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

Local Protocol #: 4B-10-4

Protocol Title: Single Arm Phase II Study of Docetaxel and Lapatinib in Metastatic Transitional Cell Carcinoma in Bladder as Second-Line Treatment.

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STUDY PHASE: **Phase II**

STUDY ARMS: **Single Arm**

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LIST OF ABBBREVIATIONS:

CTC	=	Circulating tumor cells
EGFR	=	Epidermal growth factor receptor
GC	=	Gemcitabine plus cisplatin
IHC	=	Immunohistochemistry
ITT	=	Intent-to-treat
MTD	=	Maximum tolerated dose
MVAC	=	Methotrexate, cisplatin, doxorubicin and vinblastine
NCI-CTC	=	National Cancer Institute Common Toxicity Criteria
OS	=	Overall survival
PFS	=	Progression free survival
RECIST	=	Response Evaluation Criteria in Solid Tumors
SAE	=	Serious Adverse Events
TCC	=	Transitional cell carcinoma
TTP	=	Time to progression
TURBT	=	Transurethral resection of bladder tumor

Summary of Amendments:

Amendment dated 5/9/2013
This amendment clarifies the dosing of docetaxel in the study after 6 patients were treated at a starting dose of 60mg/m2 and **did not experience unacceptable toxicity**. All subsequent patients are to be treated with docetaxel 75mg/m2 intravenously every 3 weeks and lapatinib 1250mg orally daily from the first cycle.

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1.0 BACKGROUND

Transitional cell carcinoma (TCC) is the fifth most common malignancy in the United States. The surveillance epidemiology and end results from national cancer institute estimated 70,980 new cases, and 14,330 deaths from cancer of the urinary bladder in 2009(1, 2).

Yet advanced TCC has seen few significant advances in the last decade. Standard of care in the United States consists of a cisplatin based upfront therapy (gemcitabine plus cisplatin (GC), or methotrexate, cisplatin, doxorubicin and vinblastine (MVAC). Once patients progress through one of these regimens, there is no second-line standard of care. Many agents, including docetaxel, paclitaxel and ifosfamide, have shown single agent responses (between 10-20%, which improve with combination therapy), yet no randomized trial has shown the benefit of one over another (3-6). In fact, no second-line trial has demonstrated improved survival with any chemotherapy agent.

With the wider application of chemotherapy and standard care of cisplatin based chemotherapy, GC or MVAC, the proportion of metastatic cancer patients with cisplatin refractory disease is increasing (7), along with the concern of treating a patient population with depleted bone marrow and impaired renal function. Because of this lack of a gold standard, and above concerns related to cisplatin, practice patterns differ although taxanes therapies are the most commonly used second line treatment (either in combination or as single agents). Please see the attached Table 2, which summarized second line therapy outcomes in TCC.

A study by Chow N, et al. showed the epidermal growth factor receptors (epidermal growth factor receptor) and ErbB2 (HER2) expression were detected in 72.2% and 44.5% of bladder cancer cases, respectively. Co- Expression of EGFR and HER2 was 33.9%(8). A study by Wulfing C, et al. showed EGFR overexpression in 30 (52%), HER2 over expression in 25 (44%), and co-expression of EGFR and HER2 in 13 (22%)(9) (Table 3). Previously several studies proved that over-expression of HER2, and co-expression of EGFR-HER2 in bladder TCC are associated with a poor prognosis (8, 10-13). These data suggest that EGFR and HER2 are of potential importance in TCC and represetnt potential therapeutic targets. Given the poor outcomes for patients with advanced, refractory metastatic TCC, the addition of Lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinases encompasses a rational approach to improve the response of metastatic TCC as a second line treatment compared with docetaxel alone.

A phase 3, randomized study in breast cancer has showed that the addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression (14). A pre-clinical study investigated the potential utility of lapatinib as an adjunct to chemotherapy gemcitabine and cisplatin in human bladder cancer cell lines. The study suggests that lapatinib cooperates with clinically relevant cytotoxic agents and may have therapeutic utility in the management of metastatic bladder cancer(15).

