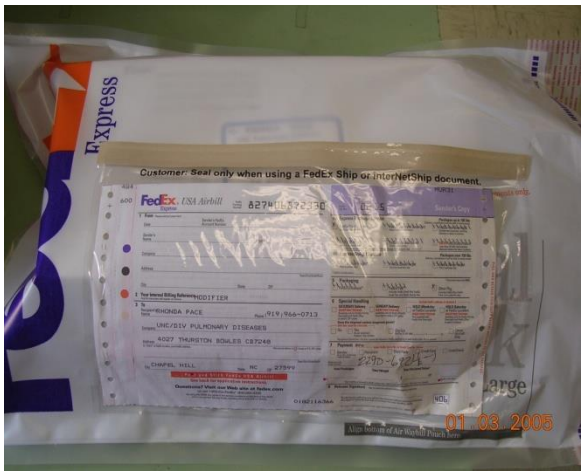
Labeled box should be inserted into the FedEx Diagnostic Shipping Bag as usual for shipment via FedEx.

904 GENERAL REQUIREMENTS

Carbon dioxide, (dry ice, LN_2), when offered for transport by air, must be in packaging designed and constructed to permit the release of carbon dioxide gas and to prevent a build-up of pressure that could rupture the packaging.

The net weight of the Carbon dioxide, solid (dry ice) must be marked on the outside of the package.

Arrangements between shipper and operators must be made for each shipment to ensure ventilation safety procedures are followed. When a Shipper's Declaration is not required, the information as required by 8.2.3 for dry ice (LN_2) must be contained in the "Nature and Quantity of Goods" box on the air bill, excluding the packing instruction number and packing group.



APPENDIX F
SOP for Investigator INDs Held by Physician Members of the UAB Comprehensive Cancer Center (available upon request)

APPENDIX G
Prohibited Medications

Drug Class	Agent	Washout[1]
CYP3A4 Inducers		
Antibiotics	All rifamycin class agents (e.g. rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (e.g. phenobarbital)	
Antiretrovirals	Efavirenz, nevirapine, tipranivir, etravirine	
Glucocorticoids (oral)	Cortisone (>50 mg), Hydrocortisone (>40 mg), prednisone (>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	7 days
Antifungals	Ketoconazole, itraconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	Delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir, atazanavir	
Calcium channel blockers	Verapamil, diltiazem	
Antidepressants	Nefazodone, fluvoxamine	
GI Agents	Cimetidine, aprepitant	
Fruits/fruit juices	Grapefruit, star fruit, and papaw	
Other	Amiodarone	6 months

Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennies	1 hr before/after dosing
Herbal/dietary supplements[3]	Ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	14 days

1. At the time of screening, if a subject is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of lapatinib and throughout the study period in order for the subject to be eligible to participate in the study.

2. Glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone are allowed. Glucocorticoid conversions are provided in parentheses.

3. Because the composition, pharmacokinetics, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is strongly discouraged during the study.

APPENDIX H
Suggested Management of Dermatological Toxicities

For all patients: advise patients to use acne cleanser twice daily (face, chest, and neck), apply alcohol-free moisturizer twice daily (e.g. Cetaphil), and use sunscreen with SPF 15 or higher.

Rash Severity

1. **Mild:** Generally localized, minimal symptoms, no impact on ADL

   Intervention: - Maintain dose & monitor for change in severity
   - No Treatment OR topical Clindagel 1% BID

   Reassess after 1-2 weeks; if symptoms worsen or fail to improve, proceed to next step

2. **Moderate:** Generalized, mild symptoms (e.g. pruritus/tenderness), minimal impact on ADL

   Intervention: - Maintain dose & monitor for change in severity
   - Topical Clindagel 1% BID plus minocycline 100 mg BID or Doxycycline 100 mg BID

   Reassess after 1-2 weeks; if symptoms worsen or fail to improve, proceed to next step

3. **Severe:** Generalized, severe symptoms (e.g. pruritus, tenderness), significant impact on ADL

   Intervention: - Consider drug holiday; continue treating as below:
   - Topical Clindagel 1% BID plus minocycline 100 mg BID or doxycycline 100 mg BID plus Medrol Dose-Pak

   Reassess after 1-2 weeks; if symptoms worsen or fail to improve, consider dose reduction

APPENDIX I
Diarrhea Management Guidelines

Diarrhea Management Guidelines

Background

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%) (Crown, 2008).

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

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

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

It is strongly recommended to give subjects receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below. Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

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

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

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

Definitions

National Cancer Institute (NCI) guidelines define diarrhea compared to baseline (Table 1).

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

Adverse Event Grade	Diarrhea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
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)
4	Life-threatening consequences; urgent intervention indicated
5	Death

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

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 Guidelines for Subjects Receiving Lapatinib Alone or as Combination

A) Uncomplicated Diarrhea

I. CTCAE Grade 1

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

1. Administer loperamide*****
   a. Initial dose 4mg followed by 2mg after every unformed stool. Re-evaluate after 24 hours, if:
      i. Diarrhea is resolving:
      - Continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
        - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns

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

   b. If Grade 1 diarrhea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (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 subject can begin to gradually re-introduce foods from their normal diet. If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications. Continue with study treatment. If Grade 1 diarrhea persists for ≥2 weeks, refer to the management guidelines for Persistent Grade 2 Diarrhea.

II. CTCAE Grade 2

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

1. Administer loperamide*****
   a. Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:
      i. Diarrhea is resolving, continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
      ii. Diarrhea is not resolving, consider loperamide dose of 2mg every 2 hours for 24 hours. If Grade 2 diarrhea persists after total of 48 hours of loperamide treatment, start second-line agents (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 subject can begin to gradually re-introduce foods from their normal diet. Refer to Section IV "Recurrent Diarrhea" for study treatment guidelines. If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications.

