Document Coversheet

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A Phase I Dose Escalation Study on the Safety of Lapatinib with Dose-Dense Paclitaxel in Patients with Platinum-Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer

Short Title: Lapatinib in Platinum-Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer

PROTOCOL FACE PAGE FOR
MCC INTERVENTIONAL THERAPEUTIC PROTOCOL

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PROTOCOL HISTORY & ABBREVIATIONS

Protocol Development History – Original Version to Current Version, w/ major Summary of Changes noted	
Original Protocol, v1 6/12/2020	PRMC full review. *Resolution*: Changes required.
Original, Revision v2 6/19/2020	Revision of original protocol to address PRMC critiques
7/8/2020	PRMC approved Revision version 2.
7/8/2020	UKHC CRSO completed Medicare coverage analysis.
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Original, Revision v3 8/28/2020	Protocol revised based on creation of order sets.
9/22/2020	PRMC approved Revision version 3.
Original, Revision v4 10/2/2020	Minor revisions to protocol stemming from creation of data capture forms.
Original, Revision v5 10/28/2020	Clarifying that physical exams and ECOG are only performed on Day 1 of each cycle. Clarifying that patients with active HIV are excluded except w undetectable viral load.
11/17/2020	**Open to Accrual**
Amendment 1 3/5/2021	Protocol amended to clarify that peritoneal and fallopian tube cancers are also included, in addition to ovarian cancer.
Amendment 2 10/07/2021	Protocol amended to clarify patients with grade 2 or less anemia are not required to recover to grade 1 to proceed on study.
Amendment 3 12/13/2021	Protocol amended to clarify follow-up for toxicity and disease response (Study Calendar, 6.7, 12.1.1).
Amendment 4 02/01/2023	The 13DEC2021 protocol was updated to now include: 1) Cover Page: Remove the following personnel no longer at UK: McKayla J. Riggs, MD Kara Larson, PhD Holly Gallion, MD John Wu, PhD 2) Cover Page: Add Donglin Yan, PhD, the new study statistician 3) Section 6.3: Added the following as a DLT criteria: All patients will be evaluable for toxicity. Patient's requiring a dose reduction or delay in Cycle 1 will be considered a DLT. Patients with a Cycle 1 dose reduction or delay are allowed to continue on study treatment provided adverse effects have resolved or decreased to acceptable levels as outlined in section 7. Patients with does delays or reductions in Cycle 1 are evaluable for efficacy provided they receive 80% or more of planned dose intensity during Cycle 1 study treatment.

PROTOCOL ABBREVIATIONS	
ABC	ATP Binding Cassette
BOIN	Bayesian optimal interval
CA125	Cancer Antigen 125
DLT	Dose-limiting toxicity
FDA	U.S. Food and Drug Administration
IND	Investigational New Drug
Mg	Milligrams
MTD	Maximum tolerated dose
P-gp	P-Glycoprotein
RP2D	Recommended Phase 2 Dose
TKI	Tyrosine Kinase Inhibitors

SCHEMA

We will conduct a phase I dose escalation study of lapatinib and paclitaxel using a Bayesian optimal interval (BOIN) design. The primary objective of this study is to determine the recommended phase II dose of the combination of lapatinib and paclitaxel in recurrent platinum-resistant ovarian, peritoneal, or fallopian tube cancer.

	Cycles 1 – 3 *&					
	Day 1	**Days 6 - 7**	**Day 8**	**Days 13 - 14**	**Day 15**	**Days 16-28**
Drug Administration	*Paclitaxel*	*Lapatinib*	*Paclitaxel*	*Lapatinib*	*Paclitaxel*	This is the off-weeks period of the cycle, where no therapy is administered.
Sample Collection	Streck, cfRNA EDTA for PK		Streck cfRNA EDTA for PK		Streck cfRNA EDTA for PK	

*Cycle is 28 days, no treatment is given on Days 16-28;

&Patients may continue Paclitaxel as long as clinically indicated, however they will go off study treatment (Lapatinib) after 3 cycles of the Lapatinib-Paclitaxel combination treatment

On Day 1, patients will be initiated on standard of care paclitaxel at a dose of 80 mg/m^2. See **table above.** Blood samples will be obtained for analysis of lapatinib concentrations, and cell-free RNA.

On Days 6, 7, 13, and 14, lapatinib will be self-administered twice a day. The starting dose of lapatinib is 750 mg twice a day and will be escalated, with three patients per cohort. Subjects will be asked to record lapatinib administration on a pill diary.

On Days 8 and 15, additional doses of paclitaxel will be administered. Blood samples will be obtained for analysis of lapatinib concentrations prior to paclitaxel administration on days 8 and 15.

After Cycle 1, patients will continue on paclitaxel and lapatinib combination treatment for up to 2 additional cycles.

DLT will be defined as any grade 3 or greater non-hematological toxicity per CTCAE version 5.0 or any grade 4 hematological toxicity and will be assessed after 1 cycle (4 weeks) of treatment.

Standard of care **response assessments** will be performed after 3 cycles of combination Lapatinib and Paclitaxel treatment.

Table 1. Dose Escalation Scheme

Dose Level	**Lapatinib ***	**Paclitaxel # &**
Level -1	500 mg PO BID	80 mg/m^2, Days 1, 8, 15
Level 1	750 mg PO BID	
Level 2	1500 mg PO BID	
Level 3	2000 mg PO BID	

* Day 6-7 week 1 (prior to dose 2 of Paclitaxel) and week 2 (prior to dose 3 of Paclitaxel)

weekly x3 in a 28-day cycle, until progression or intolerance;

& patients may continue Paclitaxel as long as clinically indicated, however they will go off study treatment (lapatinib) after 3 cycles of Lapatinib-Paclitaxel combination treatment

TABLE OF CONTENTS

PROTOCOL HISTORY & ABBREVIATIONS 2
SCHEMA 4
1. OBJECTIVES 7
1.1 Primary Objective 7
1.2 Secondary Objectives 7
1.3 Exploratory Objective 7
2. BACKGROUND 7
2.1 Platinum Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer 7
2.2 ABCB1 8
2.3 Lapatinib 8
2.4 Study Rationale 13
2.5 Correlative Studies Rationale Background 13
3. PATIENT ELIGIBILITY 14
3.1 Inclusion Criteria 14
3.2 Exclusion Criteria 14
3.3 Inclusion of Men and Minorities 15
4. INVESTIGATOR REQUIREMENTS AND REGISTRATION PROCEDURES 16
4.1 Investigator and Research Associate Registration with MCC 16
4.2 Clinical Trial Registration with clinicaltrials.gov and release of trial results 16
4.3 Enrollment Guidelines 16
4.4 Informed Consent 16
4.5 Patient Registration 17
4.6 General Guidelines 18
5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES 18
5.1 Summary Table for Specimen Collection 18
6. TREATMENT PLAN 18
6.1 Enrollment and Screening Process 18
6.2 Administration of Lapatinib and Paclitaxel 19
6.3 Definition of Dose-Limiting Toxicity: 20
6.4 Compliance 21
6.5 General Concomitant Medication and Supportive Care Guidelines 21
6.6 Duration of Therapy 21
6.7 Duration of Follow-Up 22
7. DOSE MODIFICATIONS of lapatinib and Paclitaxel 22
7.1 Lapatinib 22
7.2 Treatment modifications of Paclitaxel 24
8. PHARMACEUTICAL INFORMATION for Lapatinib and paclitaxel 26
8.1 Lapatinib 26
8.2 PHARMACEUTICAL INFORMATION for Paclitaxel 30
9. STATISTICAL CONSIDERATIONS 34
9.1 Study Design/Endpoints 34
9.2 Sample Size/Accrual Rate 34
9.3 Analysis of Primary Endpoint 34
9.4 Analysis of Secondary Endpoints 35
9.5 Analysis of Correlative Endpoints 35
10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 35
10.1 Comprehensive Adverse Events and Potential Risks (CAEPR) list for lapatinib

(GW572016, NSC 727989) in combination with paclitaxel 35
10.2 Adverse Event Characteristics 39
10.3 MCC Expedited Adverse Event Reporting Guidelines 39
10.4 Expedited Reporting to External Agencies 41
10.5 Expedited Reporting to UKHC Hospital Risk Management 41
10.6 Routine Adverse Event Reporting 41
10.7 Pregnancy 41
10.8 Secondary Malignancy 41
10.9 Second Malignancy 41
11. STUDY CALENDAR 42
12. MEASUREMENT OF EFFECT 43
12.1 Response Criteria 43
13. STUDY APPROVAL, OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS 44
13.1 Protocol Review and Monitoring Committee and Institutional Review Board 44
13.2 Quality Assurance 44
13.3 Data and Safety Monitoring Committee 45
13.4 Data Reporting 46
13.5 Data Management 46
13.6 Compliance with Laws and Regulations 46
14. REFERENCES 48
APPENDIX A. PERFORMANCE STATUS 51
APPENDIX B. PATIENT DRUG INTERACTIONS 52
APPENDIX C. Pill Diary – Lapatinib 53
APPENDIX D. Drug Accountability Form 60

1. OBJECTIVES

1.1 Primary Objective

To determine the recommended phase II dose of the combination of lapatinib and paclitaxel.

1.2 Secondary Objectives

1.2.1 To determine the adverse effects of the combination of lapatinib and paclitaxel

1.2.2 To assess the plasma concentrations of lapatinib

1.2.3 To determine the proportion of patients with clinical benefit defined as clinical progression free survival at one year from start of protocol therapy.

1.3 Exploratory Objective

1.3.1 ABCB1 expression will be evaluated in cell-free RNA in collaboration with the Markey Cancer Center Oncogenomics Shared Resource Facility using blood samples obtained at the same time as the PK blood samples. They will be extracted with the Norgen RNA extraction kit and analyzed with the NanoString nCounter PanCancer Progression Panel.

2. BACKGROUND

2.1 Platinum Resistant Ovarian, Peritoneal, or Fallopian Tube Cancer

In clinical practice and research, the term “ovarian cancer” is used to describe cancers that are histologically similar and originate in either the ovary, fallopian tube, or peritoneum. These cancers arise from the same epithelial tissue found on the surface of the ovary, the lining of the peritoneum, or the fallopian tube. As such, it is often difficult to determine precisely where the cancer started. Regardless of the site of origin, the diagnosis and treatment of these cancers is the same. Ovarian cancer is the most deadly gynecologic malignancy. 80% of women with ovarian cancer are diagnosed with advanced-stage disease with a 5-year survival of only 40 to 50% [1]. Approximately 70% of patients will experience recurrence after primary cytoreductive surgery and standard first-line chemotherapy with carboplatin and paclitaxel. This most often occurs in the first two years after diagnosis. Platinum-resistance is defined as either cancer progression or recurrence three to six months following platinum treatment exposure. Platinum-resistance is the strongest prognostic factor for overall survival. While most agents have an accepted RR of 20-30% in the platinum-resistant setting, some reports have suggested response rates as high as 50% for weekly paclitaxel (not q 3 week regimen).[2-4] [5]. Rapid development of paclitaxel resistance contributes to the poor outcomes observed in this setting.

2.2 ABCB1

Resistance to cancer chemotherapy, commonly referred to as multidrug resistance (MDR), is a pervasive impediment to successful treatment of solid tumors, including ovarian cancer. MDR is commonly driven by elevated expression of the ATP binding cassette (ABC) family of transmembrane transporters that can limit intracellular drug levels and therapeutic efficacy. *ABCB1* encodes multidrug resistance protein (MDR1), an ATP-binding cassette member responsible for cellular efflux of paclitaxel. Upregulation of *ABCB1* is significantly associated with both drug resistance and poor prognosis in ovarian cancer and develops as a response of the cancer cell to chemotherapy administration [6]. While *ABCB1* upregulation after paclitaxel administration is well known, there is currently no clinically available method for preventing or overcoming it.

Clinical development of small molecule inhibitors of ABC transporters to prevent MDR has been ongoing for more than three decades. P-glycoprotein (P-gp), encoded by the *ABCB1* gene, was the first ABC transporter identified and is perhaps the best characterized ABC family member. P-gp functions to protect cells from the damage of xenobiotic and toxic substances, including chemotherapeutic agents (e.g., taxanes, vinca alkaloids, anthracyclines) [7]. Elevated P-gp expression reduces sensitivity to paclitaxel across a wide variety of cancer cell lines [8-10] and is linked to unfavorable clinical outcomes among ovarian cancer patients [11]. Clinical use of P-gp inhibitors was initially confined to drugs that had been developed for other purposes, but these agents (e.g., verapamil, quinine, and cyclosporine) required high doses to inhibit P-gp function and proved to be too toxic [12, 13]. Better tolerated second, third, and fourth-generation P-gp inhibitors have subsequently been developed; however, clinical benefit remains elusive [14, 15]. Evidence suggests that another class of widely used anti-cancer drugs also has potential off-target effects that disrupt P-gp function. Tyrosine kinase inhibitors (TKI) are targeted anti-cancer agents developed to antagonize tyrosine kinases, a class of enzymes frequently overexpressed in tumor cells. Remarkably, many of these TKIs (e.g., dasatinib, gefitinib, sorafenib, vandetanib, lapatinib) also inhibit the function of P-gp [16-21].

2.3 Lapatinib

Lapatinib (Tykerb; GlaxoSmithKline, Research Triangle Park, NC) is a compound that potently and specifically inhibits both EGFR and HER2 [22]. This orally available drug is a small-molecule reversible inhibitor of both EGFR and HER2 TKs [23]. The United States Food and Drug Administration (FDA) recently approved lapatinib in combination with capecitabine for the treatment of advanced HER2+ breast cancer [24].

Lapatinib (originally known as GW572016) is a 4-anilinoquinoline derivative. It is a large head group quinazoline, and differs in structure from the small head group quinazolines, such as erlotinib [22]. Lapatinib's bulky aniline head group reaches deep into an opened back pocket of EGFR. This difference in structure may explain lapatinib's slow disassociation rate with a half-life of more than 300 minutes from the EGFR and subsequent prolonged inhibition of EGFR. Lapatinib binds the kinase ATP-binding cleft of EGFR-TK during its inactive conformation [22]. However, it may not readily bind active-state EGFR-TK [25].

Lapatinib potently but reversibly binds to the intracellular TK domains of EGFR and HER2, leading to inhibition of substrate phosphorylation. This inhibition blocks downstream mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) proliferation and survival signaling pathways both in vitro and in vivo [26, 27]. Depending on tumor type, lapatinib-treated cells may undergo either apoptosis or growth arrest. Lapatinib is highly potent, with a 50% inhibitory concentration (IC_{50}) <0.2 μM for both, EGFR and HER2. Additionally, lapatinib is selective for EGFR and HER2 [22]. When tested against a panel of other kinases, IC_{50} to achieve inhibition were > 1000 fold greater than that required for EGFR and HER2[27] [24].