A single-arm, multicenter, open-label phase 2 study of single-agent lapatinib as second or third-line treatment of patients with locally advanced or metastatic transitional cell carcinoma who had progressed after platin-based chemotherapy did not meet the primary endpoint of an overall response rate (ORR) >10% (one patient with PR, ORR 1.7%; [95% CI], 0.0%-9.1%). However, nearly one-third of patients (32%, n=19) experienced clinical benefit with non-progressing disease for at least 8 weeks. The median time to progression (TTP) and median overall survival (OS) are 8.6 weeks and 17.9 weeks,

respectively. The subset of patients with EGFR-over-expressing and/or HER-2–over-expressing tumors demonstrated a significant prolongation of median OS (30.3 weeks; 95% CI, 17.6 weeks-49.9 weeks) compared with the intent-to-treat (ITT) patient population, which comprised all patients who enrolled in the study and received the study drug, (17.9 weeks; 95% CI, 13.1 weeks-30.3 weeks), or patients with low expression of EGFR or HER-2 (10.6 weeks; 95% CI, 5.0 weeks-17.6 weeks) (9). These data suggest that lapatinib has biological activity in transitional cell carcinoma and that benefit from this drug may accrue preferentially to patients whose tumor tissue over-expresses EGFR or HER2 or both. EGFR and HER2 over-expression was determined by immunohistochemistry in archival paraffin-embedded tumor material. The expression of EGFR (PharmDx) and HER-2 (HercepTest) were detected by Immunohistochemistry (IHC) using DakoCytomation kits (DakoCytomation, Carpinteria, Calif). The testing was performed centrally in a blinded, independent manner using archival paraffin-embedded tissue taken from primary and/or metastatic tumor sites. EGFR/HER-2-negative tumor was defined as the absence of membranous staining above background in all tumor cells. EGFR/HER-2-positive tumor (1+, 2+, and 3+) was defined as any membranous staining of the cell above background level of the cell in >10% of the tumor cells. A tumor with an intensity score of 2+ or 3+ was classified as an EGFR- or HER-2-overexpressing tumor. The major toxicities in the study were diarrhea (39%, ≥grade 3 in 3%), nausea (27%), vomiting (22%; ≥grade 3 in 7%), acne (14%), asthenia (12%) and fatigue (10%). Dehydration and hyponatremia ≥grade 3 were each seen in 3% of patients. Asymptomatic LVEF decline to 27% was seen in one patient after 8 weeks of lapatinib therapy.

The Lapatax trial, a phase I design was used to evaluated Lapatinib plus docetaxel in patients with HER2+ (ErbB2+) locally advanced breast cancer in the neoadjuvant setting to determine the maximum tolerated dose (MTD) based on the observed safety profile. HER2+ was defined by immunohistochemistry, fluorescent in situ hybridization, and/or chromogenic in situ hybridization in tumor tissue. Patients had had no prior chemotherapy for their cancer. A stepwise, dose escalation regimen of lapatinib was administered in combination with docetaxel. The MTD, defined during cycle 1 was: any grade 3-4 non hematological toxicity, ANC<0.5 G/L lasting for 7days or more, Febrile neutopenia or thrombocytopenia <25 000 cell per microliter, and without administration of G-CSF, was reached at dose level 4 - lapatinib 1250mg daily orally and docetaxel 85 mg/m2 every 3 weeks (16).

LoRusso and colleagues undertook a phase I trial of lapatinib and docetaxel every 3 weeks in solid tumors with regulated G-CSF given prophylactically 24 hours after docetaxel (17). In this context the “optimal therapeutic dose” was lapatinib 1250mg daily and docetaxel 75mg/m3 every 3 weeks. There was no pharmacokinetic interaction between the drugs.