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

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

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

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

B) Complicated Diarrhea

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. Subject **must** call physician immediately for any complicated severe diarrhea event
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool*****
3. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhea
4. For dehydration use intravenous fluids as appropriate, if subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolytes and other tests as appropriate
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia

   Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤Grade 1 (without complicating features) and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750mg, contact *medical monitor for further guidance*): **INFO:** FOR ISS: remove the italicized guidance

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 subjects most at risk for life threatening complications

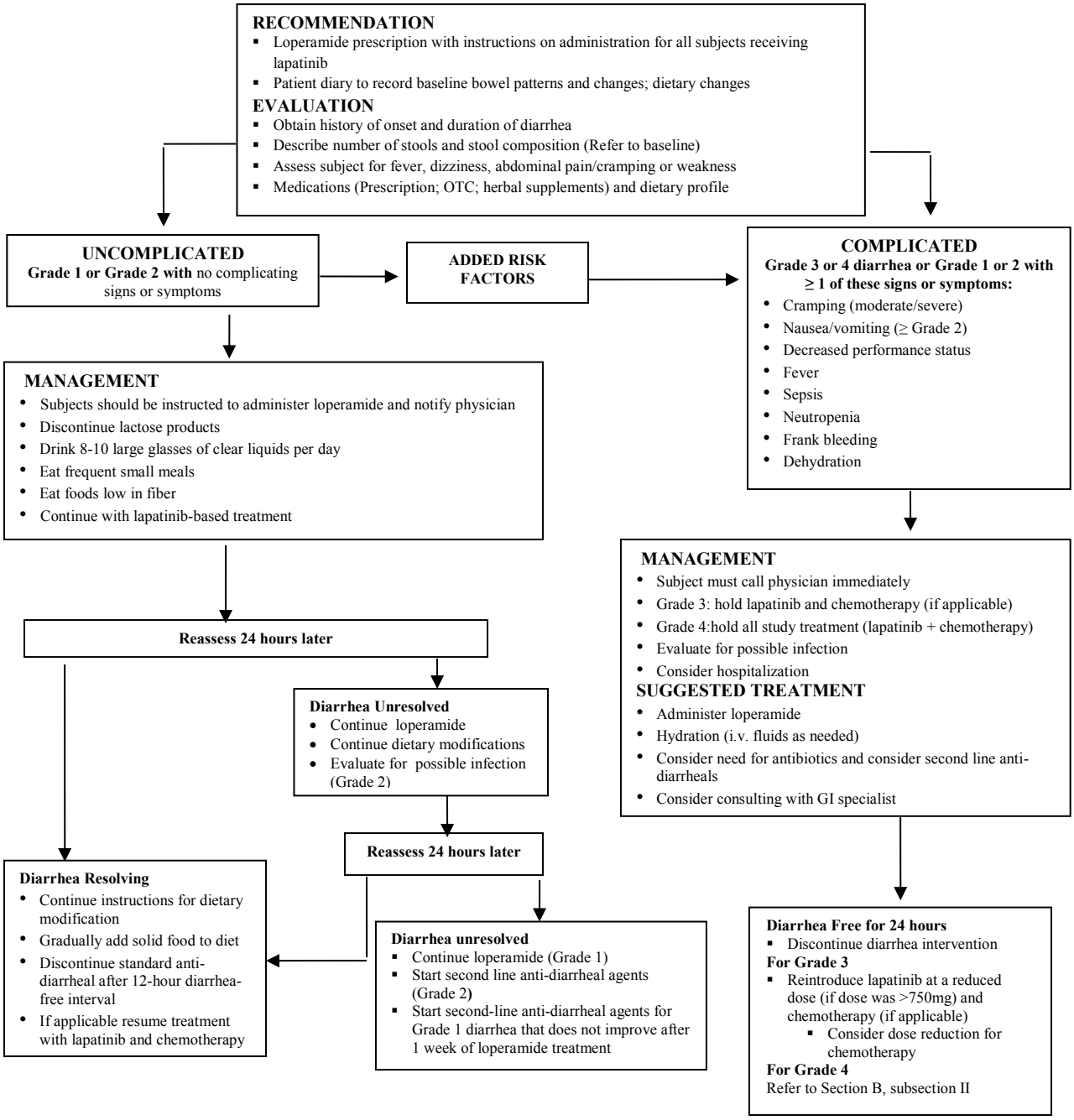
II.CTCAE Grade 4

1. Subject must call physician immediately for any Grade 4 diarrhea event
2. Hold treatment with lapatinib, hold chemotherapy or other concurrent anticancer therapy (if applicable)
   - Contact the Medical Monitor to discuss the patient case history and the possibility of re-initiation of study treatment, including dose modifications, following resolution of diarrhea (≤Grade 1)
     (***INFO: NOTE****: Can Modify Figure 1Grade 4 with this guidance; For Investigator sponsored studies substitute the above recommendation with the following:* 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 subject presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolyte and other tests as appropriate
6. Recommend consulting with GI specialist
7. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
8. Supportive care and other intervention should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for subjects most at risk for life threatening complications

*****It is recommended that the maximum cumulative daily dose of loperamide follows local guidance

Refer to and follow the recommended supportive care guidelines in the previous sections and as depicted in Figure 1.

Figure 1: Algorithm for the management of diarrhea in subjects treated with lapatinib-based therapy



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

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