Lapatinib effectively inhibits human tumor cell lines that overexpress EGFR or HER2, indicating selectivity for cancer cells that over-express these receptors. In murine xenograft models, lapatinib inhibited auto-phosphorylation of EGFR and ErbB2 as well as downstream MAPK/Erk1/2 and P13k/AKT pathways. A favorable toxicity profile in rodents and dogs was seen without evidence of cardiac toxicity during high exposure over 6 and 9 months respectively.

Pharmacokinetics
The PKs of lapatinib have been described in healthy volunteers using single- and multiple-dose designs [28]. Sixteen patients received a single dose of lapatinib ranging from 10-250 mg; 27 patients received lapatinib doses ranging from 25-175 mg daily for eight consecutive days. Lapatinib was well tolerated at repeat doses up to 175 mg/day. For the single-dose study, the area under the curve extrapolated to infinity (AUC_{∞}) increased with a geometric mean slope of 1.17 (90% CI 1.09-1.25). Mean half-life ranged from 6-9 hours, increasing in a dose dependent manner. Peak serum concentrations were reached at 3-4 hours. On the multiple-dose study, average half-life was approximately 7 hours on day 1, and increased to 11 hours on day 8 for the 175 mg dose. Peak serum concentrations were reached at 3-4 hours, and did not significantly change over time.

In phase I studies, doses up to 1800 mg/day were used. Sixty-seven patients were randomly assigned to 500, 650, 900, 1200 and 1600 mg/day of lapatinib administered continuously for 21 days. Serum concentration peaks were reached 3-6 hours after dosing, and with repeated dosing a nearly two-fold accumulation occurred on day 20. Although variable, the maximum concentration (Cmax), the minimum concentration (Cmin) and AUC generally increased with increasing dose.

Clinical Toxicology
Lapatinib monotherapy produces minimal side effects. Burstein et al. reported the most common toxicities as diarrhea, nausea and rash for a once daily dose of 1500 mg [29]. The incidence of grade 3 diarrhea was 10%, grade 3 nausea 3%, grade 3 rash <1%. Interestingly, a phase II study of lapatinib monotherapy in inflammatory breast cancer (IBC) noted somewhat different toxicities despite using the same dose. Johnston et al. noted grade 3/4 diarrhea (11%), musculoskeletal pain (16%), and dyspnea (11%, with 9% pleural effusion although no grade 3/4 decreases in LVEF occurred on study) [30].

Lin et al. treated a different patient population, with a higher effective dose of 750 mg given twice-daily [31]. The most common grade 3 toxicities were diarrhea (21%), fatigue (15%), headache (10%) and increased transaminases (8%). Grade 3 nausea and rash were noted, but occurred in 5% or fewer of patients. Gomez et al. compared 1,500mg per day to 500mg twice daily and noted no significant differences in toxicity between the once-daily and twice-daily dosing schedule. The

most common toxicities included diarrhea, rash, pruritus and nausea; grade 3 toxicity occurred less than 5% for all, regardless of treatment arm.

As expected, more adverse events occurred with chemotherapy combination therapies, although most toxicity remained grade 1 or 2. Therapy discontinuation due to adverse events did not differ significantly between the two arms of NCT00078572 (13% vs. 12%) [24]. Minimal cardiac toxicity was seen regardless of treatment arm, despite patients having previously received treatment with anthracyclines (97%) and trastuzumab (96% for combination therapy arm.) Five asymptomatic cardiac events were reported: 4 on combination therapy and 1 on monotherapy.

Cardiac toxicity has been noted with lapatinib, although at very low frequency. In the phase II study by Burstein et al., only one patient experienced a grade 3 decrease in left ventricular ejection fraction (LVEF) despite heavy pre-treatment with anthracyclines and trastuzumab. Lin et al. did not report any symptomatic congestive heart failure (CHF) on study; although four patients had an asymptomatic decline in LVEF below 50% (these patients had received a median of two prior trastuzumab-containing chemotherapies.) Treatment was continued in at least two of these patients, with subsequent normalization of LVEF.

Cardiac toxicity from lapatinib has been noted in patients with non-breast malignancies. These patients would not have routinely received anthracyclines or trastuzumab, and these data suggest that lapatinib effects cardiac function even in the absence of prior cardiotoxic treatment. A phase II trial of patients with adenocarcinomas of the salivary glands, found two patients (5%) had asymptomatic LVEF declines of at least 10% [32]. Safran and colleagues reported two patients with pancreaticobiliary cancers developed to declines in LVEF$\geq$ 20% while receiving lapatinib on a phase I trial [33].

Perez et al. presented aggregate data for over 2,812 patients treated with lapatinib [34]. Lapatinib-associated LVEF decrease (NCI CTC grade 3 or $\geq$20% decline from baseline) occurred with a frequency of 1.3%. This decrease in LVEF was rarely symptomatic and generally reversible with cessation of drug. The majority of events (68%) occurred within nine weeks of starting lapatinib. Surveillance recommendations for cardiac toxicity associated with lapatinib have not been formally issued. Moy and Goss suggested following the standards set by the consensus guidelines issued for trastuzumab [35]. However, decisions about the frequency with which cardiac function is assessed, whether to stop for asymptomatic declines in LVEF, and whether to restart treatment after a decline in LVEF need to be made following an individual risk-benefit analysis. Using lapatinib in the setting of an abnormal LVEF remains controversial.

Hepatic/Renal Dysfunction
Lapatinib has not been studied in patients with renal dysfunction. However, as less than 2% of the drug is excreted unchanged by the kidney, dose adjustments for renal dysfunction should not be required. In contrast, while lapatinib has not been extensively studied in patients with hepatic dysfunction, preliminary studies suggest that those with severe hepatic impairment (Child Pugh Class C) have increased exposure to lapatinib and dose reductions should be considered [35].

Developmental/Reproductive Toxicity
Lapatinib administration has not been studied in pregnant or nursing women [36]. A case report

exists of a pregnant woman who received lapatinib through a clinical trial. She received approximately 11 weeks of lapatinib during the first and second trimesters, and delivered a healthy baby at the end of an otherwise uncomplicated pregnancy [37]. While lapatinib was not shown to be mutagenic by in vitro assays, use in pregnancy and by nursing mothers should be avoided.

Drug and Food Interactions
Drug Effects. Lapatinib is eliminated via excretion in the feces and hepatic metabolism. Hepatic metabolism occurs principally via cyctochrome P450 (CYP) 3A4 [35]. A clinical study in healthy volunteers demonstrated that concurrent administration of the strong CYP3A4 inhibitor ketoconazole increased the AUC of lapatinib and prolonged the half-life and that concurrent administration of the CYP3A4 inducer carbamazepine reduced the AUC of lapatinib by 72% (package insert). Therefore, strong inhibitors of CYP3A4, including grapefruit juice should be avoided, as they may increase plasma concentrations of lapatinib and increase toxicity. If a strong inhibitor must be used concurrently, a dose reduction of 500 mg/m^2 may be considered. Likewise, concurrent use of strong inducers of CYP3A4 may lower plasma concentrations of lapatinib and decrease efficacy, and should be avoided. If strong inducers must be administered concurrently, dose escalation based on tolerability can be considered.

Lapatinib is also an inhibitor of CYP3A4 and CYP2C8 at clinically relevant concentrations. Drugs metabolized or excreted by CYP3A4 and CYP2C8 should be avoided or used with caution in patients receiving lapatinib. Additionally, modifications in gastric pH could affect absorption of lapatinib. It has been recommended that antacids be avoided for 2 hours before and after lapatinib use.

Food Effects. Absorption of lapatinib is impaired by low solubility and first-pass metabolism by CYP3A4/5 [38]. In addition, the impact of food on the PKs of lapatinib has been assessed and clinical pharmacokinetic studies demonstrate that high fat meals (54g, 50% fat) significantly increase the bioavailability of lapatinib [39]. While some authors have recommended exploiting this food-drug effect to use lower doses of lapatinib, and decrease cost, others have demonstrated that the effect of food on bioavailability has significant interpatient variability, with 68% variability in the exposure between patients, even when eating an identical meal [40, 41]. Given the unpredictable variability in plasma concentration with food, the inability to maintain a standard diet with chronic dosing, and the risk of adverse effects secondary to high interpatient variability, the safest approach appears to be administration of lapatinib on an empty stomach.

Lapatinib Monotherapy
Lapatinib is approved for the treatment of human epidermal growth receptor type 2 (HER2) overexpressing advanced or metastatic breast cancer (in combination with capecitabine) in patients who have received prior therapy (with an anthracycline, a taxane, and trastuzumab); HER2 overexpressing hormone receptor–positive metastatic breast cancer in postmenopausal women where hormone therapy is indicated (in combination with letrozole). The Lapatinib dose used in combination with capecitabine is 1250 mg once a day and the dose used in combination with letrozole is 1500 mg once a day.

Once-daily dosing schedules. Burris et al. conducted a phase I clinical trial of lapatinib in patients with advanced solid malignancies (n = 67) [38]. Lapatinib was tolerated at daily doses up to 1600

mg/day, with clinical activity at doses as low as 500 mg/day. A maximum tolerated dose was not reached, and dose escalation was instead limited by pill burden [42]. DLTs consisted of diarrhea and skin rash. Thirty patients in this trial had advanced breast cancer. Four of these patients, all HER2+, experienced a PR to therapy. All four patients had previously progressed on trastuzumab and taxane- or anthracycline-based chemotherapy. An additional 10 patients with breast cancer experienced SD, with the majority having SD for > 6 months.

Minami et al. reported similar findings from a comparable phase I study in Japan. The pharmacokinetic parameters were similar to Western patients, and common toxicities included rash, diarrhea, anorexia, fatigue, stomatitis, nausea and emesis. The phase II dose recommended by Minami et al. was 1600 mg/day continuously of lapatinib [43].

Twice-daily dosing schedules. Twice-daily dosing of lapatinib was explored early on in phase I testing, with doses up to 900 mg twice daily tolerated [44]. Division of the total daily dose results in roughly twice the drug exposure. In subsequent phase I studies, Burris et al. noted an association between diarrhea and dose, but not concentration of drug [38]. Diarrhea might therefore partly be the result of local effects on the gut epithelium.

Lapatinib 750 mg twice daily has been used in a phase II study evaluating the efficacy and safety profile of lapatinib in the treatment of HER2+ breast cancer metastatic to the brain [31]. Patients with HER2+ breast cancer and documented progression of brain metastases after whole brain radiotherapy, stereotactic radiosurgery or both were eligible. The primary endpoint was RR in the central nervous system (CNS). Thirty-nine patients were enrolled and lapatinib administered continuously on a 28-day cycle.

Lapatinib and Paclitaxel Combinations
Lapatinib and paclitaxel have been studied in combination with two general strategies; at standard doses in the neoadjuvant breast setting in combination with paclitaxel and with escalated doses as a single agent in the metastatic setting. In the neoadjuvant setting, in patients treated with standard doses for 12 weeks, the combination is well tolerated and effective. In the metastatic setting, pulse-dose, escalated, lapatinib has been reported in two clinical trials. Chien and colleagues conducted a phase I dose escalation study of lapatinib given as a 2-day pulse before nab-paclitaxel (Abraxane) dosed at 100 mg/m^2 per week. The maximum tolerated dose of lapatinib was 5250 mg/day in divided doses. Dose-limiting toxicities included Grade 3 vomiting and Grade 4 neutropenia. The majority of enrolled patients had lung cancer, and 65% of evaluable patients experienced a partial or stable response to this therapy, 72% of whom were previously taxane-refractory. Mean lapatinib concentration after the 2-day pulse was ~4000 ng/mL in the 4000 mg daily dose cohort. In another phase I study conducted by these investigators in patients with advanced, HER2 overexpressed breast cancer, single-agent lapatinib was escalated to 7000 mg a day in divided doses, administered for 5 days without dose-limiting toxicities. Despite the majority of patients having prior treatment with lapatinib, 13 of 41 (31%) either responded or had stable disease. Notably, mean lapatinib concentration was significantly higher in patients who derived clinical benefit than those who did not respond (5,727 ng/mL vs 2,174 ng/mL, respectively; $p < .001$).

2.4 Study Rationale

While *ABCB1* upregulation after paclitaxel administration is well known, there is currently no clinically available method for preventing or overcoming it. To develop a therapy able to prevent *ABCB1* upregulation and paclitaxel resistance, we have evaluated several *ABCB1* inhibitors in combination with paclitaxel in preclinical model systems. As described in our preliminary data, we have demonstrated that pulsed-dose lapatinib and paclitaxel are synergistic and that inhibition of *ABCB1* by lapatinib increases sensitivity to paclitaxel. Lapatinib is FDA approved, orally available, and previously studied in combination with weekly paclitaxel for breast cancer at doses of 1000mg to 1250mg daily (7000-8250mg per week) [45]. We are proposing to use twice daily dosing of lapatinib at a starting dose of 750 mg for 2 days (1500mg a day and 3000mg weekly dose), which is less than half of the continuous dose and has been shown to achieve plasma concentrations at 48 hours that are associated with synergy therefore, we can rapidly translate our findings into a novel, well-tolerated, and convenient combination regimen with significant potential for clinical activity. In this study, we propose to conduct a phase I dose-escalation study of lapatinib and paclitaxel for platinum-resistant ovarian, peritoneal, or fallopian tube cancer, which will establish the phase II dose for subsequent efficacy trials.

Lapatinib, in combination with weekly nab-paclitaxel is well tolerated at doses up to 5250 mg daily and resulted in clinical benefit in 65% of heavily pretreated subjects and plasma concentrations of lapatinib ranged from 2000-4000 ng/mL. In combination with paclitaxel, lapatinib concentrations of > 2000 nM (1200 ng/mL) are associated with synergy in preclinical models. Therefore, we are proposing a twice daily dosing schedule, as this regimen is associated with higher drug exposure, than once daily dosing schedules increasing the likelihood of achieving therapeutic concentration of > 2000 ng/mL.

Since twice-daily dosing lapatinib has not been studied in combination with paclitaxel, we are proposing a phase I dose escalation study to determine the dose able to achieve concentrations > 2000ng/mL while still being tolerable to patients. We anticipate that a short course of lapatinib, started two days prior to paclitaxel, will achieve adequate therapeutic concentrations, be well tolerated, and have a synergistic effect with paclitaxel by blocking P-gp.

2.5 Correlative Studies Rationale Background

2.5.1 Lapatinib and Paclitaxel Concentrations

Lapatinib plasma concentrations will be measured to assess the ability of this regimen to achieve concentrations associated with synergistic effect in prior studies.