Given the mechanism of the action of lapatinib, we propose a single arm phase II trial investigate the efficacy of the combination of lapatinib and docetaxel as a second line treatment for metastatic bladder cancer with an endpoint of progression free survival (PFS). This trial chooses docetaxel since there is no standard of care in relapsed, refractory metastatic TCC and docetaxel is a widely-used option in this situation. Docetaxel given every three weeks is the current control “backbone” for a randomized phase II trial of testing docetaxel and vandetanib led by colleagues at the Dana Farber Cancer Center (DFCI) to which USC has accrued 10 patients. The results of PFS from groups, docetaxel only group and docetaxel + vandetanib group, will be presented at the 2011 Genitourinary Cancers Symposium. DFCI colleagues have agreed to provide de-

identified but annotated data on the docetaxel only patients from that trial to compare to patients given docetaxel with lapatinib in this proposal. The data and the result of PFS at 12 weeks of the docetaxel only group from DFCI study will be available before this proposed study is completed.

Lapatinib 1250 mg daily and docetaxel 75mg/m2 were chosen based on phase I studies of lapatinib and docetaxel in breast cancer and solid tumors as mentioned above, which was the optimal therapeutic dose (16, 17). Dosage reduction will permitted in cases of drug-related toxicity grade 3 as defined by National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 4.0), Lapatinib related toxicity reduced dosage will be 1000 mg/day; Docetaxel related toxicity reduced dosage will be 60mg/m2.

Detection of circulating tumor cells (CTC) in metastatic cancer represents a novel prognostic strategy in patients with metastatic cancers and may serve as a surrogate marker for prospective therapeutic clinical trials (18, 19). Studies have shown that CTC baseline number and change in response to therapy provide predictive and prognostic information in patient with metastatic breast, colorectal and prostate cancer (18, 20-24). Previous studies in metastatic breast cancer have shown evidence of a strong correlation between CTC results and radiographic disease progression in patients receiving chemotherapy or endocrine therapy (19). A study in serial monitoring of circulating melanoma cells during neoadjuvant biochemotherapy for melanoma showed monitoring CTCs in blood may be useful for prediction of outcome of patients receiving treatment for metastatic melanoma (25). In a study to detect the circulating tumor cells in thirty-three patients with urothelial cancer, fourteen of them (44%; 95% confidence interval 27% to 59%) had a positive assay (range 0-87 cells/7.5 ml of blood) with 10 patients (31%) having five or more CTCs (26).

In this proposed study, a platform which captures live CTCs on a parylene-C slot microfilter will be used for CTC detection and characterization (27). The circulating tumor cells will be tested for expression of EGFr and Her2 expression by cytochemistry (28-30). CTC numbers will be monitored prior and post chemotherapy to evaluate CTC as a predictor for the disease progression and indicator for response of treatment in bladder cancer in the setting of combination therapy of lapatinib and docetaxel. These assessments are not intended to be definitive but will provide data for further more definitive assessment in future studies.

Lapatinib is a selective inhibitor of both epidermal growth factor receptor (EGFR) and HER-2 tyrosine kinases. Pre-clinical studies further characterize lapatinib activity and analyze whether EGFR and HER-2 expression or changes induced in the activation of EGFR, HER-2, AKT, or extracellular signal-regulated kinase (ERK) are markers of drug activity in breast cancer and gastrointestinal cell lines. Studies showed that response to lapatinib was significantly correlated with HER-2 and EGFR expression and its ability to inhibit HER-2, EGFR, and AKT/ERK phosphorylation (31-35). In this study, three antibodies targeting HER2, AKT and ERK, will be added on the CTCs to evaluate the phosphorylation of AKT and ERK. These will be collected using slot filter technology from a single sample. We will evaluate the effect of lapatinib in human circulating urothelial tumor cells at the molecular level by targeting the phosphorylation activity of the AKT/ERK on pathway on CTC prior and during the lapatinib treatment.

USC is currently involved in a phase II study with zactima (vandetanib) given in combination with docetaxel compared with the efficacy of docetaxel combined with

placebo in prolonging progression-free survival of subjects with metastatic, previously treated TCC, which was led by colleagues at the Dana Farber Cancer Center as mentioned before. As targeting therapy is a potential future in bladder cancer, a comparison of efficacy of these two trials in the same institution, one with zactima and docetaxel, the other is lapatinib and doxetaxel, is intriguing. More saliently, the proposed study will use the control arm of placebo and docetaxel in USC as a historical control group for comparison at the time of statistical analysis.

2.0 OBJECTIVES

2.1 Primary Objectives:

2.1.1 To assess the efficacy of 1250 mg of lapatinib given in combination with docetaxel in prolonging progression-free survival of subjects with metastatic, previously treated TCC relative to historical controls.

2.2 Secondary Objectives:

2.2.1 To assess the efficacy of 1250 mg of Lapatinib given in combination with docetaxel in the objective response rates and overall survival.

2.2.2 To study the tolerability and safety of 1250 mg of lapatinib given in combination with docetaxel by assessing the incidence and nature of Grade 3, 4 and serious adverse events (AEs).

2.3 Exploratory Objectives

2.3.1 To assess the expression status of EGFR or HER-2 in tumor tissue and/or CTCs as potential predictors of response to therapy.

2.3.1 To evaluate the number of circulating tumor cells present in 7.5mLs of peripheral blood as a predictor for disease progression and response of treatment in bladder cancer in the setting of combination therapy of lapatinib and docetaxel.

2.3.3 To evaluate the effect of lapatinib in human at molecular level by targeting the phosphorylation activity of the AKT/ERK on pathway prior and during the treatment with lapatinib.

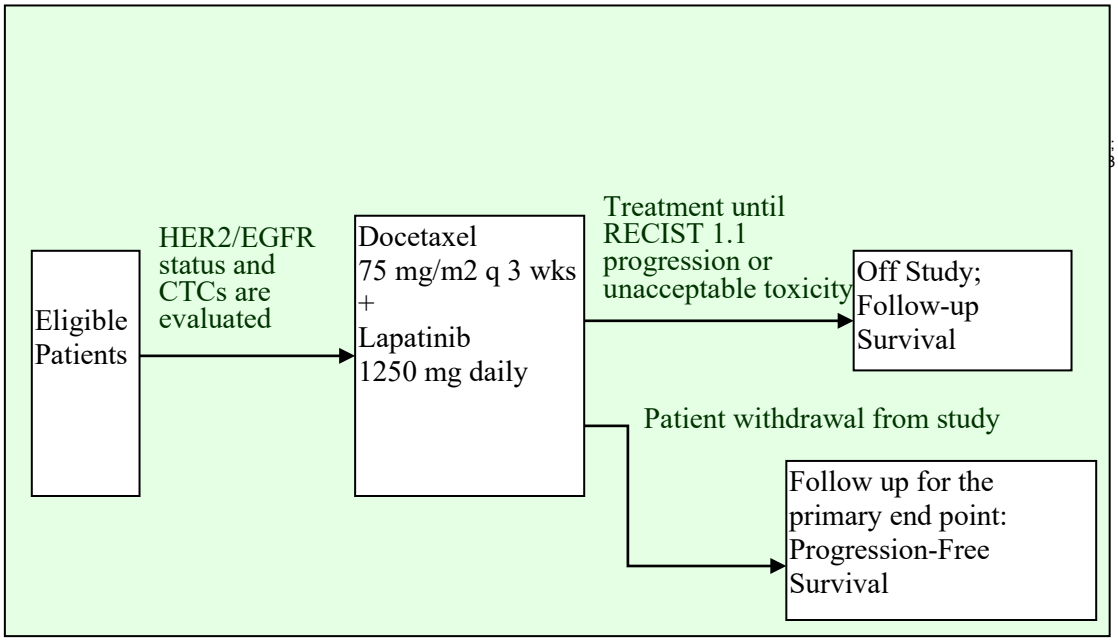
3.0 STUDY DESIGN

3.1 Study Design

This is a single arm 2-stage phase II clinical trial, with a progression-free survival rate at 12 weeks as the primary endpoint. A total of 40 subjects will be enrolled. One interim analysis will be used to assess efficacy.

Treatment will continue until RECIST 1.1 progression, toxicity, or withdrawal.