2.5.2 ABCB1 Expression

Synergy is dependent on inhibition of ABCB1 and independent of ErbB2 inhibition. The Nanostring sequencing will be performed to determine how paclitaxel is affecting ABCB1. Nanostring utilizes the nCounter® platform to provide direct DNA detection and transcript quantification without requiring reverse transcription and PCR amplification. Nanostring has been utilized in 3,100 publications to date.

3. PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patients with histologically or cytologically confirmed ovarian, peritoneal, or fallopian tube cancer who recur within 12 months after platinum-based chemotherapy for which no standard curative measure exists. Recurrence defined by treating physician discretion.

3.1.2 Age ≥18 years.

3.1.3 ECOG performance status ≤ 2 (see Appendix A).

3.1.4 Adequate organ and marrow function at baseline (pre-study) as defined below:

- Absolute neutrophil count ≥1,000/mcL
- Platelets ≥75,000/mcL
- Total Bilirubin ≤ institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤ institutional upper limit of normal
- Glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2

3.1.5 Patients with a prior or concurrent malignancy (non-ovarian, non-peritoneal, or non-fallopian tube) whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen as determined by the treating physician are eligible.

3.1.6 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 History of hypersensitivity to lapatinib or paclitaxel

3.2.2 Uncontrolled intercurrent illness such as active infections. Other illnesses will be evaluated and eligibility status determined at the discretion of the treating physician and the investigator.

3.2.3 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP 450 3A4 are ineligible unless they can be transitioned off this medication prior to study drug initiation. Lists including medications and substances known or with the potential to interact with the CYP3A4 isoenzymes are provided in Appendix B.

3.2.3.1 Patients on strong inhibitors or inducers will become eligible if they discontinue all such medications at least 5 days prior to start of therapy and no further doses are anticipated for the duration of investigational therapy.

3.2.3.2 Patients currently taking weak CYP3A4 substrates, inducers, and/or inhibitors (Appendix B) are eligible but should be transitioned to an acceptable alternative if available (as determined by the treating physician.)

3.2.4 Patients with malabsorption syndrome or other condition that would interfere with intestinal absorption. Patients must be able to swallow tablets.

3.2.5 Congestive heart failure (CHF) is a known but rare complication of lapatinib. Therefore, patients with a left ventricular ejection function (LVEF) less than 50% or the lower limit of institutional normal are ineligible.

3.2.6 Pregnant and/or lactating women are excluded because of risk of teratogenic or abortifacient effects. Women of childbearing potential and men should use contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

3.2.7 Patients with active HIV are excluded, with the exception of Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2.8 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.2.9 Patients may not be receiving any other anti-cancer investigational agents.

3.2.10 Patients with baseline neuropathy > Grade 1

3.3 Inclusion of Men and Minorities

Ovarian, peritoneal, and fallopian tube cancers occur exclusively in women, so men are excluded from this study.

4. INVESTIGATOR REQUIREMENTS AND REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with MCC

All investigators must be qualified by education, training and experience to assume responsibility for the proper conduct of human subject research. Investigators are responsible for being able to provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation and training per institutional, state and federal guidelines. All investigators conducting MCC trials will register with the MCC Clinical Research Office and complete all requisite training and registrations per MCC SOPs.

4.2 Clinical Trial Registration with clinicaltrials.gov and release of trial results

The MCC-CRO Regulatory unit will assist with registration. Results will be released on clinicaltrials.gov according the data guidelines and requirements of clinicaltrials.gov.

4.3 Enrollment Guidelines

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be screened in the University of Kentucky Markey Cancer Center clinics by the investigators and study personnel with oversight by the Principal Investigator (PI). Upon obtaining proper consent, patients will be enrolled into the study.

4.4 Informed Consent

The goal of the informed consent *process* is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent *document* provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent *document* is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that she may withdraw from the study at any time and

that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.4.1 Delegation of Tasks Log (DTL)

All MCC studies require a Delegation Task Log, which is maintained by the MCC Regulatory Unit of the Clinical Research Office. The DTL for this study has training requirements as follows:

In order to be added to the DTL for a given study, each staff member must have appropriate training to conduct assigned duties including but not limited to protocol specific training and review of the final protocol. Site initiation visit training will be set up by the MCC Regulatory and Quality Assurance Program members. The DTL log will identify the protocol version on which each staff member was trained when being added to a study.

The protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The protocol Principal Investigator and statistician have access to the data at all times through OnCore.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the protocol Principal Investigator.

4.5 Patient Registration

To enroll a patient, the following information should be reviewed by the clinical research nurse (CRN) / clinical research associate (CRA) with the study physician per MCC SOPs to confirm eligibility:

- Copy of required laboratory tests
- Pathology reports
- Physician dictations
- Imaging reports
- Signed patient consent form
- HIPAA authorization form
- Referring physician records as available
- Other required screening procedures when applicable
- Eligibility Checklist

Once eligibility is confirmed by completion of the Eligibility Checklist, the CRN/CRA will complete subject enrollment in the OnCore database. To complete the enrollment process, the CRN/CRA will complete the OnCore on-study form, which comprises the following:

- Assignment of a patient study number
- Diagnosis
- Date of diagnosis
- Enter an On-Study date

4.6 General Guidelines

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following enrollment, the PI and the statistician must be consulted as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Specimen Collection and Handling		
Research labs for correlative studies	• Blood specimens for analysis of lapatinib plasma concentrations • Blood specimens for cell-free RNA extraction using the Norgen RNA extraction kit and analysis with the NanoString nCounter® PanCancer Progression Panel	Research labs are drawn by phlebotomists in clinic and sent to institutional central lab for processing and analysis

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Day 1 Cycles 1-3: Lapatinib plasma concentrations and cfRNA		
	• 20 mL blood in cfRNA Streck (mandatory)	BPTP
	• 10mL blood in EDTA (mandatory)	BPTP
Day 8 Cycles 1-3		
	• 10mL blood in EDTA (mandatory) • 20 mL blood in cfRNA Streck (mandatory)	BPTP BPTP
Day 15 Cycles 1-3		
	• 10 mL blood in EDTA (mandatory) • 20mL blood in cfRNA Streck (mandatory)	BPTP BPTP

6. TREATMENT PLAN

6.1 Enrollment and Screening Process

Patients who satisfy all inclusion and none of the exclusion criteria specified in Section 3 will then

be approached to participate in the study. Prior to any study-required tests, subjects must first provide written informed consent to participate in this study. All lab tests and radiographic studies should be completed within 4 weeks prior to initiation of treatment.

Within 4 weeks of enrollment, all patients will undergo a history and physical exam, ECOG performance status evaluation, complete blood count with differential and platelets, and serum chemistries (including sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, BUN, creatinine, AST, alkaline phosphatase, and total bilirubin). Standard of care scans will be used to verify eligibility and appropriate stage of disease.

6.2 Administration of Lapatinib and Paclitaxel

6.2.1 Lapatinib

Treatment with lapatinib will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications described in Section 7. Avoid antacids within two hours of administration.

Regimen Description					
Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Paclitaxel	Premeds: Dexamethasone 12mg 30 minutes prior to paclitaxel; diphenhydramine 25-50 mg IVP or PO, loratadine 10mg PO (or cetirizine per SOC) and famotidine 20mg IV or PO.	80 mg/m2	IV over 2 hours +/- 15 minutes	Days 1, 8, 15	28 days (4 weeks)
Lapatinib	No pre-meds required per standard of care.	** see Table 1 dose assignment	PO on empty stomach.	Days 6-7 and 13-14	

Table 1. Pre-defined dose levels of lapatinib	
Cohort	**Lapatinib titration dose and schedule**
Dose level -1	Lapatinib 500 mg PO twice daily days 6-7 and 13-14
Dose level 1	Lapatinib 750mg PO twice daily days 6-7 and 13-14
Dose level 2	Lapatinib 1500mg PO twice daily days 6-7 and 13-14
Dose level 3	Lapatinib 2000mg PO twice daily days 6-7 and 13-14
Starting Dose may be adjusted for patients exhibiting abnormal liver function; see Section 7.1	

6.2.2 Paclitaxel

Treatment with paclitaxel will be administered during a scheduled infusion clinic appointment. Reported adverse events and potential risks are described in Sections 8 and 10. Appropriate dose modifications described in Section 7.

Table 1. Pre-defined dose levels of paclitaxel	
Cohort	**Paclitaxel titration dose and schedule**
Dose level 1	80 mg/m^2, Days 1, 8, 15

6.3 Definition of Dose-Limiting Toxicity:

DLT will be assessed after the first cycle (4 weeks) of treatment. DLT will be defined as the occurrence of any of the following events in the first 4 weeks of treatment (cycle 1) in the dose escalation cohorts that is possibly, probably or definitely related to this combination (Lapatinib with Paclitaxel).

Hematologic

- Febrile neutropenia (ANC <1000/ul and temperature ≥ 38.5C)
- Grade 4 neutropenia lasting > 5 days
- Grade 4 thrombocytopenia
- Grade 4 anemia that is not explained by underlying disease

Gastrointestinal

- Grade 3 or 4 nausea, vomiting, or diarrhea that persists >72 hr despite optimal anti-emetics and anti-diarrheal treatment

Others

- Any Grade 3 or greater adverse effect OR any >Grade 2 not improved after stopping the drug combination for more than a two-week period assuming all toxicities are related to lapatinib and occur during the first 4 weeks of treatment.
  - All patients will be evaluable for toxicity. Patient's requiring a dose reduction or delay in Cycle 1 will be considered a DLT. Patients with a Cycle 1 dose reduction or delay are allowed to continue on study treatment provided adverse effects have resolved or decreased to acceptable levels as outlined in section 7. Patients with dose delays or dose reductions in Cycle 1 are evaluable for efficacy provided they receive 80% or more of planned dose intensity during Cycle 1 study treatment.

Toxicity is graded by the Common Terminology Criteria for Adverse Events version 5, or any subsequent version released during the conduct of this study. Please refer to the following resource for further details: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0_2017-11-27_QuickReference

Patients incurring a DLT should go off protocol treatment. Patients requiring a delay of more than 2 weeks or more than two dose reductions should go off protocol therapy.

Management and Dose Modifications associated with the above adverse events are outlined in Section 7.

6.4 **Compliance**

Compliance with oral lapatinib will be documented by a medication diary and pill counts on returned study medication bottles by study staff as per MCC SOPs (See Appendices C and D). The patient will be requested to maintain a medication diary, documenting each dose of medication (see Appendix C). The medication diary will be returned to research team staff at the end of each course.

6.5 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of lapatinib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator or co-investigators should be alerted if the patient is taking any agent with potential drug interactions. Patients on strong inhibitors or inducers must discontinue all such medications at least 5 days prior to start of therapy. Patients currently taking weak CYP3A4 substrates, inducers, and/or inhibitors (Appendix B) should be transitioned to an acceptable alternative if available (as determined by the treating physician).

All supportive care, including, but not limited to, antiemetics, growth factors, blood products will be per the treating physician and will be standard of care.

6.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment with lapatinib may continue for 3 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of lapatinib
- Patient decides to withdraw from the study
- Unacceptable adverse effects
-
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason for early discontinuation of lapatinib/paclitaxel combination therapy and the corresponding Off-Treatment date must be documented in the OnCore Case Report Form (eCRF). For clarity, "off treatment" is the date when all courses have been completed (including the normal observation period) or discontinued due to one of the factors above, and no further treatment courses are planned. This is the date the patient has been officially taken off treatment. "Off study" is the date after which no further follow-up of the patient will occur.

6.7 Duration of Follow-Up

Safety Follow-up of Lapatinib: Patients will be followed for AEs for a total of 30 days after discontinuation (last dose) of lapatinib.

Patients removed from the study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients will be followed for disease response and survival for total of one year after initiation of protocol therapy or death, whichever occurs first.

7. DOSE MODIFICATIONS OF LAPATINIB AND PACLITAXEL

7.1 Lapatinib

7.1.1 Dose Delays/Modifications on Hepatotoxicity

Abnormal LFTs	**Management/Next dose for lapatinib**
AST and/or ALT >1 time ULN and normal total bilirubin	No change in dose
AST and/or ALT > 3 times ULN and normal total bilirubin level	Hold until AST and or ALT < 1times ULN
AST and/or ALT >2 times ULN and total bilirubin < 2 times ULN	Hold until AST and or ALT < 1 times ULN and normal total bilirubin level
AST and/or ALT >3 times ULN and total bilirubin ≥2 times ULN	Discontinue treatment
Sustained AST and/or ALT > 5 times ULN	Discontinue treatment

7.1.2 Other dose delays/modifications of Lapatinib

CNS toxicity	**Management/Next dose for lapatinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >one dose reduction should go off protocol therapy.	

Anemia	**Management/Next dose for lapatinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.***
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >one dose reduction should go off protocol therapy. ***Patients who start treatment with a grade 2 or less anemia, as allowed by the inclusion criteria are not required to re-cover to grade 1 to proceed	

Neutropenia	**Management/Next dose for lapatinib**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >one dose reduction should go off protocol therapy.	

Thrombocytopenia	**Management/Next dose for lapatinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >one dose reduction should go off protocol therapy.	

Diarrhea, Nausea or Vomiting	**Management/Next Dose for lapatinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring >one dose reduction should go off protocol therapy.	

7.1.3 Other Grade 3 or 4 Non-hematologic toxicities

Hold all treatment until toxicities resolve to < Grade 2 and discuss with PI prior to restarting.

7.2 Treatment modifications of Paclitaxel

7.2.1 Overview

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation of paclitaxel is planned for this study.

7.2.2 Individual Dose Modification Levels of Paclitaxel

All modifications are relative to the actual starting doses for the specific regimen. For application of individual dose modifications, see specific guidelines below. Allowable drug dose levels and instructions are summarized in Table A in Section 8.5.

7.2.3 General Guidelines for Hematologic Toxicity - Paclitaxel

Initial treatment modifications will consist of cycle delay and/or dose reduction as directed.

Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

7.2.4 Lower Limits for ANC and Platelet Count with Paclitaxel

Courses of treatment with cytotoxic chemotherapy (paclitaxel) will not begin until the ANC is $\geq$ 1,000 cells/mm^3 (CTCAE Grade 1) and the platelet count is $\geq$ 75,000/mm^3. All treatment will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two-week delay will no longer receive protocol-directed cytotoxic therapy (both lapatinib and paclitaxel). If paclitaxel is discontinued, lapatinib will also be discontinued.

7.2.5 Use of Hematopoietic Cytokines and Protective Agents with Paclitaxel

The use of hematopoietic cytokines and protective reagents are restricted as noted:

- In general, patients will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays or recurrent neutropenic complications after treatment modifications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with the NCCN clinical treatment guidelines and facility standard of care treatment practices (note: Neulasta may be administered on the same day as the chemotherapy if prescribed by the attending physician).

- Patients should not receive erythropoietin (EPO). Patients may receive iron

supplements, and/or transfusions as clinically indicated for management of anemia.

7.2.6 Dose Modifications for Paclitaxel

7.2.6.1 Hematology

Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,000 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,000 cells/mm^3 and platelets recover to a level >75,000 cells/mm^3. For patients to receive PACLitaxel on Days 8 and 15 of this trial, a platelet count of greater or equal to 50,000/mm3 and an ANC of greater than or equal to 500/mm3 are required, as per institutional SOC guidelines. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

7.2.6.2 Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to products containing polyoxyl 35 castor oil (e.g., cyclosporine for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel injection, USP. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be pre-medicated with corticosteroids (such as dexamethasone), diphenhydramine and H2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with paclitaxel.

7.2.6.3 Cardiovascular

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

7.2.6.4 Nervous System

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of paclitaxel IV, USP.

7.2.6.5 Hepatic

There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times the upper limit of normal. Extreme

caution should be exercised when administering paclitaxel to such patients, with dose reduction as recommended in Section 7.

7.2.7 Adjustments for Non-Hematologic Toxicity

Table A: Modifications for Non-Hematologic Toxicity			
Drug	**Regimen -2**	**Regimen -1**	**Regimen Starting Dose**
Paclitaxel	50 mg/m^2	65 mg/m^2	80 mg/m^2

Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy (both paclitaxel and lapatinib) for up to three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, then paclitaxel should be discontinued (along with lapatinib).

Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity.

Hepatic toxicity is not expected as a direct complication of chemotherapy in this patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

There will be no dose modifications of paclitaxel for alopecia, nausea, constipation, or diarrhea. It is recommended that routine medical measures be employed to manage nausea, constipation, and diarrhea.

In general, the occurrence of a hypersensitivity reaction to paclitaxel is not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug (paclitaxel) results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study.

7.2.8 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs.

8. PHARMACEUTICAL INFORMATION FOR LAPATINIB AND PACLITAXEL

8.1 Lapatinib

8.1.1 Lapatinib, oral tablet, Mechanism of Action, PDs and PKs

Name: lapatinib (NSC 727989)

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

Excipients present in the tablet include: microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate

The film-coat contains: Hydroxypropyl methylcellulose, titanium dioxide, macrogel/PEG 400, Polysorbate 80, FD&C Yellow No. 6, and FCF aluminum lake

Other Names: GW572016, Tykerb®

8.1.2 **Molecular Formula**: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$ **M.W.:** 943.48

Approximate Solubility: 0.007 mg/mL in water and 0.001 mg/mL in 0.1 N HCl at 25°C

8.1.3 Mechanism of Action - Lapatinib

Dual inhibitor of epidermal growth factor receptor (EGFR or ErbB1) and ErbB2 tyrosine kinases.

8.1.4 Pharmacodynamics - Lapatinib

The effect of lapatinib on the QT-interval was evaluated in a single-blind, placebo-controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumors (N = 58). During the 4- day treatment period, three doses of matching placebo were administered 12 hours apart in the morning and evening on Day 1 and in the morning on Day 2. This was followed by three doses of lapatinib 2000 mg (1.3 – 1.6 times the recommended dosage) administered in the same way. Measurements, including ECGs and pharmacokinetic samples were done at baseline and at the same time points on Day 2 and Day 4. In the evaluable population of subjects who had complete dosing and ECG assessments (N = 37), the maximum mean ΔΔQTcF (90% CI) of 8.75 ms (4.08, 13.42) was observed 10 hours after ingestion of the third dose of lapatinib 2000 mg. The ΔΔQTcF exceeded the 5 ms threshold and the upper bound 90% CIs exceeded the 10 ms threshold at multiple time points. There was a concentration-dependent increase in QTcF effects.

8.1.5 Pharmacokinetics - Lapatinib

Absorption
Absorption following oral administration of lapatinib is incomplete and variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hours). Peak plasma concentrations (Cmax) of lapatinib are achieved approximately 4 hours after administration. Daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an

effective half-life of 24 hours. At the dose of 1,250 mg daily, steady-state geometric mean [95% confidence interval (CI)] values of Cmax were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.h/mL (23.4 to 56 mcg.h/mL). Divided daily doses of lapatinib resulted in approximately 2-fold higher exposure at steady state (steady-state AUC) compared to the same total dose administered once daily. Systemic exposure to lapatinib is increased when administered with food. Lapatinib AUC values were approximately 3- and 4-fold higher (Cmax approximately 2.5- and 3-fold higher) when administered with a low-fat meal (5% fat-500 calories) or with a high-fat meal (50% fat-1,000 calories), respectively.

Distribution
Lapatinib is highly bound (greater than 99%) to albumin and alpha-1 acid glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters breast cancer-resistance protein (BCRP, ABCG2) and P-glycoprotein (P-gp, ABCB1). Lapatinib has also been shown to inhibit P-gp, BCRP, and the hepatic uptake transporter OATP 1B1, in vitro at clinically relevant concentrations.
Metabolism
Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which accounts for more than 14% of the dose recovered in the feces or 10% of lapatinib concentration in plasma.

Elimination
At clinical doses, the terminal phase half-life following a single dose was 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours. Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with negligible (less than 2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of 27% (range 3% to 67%) of an oral dose.

Effects of Age, Gender, or Race
Studies of the effects of age, gender, or race on the pharmacokinetics of lapatinib have not been performed.

8.1.6 Absorption, Distribution and Elimination of Lapatinib

Absorption: Incomplete and variable

Protein binding: >99% to albumin and alpha1-acid glycoprotein

Metabolism: Hepatic- extensive via CYP3A4 and 3A5, and to a lesser extent via CYP2C19 and 2C8 to oxidized metabolites

Half-life elimination: ~24 hours

Time to peak, plasma: ~4 hours (Burris, 2009)

8.1.7 Lapatinib - Metabolism and Excretion

Metabolism: *In vitro* studies with human liver microsomes indicate that lapatinib is metabolized by CYP3A4 and CYP3A5, and to a lesser extent CYP2C19 and CYP2C8.

Excretion: Lapatinib is primarily excreted in feces, with minor renal clearance (27% as

unchanged drug; range 3% to 67%); urine (<2%).

8.1.8 Specific Populations – Hepatic Impairment, Lapatinib

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic sub-study of a monotherapy trial with lapatinib (n = 1,194). Severe liver injury (ALT greater than 5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DQA1*02:01 or DRBI*07:01 allele carriers was 8% versus 0.5% in non-carriers. These HLA alleles are present in approximately 15% to 25% of Caucasian, Asian, African, and Hispanic populations and 1% in Japanese populations. Liver function should be monitored in all patients receiving therapy with lapatinib regardless of genotype.

Administration of lapatinib in patients with severe hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction should be considered for patients who develop severe hepatic impairment during the study treatment.

CYP3A4 inhibitors: Avoid the use of concomitant strong CYP3A4 inhibitors. When a strong CYP3A4 inhibitor is discontinued, allow ~1 week to elapse prior to adjusting the lapatinib dose upward.

CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers.

8.1.9 Special Considerations - Drug Accountability, Lapatinib

The investigator has overall responsibility for the accountability. The UK Investigational Drug Service (IDS) will maintain a careful record of the receipt, dispensing and final disposition of all lapatinib per institutional guidelines. See Appendix D, and Appendix C.

A list of the adverse events and potential risks associated with lapatinib (the investigational agent administered in this study) can be found in Section 10.

8.1.10 Drug Interaction Studies, Transporters and In Vivo

In vitro studies with human liver microsomes indicate that lapatinib is metabolized by CYP3A4 and CYP3A5, and to a lesser extent CYP2C19 and CYP2C8. Co-administration of lapatinib with potent or moderate CYP3A4 inhibitors (including grapefruit juice) and all CYP3A4 inducers is prohibited. Assess risk/benefit before co-administering lapatinib with weak CYP3A4 inhibitors. CYP3A4 inhibitors may decrease lapatinib metabolism (increasing levels); while CYP3A4 inducers may increase lapatinib metabolism (decreasing levels).

In human subjects, lapatinib inhibited CYP3A4 and CYP2C8 at clinically relevant concentrations. Avoid co-administration of lapatinib with drugs that are substrates of CYP3A4 or CYP2C8 and have narrow therapeutic windows.

Lapatinib potentially interacts with warfarin and quinazoline derivatives to increase INR and bleeding. Collect INR/PT determinations as clinically indicated per standard of care during the administration of lapatinib.

8.1.11 Supply, Storage and Handling of Lapatinib

8.1.11.1 Supply

Lapatinib is supplied by commercial sources as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with either FG HLS or GS XJG. The tablets contain 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib freebase per tablet. The tablets are packaged into HDPE bottles with child-resistant closures containing 150 tablets per container.

8.1.11.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

8.2 PHARMACEUTICAL INFORMATION for Paclitaxel

8.2.1 Paclitaxel, Mechanism of Action, PDs and PKs

Name: Paclitaxel (NSC 673089)

Chemical Name or Amino Acid Sequence: 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Other Names: Taxol, Taxol A, 33069-62-4

8.2.2 **Molecular Formula**: $C_{47}H_{51}NO_{14}$ M.W.: 853.9g/mol

Approximate Solubility: Insoluble in water

8.2.3 Mechanism of Action - Paclitaxel

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

8.2.4 Pharmacodynamics -Paclitaxel

Following intravenous administration of paclitaxel injection USP, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

8.2.5 Pharmacokinetics of Paclitaxel

Vdss: 24-hour infusion: 227 to 688 L/m2; biphasic with initial rapid distribution to the peripheral compartment; later phase is a slow efflux of paclitaxel from the peripheral compartment; widely distributed into body fluids and tissues; affected by dose and duration of infusion

Protein binding: 89-98%

Half-life elimination:
Children: 4.6 to 17 hours (varies with dose and infusion duration)
Adults 3-hour infusion: Mean (terminal) ~13 to 20 hours
Adults 24-hour infusion: Mean (terminal): ~16 to 53 hours

Effects of Age, Gender, or Race: None noted with paclitaxel

8.2.6 Metabolism and Excretion, Paclitaxel

Metabolism: Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel)
Excretion: Feces (~71%; ~5% as unchanged drug); urine (~14%)

8.2.7 Special Considerations – Hypersensitivity and Pre-Medication.

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day, to reduce the risk associated with hypersensitivity reactions to these drugs. This regimen should include a standard dose of dexamethasone (12mg IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IVP or PO, or an equivalent dose of an alternate H1 blocker such as loratadine 10mg PO), and a standard dose of antihistamine H2 (famotidine 20mg IV or PO).

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients in clinical trials. Fatal reactions have occurred in patients despite premedication. Pretreat all patients with corticosteroids, diphenhydramine, and histamine H2 antagonists. Do not re-challenge patients who experience severe hypersensitivity reactions to paclitaxel.

Patients with a history of severe hypersensitivity reactions to products containing polyoxyl 35 castor oil (e.g., cyclosporine for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel injection, USP. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be pre-medicated with corticosteroids (such as dexamethasone), diphenhydramine and H2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with paclitaxel.

8.2.8 Drug Interaction Studies, Transporters and In Vivo - Paclitaxel

It is a substrate of CYP2C8 (major), CYP3A4 (major), and P-glycoprotein/ABCB1. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

Caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CTP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

CYP2C8 Inhibitors (Moderate): May increase the serum concentration of paclitaxel (Conventional). Risk C: Monitor therapy

CYP2C8 Inhibitors (Strong): May increase the serum concentration of paclitaxel (Conventional). Risk C: Monitor therapy

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Risk C: Monitor therapy

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 substrates (high risk with inducers). Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. Risk D: Consider therapy modification.

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 substrates (High risk with inhibitors). Risk C: Monitor therapy.

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 substrates (High risk with inhibitors). Risk D: Consider therapy modification.

With hepatic function impairment, plasma paclitaxel exposure is increased.

8.2.9 Supply, Storage and Handling of Paclitaxel

8.2.9.1 Supply

Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi-dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of

paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

8.2.9.2 Preparation

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted per institutional standard of care administration to achieve a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP. All patients should be pre-medicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions.

8.2.9.3 Agent Ordering

Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

8.2.9.4 Storage and Handling

Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a phase I dose escalation study with expansion cohort. Dose escalation will be determined by a Bayesian optimal interval design (BOIN) design [41]. Patients are enrolled in cohorts with three patients in each cohort. The primary endpoint is the DLT rate of lapatinib in combination with paclitaxel at each dose level (RP2D of the combination). DLT rate is calculated as the total number of patients experiencing DLTs at the current dose level divided by the total number of patients treated at the current dose level. The calculation of DLT rate will only include DLT evaluable patients. A patient is considered evaluable if she completes 75% of doses. Patients who are not evaluable will be replaced to keep a total number of 15 evaluable patients on the study. Dose escalation and de-escalation decision are only determined by all evaluable patients at current dose level. The target DLT toxicity probability is set to be 30% for the trial. **After a cohort of 3 patients are enrolled on the trial, accrual of the trial will be temporarily suspended for evaluation of DLT**. Once DLT evaluation is done for this cohort of patients, the next dose level will be determined by currently available DLT information from all evaluable patients at that dose level based on BOIN dose escalation/de-escalation rule (Table 12.1.1). Once the dose escalation is finished or 15 patients are evaluated for the DLT, the final MTD or RPh2D will be determined by isotonic regression to pool information across all dose levels.

9.1.1 Dose Escalation / De-escalation Decision Rule for target DLT probability 30%

	Number of patients Treated								
Decision Rule	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Escalate (or highest) if # DLT <=	0	0	0	0	1	1	1	1	2
De-escalate (or lowest) if # DLT >=	1	1	2	2	2	3	3	3	4
Eliminate (or stop) if # DLT >=	--	--	3	3	4	4	5	5	5

Note: If none of three decision rules are applied, then the next cohort of patients will be enrolled at current dose level.

9.2 Sample Size/Accrual Rate

We plan to enroll up to a maximum 15 DLT evaluable patients for dose escalation to establish the MTD.

9.3 Analysis of Primary Endpoint

The dose escalation is determined by BOIN decision rule (Table 9.1.1) and MTD or Ph2RD will be determined by isotonic regression to pool information across all dose levels. Safety and tolerability of lapatinib will be monitored and assessed. AE counts will be summarized by descriptive statistics.

9.4 Analysis of Secondary Endpoints

Change of lapatinib levels from baseline throughout the treatment period will be represented by longitudinal profiles and analyzed by mixed effects model. Baseline is defined as the last non-missing serum paclitaxel level measurement prior to administrating lapatinib. Lapatinib levels may be categorized and summarized by response rates with confidence intervals.