3.2 Study Schema



All eligible patients will be evaluated for HER2 and EGFR status with tissue available. At the first stage, we will recruit 14 patients; we will then analyze the patient groups based on the markers for non-progression at 12 weeks. We will continue recruit 6 more patients (2 per 4 weeks) during the 12 weeks until the interim analysis for the 14 patients (first stage) is done. After the first stage interim analysis, if one group or groups appear to benefit more relative to the recent historial contol group with docetaxel alone arm, which is from the randomized phase II trial of testing docetaxel and vandetanib led by colleagues at the Dana Farber Cancer Center, will consult GSK to determine the value of accruing an additional cohort of around 26 with that marker profile at second stage. Otherwise, we will recruit all eligible patients regardless EGFR/HER2 status if patients reach primary end point at first stage. It is intended to examine the EGFr /HER2 at this point for subsequent planning. It is exceeding unlikely that accrual will be curtailed or defined based on the profile at the first interim assessment. A more likely scenario is that patterns of disease control and response are defined based on the current two-stage cohort. If after the completion of the total planned accrual there is a potential pattern, there is provision for further amendment of the protocol to accrue another 26 patients with entry based on the biomarker.

If the patient signs the informed consent form for the clinical trial but does not qualify for the treatment by eligibility criteria after screening, the patient will have the choice to allow the use of his/her tumor block for EGFR and HER-2 expression testing, and his/her one time blood draw for circulation tumor cells collection and the testing of HER-2, AKT and ERK expressions on the circulating tumor cells, so that we could have better understanding of EGFR and HER2 expression both on tumor block and circulating tumor cells on this patients' population. The tissue testing from patients who are not eligible will defer to the protocol OS-11-5 study "Circulating tumor cell collection from cancer patients", Primary Investigator Dr. Amir Goldkorn. A separate informed consent form for the OS 11-5 study needs to be signed by the patients. We will include the results of these testing into the statistical analysis in this study.

4.0 **DRUG INFORMATION**

4.1 Docetaxel:

Name and chemical Information

Chemical name: 4-acetoxy-2α-benzoyloxy-5β, 20-epoxy-1, 7β, 10β-trihydroxy-9-oxotax-11-ene-13α-yl-(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate

Empirical formula: C43H53O14N

Molecular weight: 807.9

Appearance: White powder

Mechanism of action
In vitro, docetaxel promotes tubulin assembly into microtubules and inhibits depolymerization thus stabilizing microtubules, which is different from the action of other spindle poisons in clinical use. This can lead to bundles of microtubulesin the cell, which by blocking cells in the M phase of the cell cycle, results in the inability of the cells to divide.
Comparing docetaxel and paclitaxel using the "tubulin in vitro assay", the concentration required to provide 50% inhibition of microtubule disassembly (orIC50) is 0.2 μM for docetaxel and 0.4 μM for paclitaxel.

Toxicology
The major toxic effect of docetaxel, which limits dose, is neutropenia, which may be associated with fever and infection. Other toxic effects, which may be seen, include leukopenia, thrombocytopenia, anemia, asthenia, dysgeusia, myalgia, arthralgia, nail changes and conjunctivitis. Severe anaphylactoid reactions, characterized by a flush associated with hypo- or hypertension, with or without dyspnea, mayoccur requiring immediate discontinuation of the docetaxel infusion andaggressive therapy. All patients should be premedicated with an oralcorticosteroid prior to the initiation of the infusion of docetaxel. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. Other toxicities include cutaneous reactions (e.g., skin rash, desquamation following localized pruriginous maculopapular eruption, skinerythema with edema), hypersensitivity reactions (flushing, pruritis, fever, chills, rigors, lower back pain), dyspnea with restrictive pulmonary syndrome, pleural effusions, arrhythmias, pericardial effusions, fluid retention syndrome, ascites, myopathy, digestive tract toxicities (nausea, vomiting, oral mucositis, diarrhea, anorexia), alopecia, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, peripheral edema, reversible increase in liver function tests, hepatic failure and neurotoxicity (reversible dysesthesias or paresthesias, peripheral neuropathy, seizure, headache, lethargy orsomnolence). Patients with SGOT (AST) > 1.5 times normal and alkalinephosphatase > 2.5 times normal appear to have decreased docetaxel clearance and appear to be more likely to suffer severe toxicity, including drug-related death. Disseminated intravascular coagulation often in association with sepsis or multiorgan dysfunction has been reported. Rare cases of congestive heart failure have been reported with docetaxel used in combination with other chemotherapy agents. Very rare cases of myeloid leukemia or myelodysplasia have occurred in docetaxel, doxorubicin, and cyclophosphamide treated patients.
Please refer to the package insert for complete product instructions and toxicity.
Potential Drug Interactions: In in vitro screening assays, docetaxel was asignificant inhibitor of CYP3A4 and a moderate to weak inhibitor of CYP2D6, 2C19, 2C9 and 1A2. These preliminary data indicate that there may be some potential for interactions with co-administered drugs that are metabolized bythese isozymes although the results should be treated with caution until definitive studies are conducted.