9.5 Analysis of Correlative Endpoints

Changes in ABCB1 RNA expression will be compared pre and post paclitaxel. Post-hoc analyses will be conducted on with appropriate statistical methods depending on distribution and availability of collected data.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following lists of AEs (Section 10.1, 9.5) and the characteristics of an observed AE (Sections 10.2 and 10.3, 9.5) will determine whether the event requires expedited reporting **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks (CAEPR) list for lapatinib (GW572016, NSC 727989) in combination with paclitaxel

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AEs) associated with Lapatinib in combination with paclitaxel using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column, identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are exceptions for expedited reporting purposed to MCC (except as noted below).
NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER

Adverse Events with Possible Relationship to Lapatinib (GW572016) (CTCAE 4.0 Term) [n= 1890] – Version 2.4, January 6,2010			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			Expedited Reporting IF the AE exceeds the grade noted in parentheses
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		
	Neutropenia		***Neutropenia (Gr 3)***
	Thrombocytopenia		***Thrombocytopenia (Gr 3)***
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
ECG abnormality (Paclitaxel)			
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension***
	Abdominal pain		***Abdominal pain***
Diarrhea			***Diarrhea (Gr 2 persisting more than 72 hours)***
	Dyspepsia		***Dyspepsia***
	Flatulence		***Flatulence***
	Mucositis		***Mucositis***
	Stomatitis		***Stomatitis***
Nausea			***Nausea (Gr 2 persisting more than 72 hours)***
	Vomiting		***Vomiting (Gr 2 persisting over 72 hours)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue***
	Flu-like symptoms		***Flu-like symptoms***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		***ALT increased > 2x ULN***
	Aspartate aminotransferase increased		***AST increased > 2xULN***
	Blood bilirubin increased		***Blood bilirubin increased >2xULN***
		Electrocardiogram QT corrected interval prolonged	***Electrocardiogram QT corrected interval prolonged***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
	Dehydration		***Dehydration***

NERVOUS SYSTEM DISORDERS			
		CNS toxicity (any)	***CNS toxicity, Gr 2***
Peripheral neuropathy			***Peripheral neuropathy, Gr 1***
	Dysgeusia		***Dysgeusia***
	Headache		***Headache***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
	Dyspnea		***Dyspnea***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia		
	Alopecia		***Alopecia***
	Nail loss		
	Pruritus		***Pruritus***
	Rash acneiform		***Rash acneiform***
Rash maculo-papular			***Rash maculo-papular***
VASCULAR DISORDERS			
	Flushing		***Flushing***
OTHER NON-HEMATOLOGIC TOXICITIES			
			Other, Grade 2 or greater

10.1.1 Adverse Event List for Lapatinib

The most common adverse reactions (10% or more) for lapatinib are:

Central nervous system: fatigue and headache
Skin: Palmar-plantar erythrodysesthesia (seen in 53% with capecitabine), skin rash, alopecia, xeroderma, pruritus, nail disease
Gastrointestinal: diarrhea, nausea, vomiting, mucositis, stomatitis, anorexia, dyspepsia
Hematologic: decreased hemoglobin, neutrophils, platelet counts
Hepatic: increase in serum aspartate aminotransferase and alanine aminotransferase, and serum bilirubin
Musculoskeletal: asthenia, limb pain, back pain
Respiratory: dyspnea, epistaxis

10.1.1.1 Other AEs reported with lapatinib with undetermined attribution

Also reported on lapatinib (GW572016) trials but with the relationship to lapatinib (GW572016) still undetermined:

Cardiac disorders: atrial fibrillation, restrictive cardiomyopathy
Eye disorders: blurred vision
Gastrointestinal disorders: constipation, dysphagia, gastritis; Hemorrhage, GI; Obstruction, GI
General disorders and administration site conditions: Edema limbs; Fever; Pain
Infections and infestations: Infection

Investigations: alkaline phosphatase increased, , lymphocyte count decreased, , weight loss, white blood cell decreased
Metabolism and nutrition disorders: hyperglycemia, hypoalbuminemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia
Musculoskeletal and connective tissue disorders: arthralgia, back pain, myalgia
Nervous system disorders: cerebrospinal fluid leakage, depressed level of consciousness, dizziness, intracranial hemorrhage
Psychiatric disorders: insomnia
Renal and urinary disorders: acute kidney injury
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, epistaxis, pleural effusion
Skin and subcutaneous tissue disorders: alopecia, dry skin,
Vascular disorders: hypotension, thromboembolic event, hypovolemia

Note: Lapatinib (GW572016) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.2 Adverse Event List for Paclitaxel (other commercial agent being administered)

The most common adverse reactions (10% or more) for paclitaxel are:
Cardiovascular: Flushing (28%), ECG abnormality (14% to 23%), edema (21%), hypotension (4% to 12%)
Central nervous system: Peripheral neuropathy (42% to 70%; grades 3/4: ≤7%)
Dermatologic: Alopecia (87%), skin rash (12%)
Gastrointestinal: Nausea (≤52%), vomiting (≤52%), diarrhea (38%), mucositis (17% to 35%), stomatitis (15%; most common at doses >390 mg/m2), abdominal pain (with intraperitoneal administration)
Hematologic & oncologic: Neutropenia (78% to 98%; grade 4: 14% to 75%; onset: 8 to 10 days; median nadir: 11 days; recovery: 15 to 21 days), leukopenia (90%; grade 4: 17%), anemia (47% to 90%; grades 3/4: 2% to 16%), thrombocytopenia (4% to 20%; grades 3/4: 1% to 7%), hemorrhage (14%)
Hepatic: Increased serum alkaline phosphatase (22%), increased serum AST (19%)
Hypersensitivity: Hypersensitivity reaction (31% to 45%; grades 3/4: ≤2%)
Infection: Infection (15% to 30%)
Local: Injection site reaction (erythema at injection site, skin discoloration at injection site, swelling at injection site, tenderness at injection site: 13%)
Neuromuscular & skeletal: Arthralgia (≤60%), myalgia (≤60%), weakness (17%)
Renal: Increased serum creatinine (observed in Kaposi sarcoma patients only: 18% to 34%, severe: 5% to 7%)

10.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas have access to a copy of the CTCAE version 5.0. The CTCAE version 5.0 can be downloaded from CTEP web site:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick _Reference_8.5x11.pdf

- **For expedited reporting purposes only:**
  - AEs for lapatinib/paclitaxel combination therapy that are ***bolded and italicized*** in the CAEPR (*i.e.,* those listed in SPEER column, Section 10.1) should be reported (expedited) to the Overall PI and DSMC via OnCore only if the grade is above the grade provided in the SPEER.

- Attribution of the Adverse Event :

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly NOT related* to the study treatment
	Unlikely	The AE *is doubtfully related* to the study treatment
Related to investigational agent/intervention	Possible	The AE *may be related* to the study treatment
	Probable	The AE *is likely related* to the study treatment
	Definite	The AE *is clearly related* to the study treatment

10.3 MCC Expedited Adverse Event Reporting Guidelines

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy, as specified in the tables below. Use the MCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

10.3.1 MCC Required Forms and Reporting Structure

Study type	Expedited reporting to MCC	Expedited reporting to External Agency	Non-expedited AE	Form	IRB
IIT by MCC investigator of commercially available agent (non-IND/IDE)	• Grade 3 – Unexpected AE PLUS Possibly, Probably or Definitely Related • ALL Grade 4 Unless expected AND listed in protocol as not requiring reporting. • ALL Grade 5 (fatal) Events	FDA: Suspected AE that is serious and Unanticipated (not listed in IDB or consent)	OnCore and DSMC reporting only	Voluntary Medwatch 3500 for Serious and unanticipated OnCore for all AEs, including SAEs	Per SOPs

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted with SAE documentation.

10.3.2 MCC Expedited Reporting Guidelines for MCC IITs

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy.

Table 10.3.2 -- MCC Reportable AEs

Attribution	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	ALL Gr. 5 AE
Unrelated Unlikely	Not required	Not required	5 calendar days #	5 calendar days	24 hours *
Possible Probable Definite	Not required	5 calendar days	5 calendar days #	5 calendar days	24 hours *

If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention,
the AE should be reported within <u>24 business hours</u> of learning of the event.

10.4 Expedited Reporting to External Agencies

Overall PI will comply with the policies of all external funding agencies and the UK IRB regarding expedited reporting, as per the UK IRB's Mandated Reporting to External Agencies SOP C4.0150.

10.5 Expedited Reporting to UKHC Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

10.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions with the exception of those listed in Section 10.4. **AEs reported expeditiously to the Overall PI and DSMC via OnCore must <u>also</u> be reported in routine study data submissions.**

10.7 Pregnancy

Pregnancy is considered an unanticipated event and pregnancy as well as its outcome must be documented and reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

10.8 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an NCI IND/IDE must be reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.9 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted prior to start of investigational therapy. Scans and x-rays must be done prior to the start of therapy.

Procedures	**Pre-study Screening**	**Cycles 1-3, Day 1, 8, 15 +/- 2 days**	**Cycles 1 -3, Day 6, 7, 13, 14**	**30-day follow-up visit after last dose**	**After 3 [10] cycles +/-21 days**	**Off-treatment**	**12-mos post-treatment initiation +/- 2 weeks**	**Off-Study**
Lapatinib, oral tablet [1]			**X**					
Dispense lapatinib for cycle		**X**[11]						
Paclitaxel, IV		**X**						
Adverse Event Evaluation		X		**X**		**X**		
Assess dose-limiting toxicities [13]		**X**						
Assess oral compliance w/ Lapatinib [2]		**X**						
Informed Consent	**X**							
Demographics	**X**							
PKs, Lapatinib level (plasma) [3,7]		**X**						
Biomarkers (cf RNA) [3,7]		**X**						
Disease Assessment Imaging (CT) [4]	X				**X**	**X**	**X**	
CBC w/diff, platelets [5]	**X**	**X**		**X**				
CMP [6]	**X**	**X**		**X**				
Concomitant Meds [8]	**X**	**X**						
Medical History	**X**							
Physical exam, vitals, weight, and height [9]	**X**	**X**[14]		**X**		**X**		
ECOG performance status	**X**	**X**[14]		**X**		**X**		
EKG	**X**							
CA-125	**X**	**X**[12]						
Survival Status							**X**	**X**

NOTES:

Abbreviations for terms: CT, computerized tomography scan; PET, positron emission tomography scan; IHC; CMP, comprehensive metabolic panel; CBC w/ diff, complete blood count with differential; PT/INR, prothrombin time/ international normalized ratio; EKG, electrocardiogram;

1: Lapatinib is an oral tablet (taken by mouth), on an outpatient basis, dose as assigned.

2: Adherence with lapatinib will be conducted by study staff. (Adherence will be documented by a medication diary and pill counts on returned study medication bottles by study staff. Patients will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinical staff at the end of each course.) See Appendices C and D.

3: One sample (10mL EDTA) for lapatinib concentration and two 10 mL Streck tubes for cfRNA will also be obtained on day 1 (also on Day 8 and Day 15) of cycles 1-3 immediately prior to paclitaxel administration.

4: *Imaging at baseline, pre-study*: All eligible patients will undergo standard of care imaging to assess extent of recurrent disease at baseline; PET/CT scan, bone scan and/or CT of the chest, abdomen and pelvis, and/ or CA-125 may be performed as needed at baseline to assess extent of metastatic disease, per standard of care.

4a: *Imaging on Study as work-up for disease progression*: Once a patient is enrolled on-study, imaging to assess disease progression will proceed per standard of care, based on clinical indicators such as a rising CA-125 and/or other clinical symptoms, but will be per standard of care and approximately every 3 to 6 months and at one year. Re-evaluation of potential metastases is at the discretion of the treating physician based on clinical indicators. Notably, a rising CA-125 and/or other clinical symptoms could trigger scan/imaging.

5: CBC with diff is routine blood test conducted at clinic visits.
Per institutional guidelines, Day 1 counts thresholds prior to Paclitaxel administration are platelets (75,000 or more) and an ANC of 1,000 or more. Per institutional guidelines, the counts thresholds for Day 8 and Day 15 are platelets 50,000 or more and ANC 500 or more.

6: CMP is routine blood test during clinic visits and will be done at the discretion of the treating physician; alkaline phosphatase, total bilirubin, creatinine, glucose, electrolytes, SGOT [AST] will be recorded in the eCRF.

7: Venipuncture is at time of routine clinic draws and there is no charge for venipuncture

8: Concomitant Medications will be assessed per standard of care;

9: Height is routinely measured at clinic visit; it will only be measured and recorded once during the study period.
10: Patients may continue paclitaxel as long as clinically indicated, however they will go off study treatment (lapatinib) after 3 cycles of Lapatinib-Paclitaxel combination regimen.
11: Lapatinib dispensing: Day 6-7 Lapatinib dosing is determined by the Day 1 (pre-paclitaxel labs); similarly, the Day 13-14 Lapatinib dosing is based on Day 8 labs. Thus, on Day 1 patients will receive the lapatinib dose to be taken at home on Days 6-7, and on Day 8, to be taken on Days 13-14.
12: CA-125 will be collected once per cycle, on Day 1 only.
13: DLT is only assessed during Cycle 1 (i.e., captured at 4-weeks or earlier if a DLT occurs prior to the 4-week visit). DLT is not assessed after the first cycle.
14: Physical Exams and ECOG performance status are only performed on Day 1 of each cycle.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of lapatinib in combination with paclitaxel has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated with a CA-125 after each cycle and imaging after the third cycle, or sooner at the physician's discretion.

12.1 Response Criteria

Response and progression will be evaluated in this study using CT scans as per standard of care. Patients are routinely monitored with CA-125, and a rising CA-125 is not sufficient to document response and recurrence, however may trigger radiologic evaluation.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with lapatinib until 30 days after completion of therapy (i.e., last dose).

Evaluable for Response. The primary response evaluation is clinical disease free progression at 1 year after study entry (i.e., initiation of study treatment). All patients who receive at least one dose of study drug will be categorized as with or without progressive disease at one year.

12.1.2 Methods for Evaluation of Measurable Disease

The sensitivity of CA125 for recurrence is 62-94% and the specificity is 91-100% and is considered inadequate for response assessment as a single modality by both NCCN guidelines and the Society of Gynecological Oncology. Progression by RECIST 1.1 criteria for ovarian cancer are any new lesion or a 20% increase in the sum of the longest diameters of all lesions. Response will be assessed by RECIST 1.1 criteria per clinical standard of care, at approximately 3-6 month intervals, with PET or CT scanning per treating physician discretion.