Pharmocology, Handeling, Disposal, Preparation, Administration, And Storage
Preparation and Administration
TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to *Handling and Disposal* section.

If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOTERE Injection Concentrate requires two dilutions prior to administration. Please the preparation instructions provided below. **Note:** Both the TAXOTERE

Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **entire** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel.

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg.

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (mL)	Approximate extractable volume of diluent when entire contents are withdrawn (mL)	Concentration of the initial diluted 1.1.1 solution (mg/mL docetaxel)
Taxotere 20 mg/0.5mL	1.88 - 2.08 mL	1.8 mL	10 mg/mL
Taxotere 80 mg/2 mL	6.96 – 7.70 mL	7.1 mL	10 mg/mL

Preparation and Administration

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE

Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.

2. Aseptically withdraw the entire contents of the appropriate diluent vial (approximately 1.8 mL for TAXOTERE 20 mg and approximately 7.1 mL for TAXOTERE 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of

TAXOTERE Injection Concentrate: If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.

3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

4. The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80.

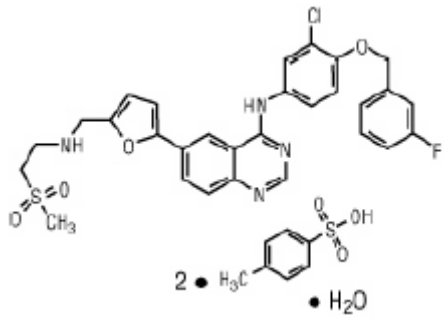
Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipates prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.
If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
2. Thoroughly mix the infusion by manual rotation.
3. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.
The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.
Stability: TAXOTERE infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).
HOW SUPPLIED
TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogenfree, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:
TAXOTERE 80 MG/2 ML (NDC 0075-8001-80)
TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.
TAXOTERE 20 MG/0.5 ML (NDC 0075-8001-20)
TAXOTERE (docetaxel)) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.
This drug is commercially available for purchase by a third party.
Storage: Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.
Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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



Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is 0.001 mg/mL at 25° C.

Each 250 mg tablet of LAPATINIB contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 398 mg of lapatinib ditosylate or 250 mg lapatinib free base.

The inactive ingredients of LAPATINIB are: *Tablet Core:* Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. *Coating:* Orange film-coat: FD&C yellow No. 6/sunset yellow FCF Aluminum Lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

Mechanism of Action

Dual inhibitor of epidermal growth factor receptor (EGFR or ErbB1) and ErbB2 or HER2 tyrosine kinases:
Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER2 [ErbB2]) receptors (estimated K_i^{app} values of 3nM and 13nM, respectively) with a dissociation half-life of ≥ 300 minutes. Lapatinib inhibits ErbB/HER-driven tumor cell growth *in vitro* and in various animal models.

An additive effect was demonstrated in an *in vitro* study when lapatinib and 5-FU (the active metabolite of capecitabine) were used in combination in the 4 tumor cell lines tested. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium *in vitro.* These *in vitro* findings suggest non-crossresistance between these two agents.

Pharmacokinetics

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 hour). 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) values of Cmax were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.hr/mL (23.4 to 56 mcg·hr/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 (5% fat-500 calories) or with a high fat (50% fat-1,000 calories) meal, respectively.

Distribution: Lapatinib is highly bound (> 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 (Pgp, ABCB1). Lapatinib has also been shown *in vitro* to inhibit these efflux transporters, as well as the hepatic uptake transporter OATP 1B1, 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 (< 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.