13. STUDY APPROVAL, OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

13.1 Protocol Review and Monitoring Committee and Institutional Review Board

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

13.2 Quality Assurance

The MCC places the highest priority on ensuring the safety of subjects participating in clinical trials and on the quality of data obtained from clinical and translation research. The MCC Quality Assurance (QA) Office oversees the maintenance of quality standards in clinical cancer research through clinical data monitoring of Investigator Initiated Trials (IITs) and routine audits.

13.2.1 Data Monitoring

The MCC QA Office will collaborate with the PI, Biostatisticians and Lead OnCore® Data Management Specialist in creating a Clinical Data Monitoring Plan (CDMP) using a risk-based approach. The CDMP will describe the scope, communication plan, and frequency of monitoring visits. In addition, describe query submissions and resolutions, action items and monitoring reports.

The QA Monitor assigned to the trial will perform the monitoring tasks in accordance with the protocol specific CDMP. The monitoring process will provide research staff and PI with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of the case report forms, assure that all protocol requirements, including applicable regulations and investigator's obligations are being fulfilled, and prompt resolution of any inconsistencies in the study records.

13.2.2 Audit

To ensure compliance with the International Conference on Harmonisation of Good Clinical Practice Guidelines and all applicable regulatory requirements, the MCC Audit Committee will conduct a quality assurance audit. A minimum of 25% of patients enrolled in the study may be selected for review. The purpose of a MCC audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

13.3 Data and Safety Monitoring Committee

The MCC Data and Safety Monitoring Committee (DSMC) will oversee the conduct of this trial. The MCC DSMC performs routine real-time data monitoring and safety review of all trials, with a special focus upon investigator-initiated trials (IITs). The MCC DSMC will conduct review of the trial on a schedule determined the MCC Protocol Review & Monitoring Committee (PRMC). The MCC DSMC will monitor the following elements of the trial: adverse event analysis, serious adverse events, protocol deviations/violations, and accrual. In addition, when applicable the MCC DMSC will review QA audits and monitoring reports, previous reviews by the DSMC, suggested actions by other committees, such as the IRB, UK Risk Management Committee, and other parameters and outcomes as determined by the DSMC. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. The MCC DSMC has the authority to amend, temporarily suspend, or terminate the trial based upon patient safety or compliance matters.

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

13.4 Data Reporting

13.4.1 Method

This study will require data submission and reporting via the OnCore Enterprise Research Clinical Trials Management System, which is the official database of the Markey Cancer Center. Instructions for submitting data is listed in study-specific guidance documents authored by a member of the MCC Data Management Team. These guidance documents may include any of the following, as appropriate for the scope of the study: eCRF Completion Guidelines, Data Management Specifications, Subject Console Guide, and Query Resolution Guide. These guidance documents will be approved and housed within OnCore to ensure access to approved versions to facilitate data submission.

13.4.2 Responsibility for Data Submission

This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee at the initial PRMC review. Study staff are responsible for submitting study data and/or data forms to OnCore as per the Markey Cancer Center SOPs. Study staff are responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

13.5 Data Management

Data management will be performed by cross-team members at MCC. These team members will include representatives from the Data Management Team, Biostatistics and Bioinformatics SRF, and the Quality Assurance Office. They will work closely with study staff to ensure timely and accurate data submission. A protocol specific Data Management Plan (DMP) will be authored by a senior data manager in collaboration with the biostatistician and Principal Investigator with each expected to review and approve the finalization of the DMP. In order to maintain best clinical practices in data management, the DMP may include, but not be limited to CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol specific DMP will additionally define the schedule at which data will be accessed by data management and study statistician to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, annual reports, interim analysis and final data analysis.

13.6 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board

(IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the MCC CRO. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee of the MCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities and compliance with protocol requirements. The MCC DSMC will review all adverse events of this IIT as per its SOP.

14. REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2019.* CA Cancer J Clin, 2019. **69**(1): p. 7-34.
2. Matsuo, K., et al., *Overcoming platinum resistance in ovarian carcinoma.* Expert Opin Investig Drugs, 2010. **19**(11): p. 1339-54.
3. Le, T., et al., *Prospective evaluations of continuous weekly paclitaxel regimen in recurrent platinum-resistant epithelial ovarian cancer.* Gynecol Oncol, 2006. **102**(1): p. 49-53.
4. Sharma, R., et al., *Extended weekly dose-dense paclitaxel/carboplatin is feasible and active in heavily pre-treated platinum-resistant recurrent ovarian cancer.* Br J Cancer, 2009. **100**(5): p. 707-12.
5. Chan, J.K., et al., *Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer.* N Engl J Med, 2016. **374**(8): p. 738-48.
6. Sun, S., et al., *Prognostic Value and Implication for Chemotherapy Treatment of ABCB1 in Epithelial Ovarian Cancer: A Meta-Analysis.* PLoS One, 2016. **11**(11): p. e0166058.
7. Kathawala, R.J., et al., *The modulation of ABC transporter-mediated multidrug resistance in cancer: a review of the past decade.* Drug Resist Updat, 2015. **18**: p. 1-17.
8. Hille, S., et al., *Anticancer drugs induce mdr1 gene expression in recurrent ovarian cancer.* Anticancer Drugs, 2006. **17**(9): p. 1041-4.
9. Schondorf, T., et al., *Induction of MDR1-gene expression by antineoplastic agents in ovarian cancer cell lines.* Anticancer Res, 2002. **22**(4): p. 2199-203.
10. Schondorf, T., et al., *Cisplatin, doxorubicin and paclitaxel induce mdr1 gene transcription in ovarian cancer cell lines.* Recent Results Cancer Res, 2003. **161**: p. 111-6.
11. Penson, R.T., et al., *Expression of multidrug resistance-1 protein inversely correlates with paclitaxel response and survival in ovarian cancer patients: a study in serial samples.* Gynecol Oncol, 2004. **93**(1): p. 98-106.
12. Choi, Y.H. and A.M. Yu, *ABC transporters in multidrug resistance and pharmacokinetics, and strategies for drug development.* Curr Pharm Des, 2014. **20**(5): p. 793-807.
13. Wang, J., et al., *Novel strategies to prevent the development of multidrug resistance (MDR) in cancer.* Oncotarget, 2017. **8**(48): p. 84559-84571.
14. Kelly, R.J., et al., *A pharmacodynamic study of docetaxel in combination with the P-glycoprotein antagonist tariquidar (XR9576) in patients with lung, ovarian, and cervical cancer.* Clin Cancer Res, 2011. **17**(3): p. 569-80.
15. Cripe, L.D., et al., *Zosuquidar, a novel modulator of P-glycoprotein, does not improve the outcome of older patients with newly diagnosed acute myeloid leukemia: a randomized, placebo-controlled trial of the Eastern Cooperative Oncology Group 3999.* Blood, 2010. **116**(20): p. 4077-85.
16. Dohse, M., et al., *Comparison of ATP-binding cassette transporter interactions with the tyrosine kinase inhibitors imatinib, nilotinib, and dasatinib.* Drug Metab Dispos, 2010. **38**(8): p. 1371-80.
17. Kitazaki, T., et al., *Gefitinib, an EGFR tyrosine kinase inhibitor, directly inhibits the function of P-glycoprotein in multidrug resistant cancer cells.* Lung Cancer, 2005. **49**(3):

p. 337-43.
18. Chua, T.C., et al., *Peritoneal carcinomatosis and liver metastases from colorectal cancer treated with cytoreductive surgery perioperative intraperitoneal chemotherapy and liver resection.* Eur J Surg Oncol, 2009. **35**(12): p. 1299-305.
19. Dai, C.L., et al., *Lapatinib (Tykerb, GW572016) reverses multidrug resistance in cancer cells by inhibiting the activity of ATP-binding cassette subfamily B member 1 and G member 2.* Cancer Res, 2008. **68**(19): p. 7905-14.
20. Ma, S.L., et al., *Lapatinib antagonizes multidrug resistance-associated protein 1-mediated multidrug resistance by inhibiting its transport function.* Mol Med, 2014. **20**: p. 390-9.
21. Mi, Y. and L. Lou, *ZD6474 reverses multidrug resistance by directly inhibiting the function of P-glycoprotein.* Br J Cancer, 2007. **97**(7): p. 934-40.
22. Wood, E.R., et al., *A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells.* Cancer Res, 2004. **64**(18): p. 6652-9.
23. Cockerill, S., et al., *Indazolylamino quinazolines and pyridopyrimidines as inhibitors of the EGFr and C-erbB-2.* Bioorg Med Chem Lett, 2001. **11**(11): p. 1401-5.
24. Geyer, C.E., et al., *Lapatinib plus capecitabine for HER2-positive advanced breast cancer.* N Engl J Med, 2006. **355**(26): p. 2733-43.
25. Stamos, J., M.X. Sliwkowski, and C. Eigenbrot, *Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor.* J Biol Chem, 2002. **277**(48): p. 46265-72.
26. Spector, N.L., et al., *Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies.* J Clin Oncol, 2005. **23**(11): p. 2502-12.
27. Rusnak, D.W., et al., *The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo.* Mol Cancer Ther, 2001. **1**(2): p. 85-94.
28. Bence, A.K., et al., *Phase I pharmacokinetic studies evaluating single and multiple doses of oral GW572016, a dual EGFR-ErbB2 inhibitor, in healthy subjects.* Invest New Drugs, 2005. **23**(1): p. 39-49.
29. Burstein, H.J., et al., *A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer.* Ann Oncol, 2008.
30. Johnston, S., et al., *Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy.* J Clin Oncol, 2008. **26**(7): p. 1066-72.
31. Lin, N.U., et al., *Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer.* J Clin Oncol, 2008. **26**(12): p. 1993-9.
32. Agulnik, M., et al., *Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands.* J Clin Oncol, 2007. **25**(25): p. 3978-84.
33. Safran, H., et al., *Lapatinib/gemcitabine and lapatinib/gemcitabine/oxaliplatin: a phase I study for advanced pancreaticobiliary cancer.* Am J Clin Oncol, 2008. **31**(2): p. 140-4.

34. Perez, E., et al., *Results of an analysis of cardiac function in 2,812 patients treated with lapatinib.* J Clin Oncol, 2006. **24**(18S): p. 583.
35. Moy, B. and P.E. Goss, *Lapatinib-associated toxicity and practical management recommendations.* Oncologist, 2007. **12**(7): p. 756-65.
36. *Tykerb (lapatinb). Package Insert*. 2007, Research Triangle Park: NC, GSK.
37. Kelly, H., et al., *Delivery of a healthy baby after first-trimester maternal exposure to lapatinib.* Clin Breast Cancer, 2006. **7**(4): p. 339-41.
38. Burris, H.A., 3rd, et al., *Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas.* J Clin Oncol, 2005. **23**(23): p. 5305-13.
39. Reddy, N., P. Cohen, and B. Whitehead, *A phase I, open-label, three period, randomized crossover study to evaluate the effect of food on the pharmacokinetics of lapatinib in cancer patients.* Clinical Pharmcacologic Therapeutics, 2007. **81**(S16): p. 16-17.
40. Ratain, M. and E. Cohen, *The Value Meal: How to save $1,700 per month or more on lapatinib.* JCO, 2007. **25**(23): p. 3397-8.
41. Koch, K.M., et al., *The value of label recommendations: how to dose lapatinib.* J Clin Oncol, 2007. **25**(33): p. 5331-2; author reply 5334-5.
42. Chu, Q.S., et al., *Phase I and pharmacokinetic study of lapatinib in combination with capecitabine in patients with advanced solid malignancies.* J Clin Oncol, 2007. **25**(24): p. 3753-8.
43. Minami, H., et al., *A phase I study of GW572016 in patients with solid tumors.* J Clin Oncol, 2004. **22**(14S): p. 3048.
44. Burris, H.A., 3rd, et al., *A phase I study of GW572016 in patients with solid tumors.* ProcAm Soc Clin Oncol, 2003. **22**(abstr 994).
45. Voigtlaender, M., T. Schneider-Merck, and M. Trepel, *Lapatinib.* Recent Results Cancer Res, 2018. **211**: p. 19-44.

APPENDIX A. PERFORMANCE STATUS

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Deceased

APPENDIX B. PATIENT DRUG INTERACTIONS

An example list of drugs that can have major/moderate interactions with lapatinib. For a list of drugs that have minor interactions with lapatinib, please refer to Micromedex or other frequently updated lists.

	DRUG CLASS
CYP2C19	Warfarin Clopidogrel Proton pump inhibitors (PPIs): Esomeprozole, Lansoprazole, Omeprazole, Pantoprazole Anti-epileptics: Diazepam, Phenytoin, S-mephenytoin, Phenobarbitone, Oxcarbazepine Anti-microbials: Isoniazid, Voriconazole Anti-depressants: Citalopram, Amitriptyline
CYP3A4	Amiodarone Clarithromycin Cyclosporine Ritonavir Conviaptan Aprepitant Amprenavir Verapamil Diltizem Erythromycin Voriconazole Aripiprazole Telithromycin Saquinavir Darunavir Bosentan Posaconazole Curcumin Midostaurin Clofazimine Telaprevir Idealisibl Stripentol Carbamazepine Itraconazole Nelfinavir Ketoconazole Midazolam Grapefruit Juice
P-glycoprotein/ ABCB1 inhibitors increase the concentrations of these medications	Afatinib Betrixaban Bilastine Brentuximab Celiprolol Colchicine Dabigatran etexilate Digoxin Edoxaban Erdafitinib Talazoparib Topotecan Venetoclax Vincristine

APPENDIX C. PILL DIARY – LAPATINIB

Pill Diary for Lapatinib – Cycle 1

***General Instructions*:** Lapatinib is an oral medication only taken on Days 6 and 7, and Days 13 and 14 in each cycle.
Lapatinib is to be taken by mouth on an empty stomach, twice a day (i.e., in the morning and in the evening).
Please note the doses you take on this medication log and bring this log with you to your clinic visits.

Example of a completed pill diary for Days 5 - 8.

Day	Date	Lapatinib Dose	Time	Mark an "X" in this column if dose was missed.	Side Effects, other notes
5	*6/30/20*	*NONE*	*N/A*	*N/A*	Lapatinib is only taken on Day 6, Day 7, Day 13 & Day 14.
6	7/1/20	*750 mg*	7 : 30 **AM**		*Nausea, mild – went away after an hour.*
		750 mg	8 : 05 **PM**		
7	7/2/20	*750 mg*	: **AM**	***X***	*Missed the morning dose today.*
		750 mg	8 : 00 **PM**		*Felt OK, no side effects.*
8	*7/3/20*	*NONE*	*N/A*	*N/A*	Lapatinib should not be taken today (Day 8).
Day	**Date**	**Lapatinib Dose**	**Time**	**Mark "X" if you missed the dose.**	**Side Effects, other notes**
1		*NONE*	*N/A*	*N/A*	**Day 1 is Paclitaxel infusion in clinic.**
2		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 1 – 5.**
3		*NONE*	*N/A*	*N/A*	
4		*NONE*	*N/A*	*N/A*	
5		*NONE*	*N/A*	*N/A*	
6		**mg**	**: AM**		
		mg	**: PM**		
7		**mg**	**: AM**		
		mg	**: PM**		
8		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 8 – 12.**

9		*NONE*	*N/A*	*N/A*	
10		*NONE*	*N/A*	*N/A*	
11		*NONE*	*N/A*	*N/A*	
12		*NONE*	*N/A*	*N/A*	
13		mg	**: AM**		
		mg	**: PM**		
14		mg	**: AM**		
		mg	**: PM**		
15		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 15 – 28.**
16		*NONE*	*N/A*	*N/A*	
17		*NONE*	*N/A*	*N/A*	
18		*NONE*	*N/A*	*N/A*	
19		*NONE*	*N/A*	*N/A*	
20		*NONE*	*N/A*	*N/A*	
21		*NONE*	*N/A*	*N/A*	
22		*NONE*	*N/A*	*N/A*	
23		*NONE*	*N/A*	*N/A*	
24		*NONE*	*N/A*	*N/A*	
25		*NONE*	*N/A*	*N/A*	
26		*NONE*	*N/A*	*N/A*	
27		*NONE*	*N/A*	*N/A*	
28		*NONE*	*N/A*	*N/A*	

Pill Diary for Lapatinib – Cycle 2

***General Instructions*:** Lapatinib is an oral medication only taken on Days 6 and 7, and Days 13 and 14 in each cycle.
Lapatinib is to be taken by mouth on an empty stomach, twice a day (i.e., in the morning and in the evening).
Please note the doses you take on this medication log and bring this log with you to your clinic visits.

Example of a completed pill diary for Days 5 - 8.

Day	Date	Lapatinib Dose	Time	Mark an "X" in this column if dose was missed.	Side Effects, other notes
5	*7/31/20*	*NONE*	*N/A*	*N/A*	Lapatinib is only taken on Day 6, Day 7, Day 13 & Day 14.
6	*8/1/20*	*750 mg*	7 : 30 **AM**		*Nausea, mild – went away after an hour.*
		750 mg	8 : 05 **PM**		
7	*8/2/20*	*750 mg*	: **AM**	***X***	*Missed the morning dose today.*
		750 mg	8 : 00 **PM**		*Felt OK, no side effects.*
8	*8/3/20*	*NONE*	*N/A*	*N/A*	Lapatinib should not be taken today (Day 8).
Day	**Date**	**Lapatinib Dose**	**Time**	**Mark "X" if you missed the dose.**	**Side Effects, other notes**
1		*NONE*	*N/A*	*N/A*	**Day 1 is Paclitaxel infusion in clinic.**
2		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 1 – 5.**
3		*NONE*	*N/A*	*N/A*	
4		*NONE*	*N/A*	*N/A*	
5		*NONE*	*N/A*	*N/A*	
6		**mg**	**: AM**		
		mg	**: PM**		
7		**mg**	**: AM**		
		mg	**: PM**		
8		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 8 – 12.**

9		*NONE*	*N/A*	*N/A*	
10		*NONE*	*N/A*	*N/A*	
11		*NONE*	*N/A*	*N/A*	
12		*NONE*	*N/A*	*N/A*	
13		mg	**: AM**		
		mg	**: PM**		
14		mg	**: AM**		
		mg	**: PM**		
15		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 15 – 28.**
16		*NONE*	*N/A*	*N/A*	
17		*NONE*	*N/A*	*N/A*	
18		*NONE*	*N/A*	*N/A*	
19		*NONE*	*N/A*	*N/A*	
20		*NONE*	*N/A*	*N/A*	
21		*NONE*	*N/A*	*N/A*	
22		*NONE*	*N/A*	*N/A*	
23		*NONE*	*N/A*	*N/A*	
24		*NONE*	*N/A*	*N/A*	
25		*NONE*	*N/A*	*N/A*	
26		*NONE*	*N/A*	*N/A*	
27		*NONE*	*N/A*	*N/A*	
28		*NONE*	*N/A*	*N/A*	

Pill Diary for Lapatinib – Cycle 3

***General Instructions*:** Lapatinib is an oral medication only taken on Days 6 and 7, and Days 13 and 14 in each cycle.
Lapatinib is to be taken by mouth on an empty stomach, twice a day (i.e., in the morning and in the evening).
Please note the doses you take on this medication log and bring this log with you to your clinic visits.

Example of a completed pill diary for Days 5 - 8.

Day	Date	Lapatinib Dose	Time	Mark an "X" in this column if dose was missed.	Side Effects, other notes
5	*8/31/20*	*NONE*	*N/A*	*N/A*	Lapatinib is only taken on Day 6, Day 7, Day 13 & Day 14.
6	*9/1/20*	*750 mg*	7 : 30 **AM**		*Nausea, mild – went away after an hour.*
		750 mg	8 : 05 **PM**		
7	*9/2/20*	*750 mg*	: **AM**	***X***	*Missed the morning dose today.*
		750 mg	8 : 00 **PM**		*Felt OK, no side effects.*
8	*9/3/20*	*NONE*	*N/A*	*N/A*	Lapatinib should not be taken today (Day 8).

Day	Date	Lapatinib Dose	Time	Mark "X" if you missed the dose.	Side Effects, other notes
1		*NONE*	*N/A*	*N/A*	**Day 1 is Paclitaxel infusion in clinic.**
2		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 1 – 5.**
3		*NONE*	*N/A*	*N/A*	
4		*NONE*	*N/A*	*N/A*	
5		*NONE*	*N/A*	*N/A*	
6		**mg**	**: AM**		
		mg	**: PM**		
7		**mg**	**: AM**		
		mg	**: PM**		
8		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 8 – 12.**

9		*NONE*	*N/A*	*N/A*	
10		*NONE*	*N/A*	*N/A*	
11		*NONE*	*N/A*	*N/A*	
12		*NONE*	*N/A*	*N/A*	
13		mg	**: AM**		
		mg	**: PM**		
14		mg	**: AM**		
		mg	**: PM**		
15		*NONE*	*N/A*	*N/A*	**Lapatinib is not to be taken on Days 15 – 28.**
16		*NONE*	*N/A*	*N/A*	
17		*NONE*	*N/A*	*N/A*	
18		*NONE*	*N/A*	*N/A*	
19		*NONE*	*N/A*	*N/A*	
20		*NONE*	*N/A*	*N/A*	
21		*NONE*	*N/A*	*N/A*	
22		*NONE*	*N/A*	*N/A*	
23		*NONE*	*N/A*	*N/A*	
24		*NONE*	*N/A*	*N/A*	
25		*NONE*	*N/A*	*N/A*	
26		*NONE*	*N/A*	*N/A*	
27		*NONE*	*N/A*	*N/A*	
28		*NONE*	*N/A*	*N/A*	

APPENDIX D. DRUG ACCOUNTABILITY FORM

Markey Cancer Center Patient Self-Administered Study Agent Compliance Log

This form is to be updated at every study contact where patient receives or returns study drug. This form may be used for multiple self-administered study agents. This form is to be used in conjunction with a note in SCM about study drug self-administration and case report form and will be maintained in the research record.

MCC Protocol Number: __MCC-20-GYN-06_____ Principal Investigator: ___Frederick Ueland, MD___________________

Protocol Title: __Lapatinib with Paclitaxel in Platinum-Resistant Ovarian Cancer__

Patient's MRN: : ______________ ______________Patient's Name: ______________________________

Patient Study ID: ________________Cycle Number : ________________

Date Dispensed	Amount Dispensed	Dose Form *(e.g., tablets, pills, bottles, capsules, syringes, vials)*	Date Returned	Actual Amount Returned	Expected Amount Taken	Expected Amount Returned	Reason for difference between actual and expected amount returned, if applicable	Site Staff Initials
____/_____/20_____ (mm/dd/yyyy)			____/_____/20______ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20______ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20______ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20______ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20______ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20______ (mm/dd/yyyy)					
____/_____/20_____ (mm/dd/yyyy)			____/_____/20____ (mm/dd/yyyy)					

Version 1, 28Aug2019- SOP Documenting Return of Oral Agents Self-administered by Patients Page ____ of ____

Markey Cancer Center
Investigational Drug Return Form

Patient Number: _____

Protocol Number: _____

Name of Investigational Drug: _____

Principal Investigator: _____

Email address of MCC CRO/PMC personnel(s) to be notified of discrepancies in final total Investigational Drug returned count:

_____

_____

_____

Date of Investigational Drug Drop off: _____

Total amount of drug returned to IDS Pharmacy (# capsules/tablets) _____

Name of MCC CRO/PMC personnel delivering returned Investigational Drug:
_____

CRA/CRN Signature: _____ Date: _____

KEY INFORMATION FOR MCC-20-GYN-06-PMC: A PHASE I DOSE ESCALATION STUDY ON THE SAFETY OF LAPATANIB WITH DOSE-DENSE PACLITAXEL IN PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

We are asking you to choose whether or not to volunteer for a research study about the good and bad effects of using the combination of lapatinib and paclitaxel, at different doses, in the treatment of ovarian cancer that has returned after receiving treatment with platinum-based chemotherapy drugs. We are asking you because your ovarian cancer has returned after receiving platinum-based chemotherapy. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn about the good and bad effects of using the combination of lapatinib and paclitaxel, at different doses, in the treatment of platinum-resistant ovarian cancer that has returned after treatment.

Lapatinib is FDA approved to be used together with another medication to treat certain types of breast cancer that has not responded to the standard treatment. Paclitaxel is FDA approved for the treatment of breast cancer, non-small cell lung cancer, and pancreatic cancer. The combination of lapatinib and paclitaxel has not been approved for ovarian cancer. However, some studies suggest that Lapatinib may help paclitaxel work better. Since twice-daily dosing lapatinib has not been studied in combination with paclitaxel, we are proposing this study to learn about whether this combination will improve your health and to learn more about the side effects associated with different dosages.

Your participation in this research will last up to about 1 year and 4 months. That includes about 4 weeks for screening and three, 28-day cycles of treatment. In addition, you will be followed for up to one year after completing treatment.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

Lapatinib may help paclitaxel work better by making tumor cells more sensitive to the drug. Lapatinib may also stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Giving lapatinib together with paclitaxel may kill more tumor cells. For a complete description of benefits, refer to the Detailed Consent.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

We do not know if the combination of lapatinib and paclitaxel will improve your health. The usual approach for patients who are not in a study is typically treatment with standard chemotherapy, or other investigational chemotherapy or biologic drugs.

Standard chemotherapy drugs that are already FDA-approved for use in recurrent ovarian, primary peritoneal, or fallopian tube cancer include paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD). Bevacizumab in combination with chemotherapy (topotecan, paclitaxel or PLD) is also FDA-approved for women with platinum-resistant recurrent cancer listed above who received no more than two prior chemotherapy treatments. The study doctor will discuss with you the risks and benefits of the study treatment compared to the standard treatment to help you decide whether or not to take part in this study.

You may not want to participate in this study because of the side effects listed in the detailed consent below. For a complete description of risks, refer to the Detailed Consent and/or Appendix.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Frederick Ueland, MD of the University of Kentucky, Department of Medicine at (859) 257-1613 or via email at fuela0@uky.edu. If you have any concerns or questions about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?
You should not participate in this study if you are:

- Under the age of 18;
- Pregnant, lactating, or intend to get pregnant during the study;
- Currently taking any other investigational agents;
- Currently taking other medications or foods (e.g. grapefruit/grapefruit juice) which are not allowed while on this study. The study doctor will review your usage of these items and discuss them with you.
- Unwilling/unable to commit to the amount of time needed to take part in this study
- There are other criteria that must be met to take part in this study that your study doctor will review with you.

WHERE WILL THE STUDY TAKE PLACE AND WHAT IS THE TOTAL AMOUNT OF TIME INVOLVED?

The research procedures will be conducted at University of Kentucky Medical Center and Markey Cancer Center facilities. You will need to come in 14 times during the study. Most visits will take between 1- 2 hours. The visits on the days you receive drug via infusion (days 1, 8, 15) during cycles 1-3, will take between 4-6 hours. The total amount of time you will be asked to volunteer for this study is about 55 hours. The amount of time will vary depending on how you respond to treatment.

WHAT WILL YOU BE ASKED TO DO?

You will be asked if you are interested in taking part in this research study. If you are interested, you will be asked to read this informed consent form and ask any questions you may have and decide whether you want to take part in the study. If you agree to be in the study, you will be asked to sign and date the last page of this form.

Pre-study Screening (completed within 4 weeks prior to initiation of treatment)

In order to find out if you can take part in the study, the following procedures will be done:

The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken in the last 90 days or are taking now.

The study doctor will collect demographic information.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also have an Electrocardiogram (EKG) to evaluate your heart's functioning.

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) via venipuncture and urine to check your heart, blood, liver, thyroid, and kidney functions. You will also be asked to provide a blood sample to test for the amount of CA 125 (cancer antigen 125) in your blood.

If you are a woman who might be able to get pregnant, you will be required to have a urine test to check for pregnancy before you start the study. If you are currently pregnant or have immediate plans to become pregnant, you may not take part in this study. Both men and women of childbearing potential who take part in the study

must agree to use an effective form of birth control (such as an intrauterine device (women only) and/or condoms) during the study, as well as 90 days after the last dose of study treatment. You should discuss birth control options for you and your partner with your study doctor prior to starting the study.

You may be asked to undergo some imaging (PET/CT scan, bone scan and/or CT of the chest, abdomen and pelvis) as per standard treatment. A computed tomography (CT) scan combines a series of X-ray images taken from different angles around your body and uses computer processing to create cross-sectional images (slices) of the bones, blood vessels and soft tissues inside your body. A Positron Emission tomography or commonly called PET scan is an imaging test that utilizes a specifically designed camera to view the internal organs of the body. It is done by injecting a radioactive tracer intravenously through the arm. Tracer is a chemical in liquid form that emits positrons that can be identified and modified into a picture of your organs and soft tissue.

All lab tests and radiographic (imaging) studies should be completed within 4 weeks prior to registration/initiation of treatment.

<u>During Cycles 1-3, on Days 1, 8, 15</u>

The study doctor will ask you about any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken in the last 90 days or are taking now.

The study doctor will collect demographic information.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life).

Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured.

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) via venipuncture and urine to check your heart, blood, liver, thyroid, and kidney functions. You will also be asked to provide a blood sample to test for the amount of CA 125 (cancer antigen 125) in your blood. Some of this blood will also be used to learn more about how your body handles the study drugs and to test for genetic biomarkers.

You will receive paclitaxel intravenously (in your vein). The study team will monitor you during the infusion for side effects. After the infusion, you will be provided lapatinib to be taken later, at home, as per the doctor's instructions.

<u>During Cycles 1 -3, on Days 6, 7, 13, 14</u>

You will take the lapatinib tablets, by mouth, as per the study doctor's instructions.

The study doctor will ask you about any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken in the last 90 days or are taking now.

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) via venipuncture and urine to check your heart, blood, liver, thyroid, and kidney functions.

You will be provided with a medication diary. In it, you will be asked to keep track of the study drug you have take since the last visit.

<u>Visit 4 weeks after start of treatment +/- 2 weeks</u>

You will also be asked about any side effects you have experienced since your last visit. Depending on the type and severity of your side effects, your next treatment may be delayed until they have resolved. In some cases you may come off study treatment.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will

evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

The study team will review your medication diary and you will return any unused medication.

After 3 cycles +/-21 days

Once you are enrolled on-study, you may be asked to undergo imaging (PET/CT scan, bone scan and/or CT of the chest, abdomen and pelvis) as per standard treatment, based on clinical indicators such as a rising CA-125 and/or other clinical symptoms. They will occur approximately every 3 to 6 months and at one year.

Off-Treatment Visit

You will be asked to complete an off-treatment visit on the last day of your treatment or if you go off treatment because your disease progresses (worsens), if you experience side effects of certain types or severities, because you decide to no longer take part in the study or for other reasons that your doctor will discuss with you.

During this visit, you will also be asked about any side effects you have experienced since your last visit. You may be asked to undergo imaging (PET/CT scan, bone scan and/or CT of the chest, abdomen and pelvis) as per standard treatment, based on clinical indicators such as a rising CA-125 and/or other clinical symptoms.

12-Month Post-Treatment Visit/Off-Study

You will be asked to come in for a follow up visit 12 months after completing study treatment. During this visit, you will also be asked about any side effects you have experienced since your last visit. You may be asked to undergo imaging (PET/CT scan, bone scan and/or CT of the chest, abdomen and pelvis) as per standard treatment, based on clinical indicators such as a rising CA-125 and/or other clinical symptoms.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

There are risks to taking part in any research study. One risk is that you may get a study drug(s) that do not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects. Everyone taking part in the study will be watched carefully for any side effects. However, researchers do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop receiving the treatment. In some cases, side effects can be serious, long lasting, or may never go away.

In a research study, all of the risks or side effects may not be known before you start the study. You should tell your doctor or a member of the study team immediately if you experience any side effects.

Lapatinib Side-Effects

The following side effects are common (occurring in greater than 30%) for patients taking lapatinib (with other commercial agent being administered):

- Diarrhea
- Hand-foot syndrome (Palmar-plantar erythrodysesthesia or PPE) -skin rash, swelling, redness, pain and/or peeling of the skin on the palms of hands and soles of feet. Usually mild, has started as early as 2 weeks after start of treatment. May require reductions in the dose of the medication.
- Low red blood cell count (anemia)
- Nausea and vomiting.
- Elevated liver enzymes (increased AST, ALT, and bilirubin levels).

These are less common side effects for patients receiving lapatinib (with other commercial agent being administered):

- Rash
- Low blood counts. Your white blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, and/or bleeding.
- Fatigue, tiredness
- Abdominal pain

- Mouth sores
- Heartburn
- Pain in arms, legs, back
- Shortness of breath
- Difficulty sleeping
- Dry skin

These are rare but serious side effects of lapatinib (with other commercial agent being administered):

- Heart problems including decreased pumping of blood from the heart, or abnormal heartbeat can occur rarely.
- Severe diarrhea, which may lead to dehydration.

Paclitaxel Side-Effects

The following Paclitaxel side effects are common (occurring in greater than 30%) for patients taking Paclitaxel:

- Low blood counts. Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding.
- Hair loss
- Arthralgias and myalgias, pain in the joints and muscles. Usually temporary occurring 2 to 3 days after Paclitaxel, and resolve within a few days.
- Peripheral neuropathy (numbness and tingling of the hands and feet)
- Nausea and vomiting (usually mild)
- Diarrhea
- Mouth sores
- Hypersensitivity reaction - fever, facial flushing, chills, shortness of breath, or hives after Paclitaxel is given. The majority of these reactions occur within the first 10 minutes of an infusion. Notify your healthcare provider immediately (premedication regimen has significantly decreased the incidence of this reaction).

The following are less common side effects (occurring in 10-29%) for patients receiving Paclitaxel:

- Swelling of the feet or ankles (edema).
- Increases in blood tests measuring liver function. These return to normal once treatment is discontinued (see liver problems).
- Low blood pressure (occurring during the first 3 hours of infusion).
- Darkening of the skin where previous radiation treatment has been given (radiation recall - see skin reactions).
- Nail changes (discoloration of nail beds - rare) (see skin reactions).

Side Effects Associated with Lapatinib in combination with paclitaxel		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia (low red blood cells)		
	Febrile neutropenia (Fever)	
	Neutropenia (Too few neutrophils, a type of white blood cells)	
	Thrombocytopenia (low level of platelets)	
CARDIAC (HEART) DISORDERS		
		Left ventricular systolic dysfunction
ECG abnormality (Paclitaxel)		
GASTROINTESTINAL (STOMACH AND INTESTINES) DISORDERS		
	Abdominal distension (swelling)	

	Abdominal pain	
Diarrhea		
	Dyspepsia (indigestion)	
	Flatulence (Gas)	
	Mucositis (Pain and inflammation of the body's mucous membrane.)	
	Stomatitis (inflammation of the mouth and lips)	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	
	Flu-like symptoms	
HEPATOBILIARY LIVER) DISORDERS		
		Hepatic (liver) failure
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
INVESTIGATIONS		
	Alanine aminotransferase increased (could indicate liver damage)	
	Aspartate aminotransferase increased (could indicate liver damage)	
	Blood bilirubin increased (could indicate liver damage)	
		Electrocardiogram QT corrected interval prolonged (your heart takes longer than usual to recover after each beat)
METABOLISM AND NUTRITION DISORDERS		
	Anorexia (low body weight)	
	Dehydration	
NERVOUS SYSTEM DISORDERS		
		Central Nervous System Toxicity (any)
Peripheral neuropathy (weakness, numbness and pain)		
	Dysgeusia (distortion of the sense of taste)	
	Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Pneumonitis
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Palmar-plantar erythrodysesthesia (burning or tingling discomfort in the hands and the soles of the feet)	
	Alopecia (hair loss)	
	Nail loss	
	Pruritus (itchy skin)	
	Rash acneiform (eruptions on the skin)	
Rash maculo-papular (flat, red areas on the skin)		
VASCULAR DISORDERS		
	Flushing (skin redness)	

CT scan risks:

Each CT scan will give a radiation dose greater than that from typical natural background exposure, but less than the limit for radiation workers and well below the levels that are considered to be a significant risk of any harmful effects.

EKG risks:

With the echocardiogram, you may feel some discomfort when the technician pulls the electrodes off your chest similar to a Band-Aid.

Blood Tests:

For most people, needle punctures for blood tests do not cause any serious problems. However, they may cause fainting, bleeding, bruising, soreness, discomfort, dizziness, infections and/or pain at the injection site. There can be mild pain, soreness or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but may only last a few minutes after blood is drawn. If you take the blood thinner warfarin or Coumadin, you may have an increased risk of bleeding from the needle used to draw your blood.

Reproductive risks:

You should not become pregnant while on this study because the drug in this study could affect an unborn child. It is not known if the drugs used in this study are harmful to an unborn or breastfed baby. If you become pregnant while receiving these drugs, potential risks could include complications such as miscarriage or birth defects. It is not known if the study drugs are transferred to breast milk. Potential subjects who are breastfeeding will be required to discontinue nursing during treatment and for an additional 30 days following treatment.

The drugs used in this study may cause fetal harm when administered to pregnant women. Animal studies have revealed evidence of harm to an unborn baby as well as birth defects. There are no controlled data in human pregnancy. If you are a female subject and you become pregnant while receiving this drug, potential risks could include complications such as miscarriage or birth defects.

If you are of childbearing potential, you must use contraception during and for 30 days after the last dose of study drug. Examples of contraceptive methods with a failure rate of less than 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of less than 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

For more information about risks and side effects, ask your study doctor.

There is always a chance that any medical treatment can harm you. The research treatments/procedures in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

We do not know if you will get any benefit from taking part in this study. Resistance to cancer chemotherapy is an obstacle to successful treatment of ovarian cancer. Lapatinib may decrease your body's resistance to paclitaxel and enable the drug to better treat your ovarian cancer. If you take part in this study, information learned may help others with your condition.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to take part in the study there are several standard chemotherapy treatments available. Standard chemotherapy drugs that are already FDA-approved for use in recurrent ovarian, primary peritoneal, or fallopian tube cancer include paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD). Bevacizumab in combination with chemotherapy (topotecan, paclitaxel or PLD) is also FDA-approved for women with platinum-resistant recurrent cancer listed above who received no more than two prior chemotherapy treatments. The study doctor will discuss the risks and benefits of the study treatment and the standard treatment options with you when you are deciding

whether or not to take part in this study.

WHAT WILL IT COST YOU TO PARTICIPATE?

You and/or your insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that you would normally receive for any conditions you may have. These are costs that are considered medically necessary and will be part of the care you receive even if you do not take part in this study. Your insurer, Medicare, or Medicaid, may agree to pay for the costs. However, a co-payment or deductible may be needed from you. The amount of this co-payment or deductible may be costly.

The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research.

Therefore, the sponsor, Markey Cancer Center, will pay for the following:

- Lapatinib tablets
- Blood testing for Pharmacokinetic and genetic analysis

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. At the University of Kentucky, data is stored at the Markey Cancer Center in locked facilities, and with limited access to records by designated research staff. The study doctor will assign you a unique code consisting of a series of numbers and only your unique code and your initials, and nothing that could identify you personally, will be entered into the study report forms.

You should know that in some cases we may have to show your information to other people. For example, the law may require us to share your information with:

- a court or agencies, if you have a reportable disease/condition;
- authorities, if you report information about a child being abused; or if you pose a danger to yourself or someone else.

To ensure the study Is conducted properly, Officials of the Food and Drug Administration, the National Cancer Institute, the University of Kentucky or its agents may look at or copy pertinent portions of records that identify you.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study.

If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.

The investigators conducting the study may need to remove you from the study. You may be removed from the study if:

- you are not able to follow the directions,
- we find that your participation in the study is more risk than benefit to you, or
- the agency paying for the study chooses to stop the study early for a number of scientific reasons.

The study intervention, medication, and/or device will no longer be provided to you and may not be available for purchase. This may occur for a number of reasons.

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may not take part in this study if you are currently involved in another research study. It is important to let the

investigator/your doctor know if you are in another research study. You should discuss this with the investigator/your doctor before you agree to participate in another research study while you are in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Frederick Ueland, M.D. at 859-257-1613 (during business hours) or at 859-323-5321 (evenings and weekends) immediately. Frederick Ueland, M.D. will determine what type of treatment, if any, is best for you at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

Medical costs related to your care and treatment because of study-related harm will be your responsibility or may be paid by Medicare or Medicaid if you are covered by Medicare or Medicaid (If you have any questions regarding Medicare/Medicaid coverage you should contact Medicare by calling 1-800-Medicare (1-800-633-4227) or Medicaid 1-800-635-2570).

A co-payment/deductible may be needed by your insurer or Medicare/Medicaid even if your insurer or Medicare/Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be costly.

You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will not receive any rewards or payment for taking part in the study.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

We will tell you if we learn new information that could change your mind about staying in the study. We may ask you to sign a new consent form if the information is provided to you after you have joined the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

Generally, tests done for research purposes are not meant to provide clinical information. We *will not* provide you with individual research results.

Do you give permission for us to contact you about research results or incidental findings that are determined to be important to you/your family's health? (Incidental findings are unforeseen findings discovered during the course of the research that may affect you or your family's health).

☐ Yes ☐ No_____ Initials

You may also withdraw your consent to be contacted with information about research results or incidental findings by sending a written request to Frederick Ueland, M.D., Clinical Research Organization, 800 Rose Street, CC140 Roach Building, Lexington, KY 40536.

WHAT ELSE DO YOU NEED TO KNOW?

If you volunteer to take part in this study, you will be one of about 15 people to do so at the University of Kentucky.

The Markey Cancer Center is providing financial support and/or material for this study.

The information or specimens that you are providing will no longer belong to you. The research may lead to new clinical or educational knowledge, tests, treatments, or products. These products could have some financial value. There are no plans to provide financial payment to you or your relatives if this occurs.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL YOUR INFORMATION (OR SPECIMEN SAMPLES) BE USED FOR FUTURE RESEARCH?

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, or date of birth.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

- Demographic Information (your name, sex, race & age.)
- Your social security number
- History and diagnosis of your disease
- Specific information about treatments you have received
- Past and present medical records pertaining to your health condition
- Your entire research record
- Your medical records held at the University of Kentucky that pertain to your health condition
- Information about other medical conditions that may affect your treatment
- Medical data, including physical examinations, laboratory test results, pathology results, and pregnancy test results
- Information on side effects (adverse events) you may experience, and how these were treated
- Long-term information about your general health status and the status of your disease
- Tissue and/or blood samples, associated data related to the analysis of the samples

The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- Authorized representatives of the University of Kentucky, UK Hospital, and Markey Cancer Center
- Representatives of the Kentucky Cancer Registry
- Representatives of the U.S. Food and Drug Administration (FDA)
- The National Institutes of Health and its affiliates including the for Human Research Protections (OHRP) and the NCI (National Cancer Institute) and their affiliates
- If necessary, your other healthcare providers who are not part of the study

If you become pregnant anytime during the study or within 30 days after stopping the study drug, you must inform the study doctor. The study doctor must then report the outcome of your pregnancy to the Sponsor (and/or the FDA).

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to Dr. Frederick Ueland c/o University of Kentucky / Department of Gynecologic Oncology / CRO / CC140 Roach Building / 800 Rose Street / Lexington, KY 40536-0293 to inform him of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

You will not be allowed to review the information collected for this research study until after the study is completed. When the study is over, you may have the right to access the information.

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.

INFORMED CONSENT SIGNATURES

This consent includes the following:

- **Key Information Page**
- **Detailed Consent**

You will receive a copy of this consent form after it has been signed.

Signature of research subject	Date
Printed name of research subject	
Printed name of [authorized] person obtaining informed consent and HIPAA authorization	Date
Signature of Principal Investigator or Sub/Co-Investigator	