How Supplied: lapatinib is supplied as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. The tablets contain 410 mg of lapatinib Ditosylate Monohydrate, equivalent to 250 mg lapatinib freebase per tablet. The tablets are packaged into HDPE bottles with child-resistant closures.
Excipients present in the tablet include: Microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate.
The film-coat contains: Hydroxypropyl methylcellulose, titanium dioxide, triacetin/glycerol triacetate, and yellow iron oxide.

Storage: The intact bottles should be stored at controlled room temperature (15°C-30°C).

Stability: Shelf life surveillance studies of the intact bottle are on-going. Current data indicates lapatinib is stable for at least 2 years at controlled room temperature (15°C - 30°C).

Route of Administration: Oral on an empty stomach (either 1 hour before or 1 hour after meals).

Kool-Aid Flavored Suspension: Prepare Lemonade or Tropical Punch Kool-Aid as directed on the package. Place 2 or 4 oz of Kool-Aid (room temperature or refrigerated) in a glass container, then add six 250 mg lapatinib tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10-20

minutes or until the tablets are completely broken up. Stir the container for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and administer (total of 4-6 oz of liquid is dispensed).

Suspension in Water: Place 4 oz of water in a glass container, and then add six 250 mg lapatinib tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10-20 minutes or until it is fully dispersed. Stir the container for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and administer (total of 6 oz of liquid is dispensed).

Lapatinib Prohibited Medication List
Gastric pH Modifiers.
GSK is no longer prohibiting gastric pH modifiers (i.e. H2 blockers and PPIs). This is based on collection of concurrent med use and the observation that PK was no different between pts on gastric pH modifiers and those not taking gastric pH modifiers.

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

Drug Class	Agent	Wash-out[1]
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)	
Antiretrovirals	efavirenz, nevirapine	
Glucocorticoids (oral)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)[2]	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir, atazanvir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant	
Other	grapefruit, star fruit, pomegranate, papaw and their juices	

	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennies	Excluded 1 hour before and after dosing
Herbal or dietary supplements	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil, and St John's Wort	14 days

At the time of screening, if a patient is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of lapatinib and throughout the study period in order for the patient to be eligible to participate in the study.
Glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed.
Glucocorticoid conversions are provided in parentheses.

TOXICITY

Clinical Trials Experience:

The safety of lapatinib (LAPATINIB) has been evaluated in more than 3,500 patients in clinical trials. The efficacy and safety of lapatinib in combination with capecitabine in breast cancer was evaluated in 198 patients in a randomized, Phase 3 trial. Adverse reactions which occurred in at least 10% of patients in either treatment arm and were higher in the combination arm are shown in Table 1.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (> 20%) during therapy with lapatinib plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmarplantar erythrodysesthesia and rash), and fatigue. Diarrhea was the most common adverse reaction resulting in discontinuation of study medication.

The most common Grade 3 and 4 adverse reactions (NCI CTC v3) were diarrhea and palmar-plantar erythrodysesthesia. Selected laboratory abnormalities are shown in Table 2.

Table 1. Adverse Reactions Occurring in 10% of Patients

	Lapatinib 1,250 mg/day + Capecitabine 2,000 mg/m^2/day (N = 198)	**Capecitabine 2,500 mg/m^2/day (N = 191)**

Reactions	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skinand subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash†	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrativesite conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						

Insomnia	10	<1	0	6	0	0

*National Cancer Institute Common Terminology Criteriafor Adverse Events, version3.
†Grade 3 dermatitis acneiform was reportedin <1% of patientsin LAPATINIB plus capecitabine group.

Table 2. Selected Laboratory Abnormalities

Parameters	Lapatinib **1,250 mg/day + Capecitabine 2,000mg/m²/day**			**Capecitabine 2,500 mg/m²/day**		
	All Grades* %	**Grade3%**	**Grade 4%**	**All Grades* %**	**Grade 3%**	**Grade 4%**
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	22	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	1	0

*National Cancer Institute Common Terminology Criteriafor Adverse Events, version 3.

Decreases in Left Ventricular Ejection Fraction: Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular cardiac function that are ≥ Grade 3 (NCI CTCAE), or a ≥ 20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal. Among 198 patients who received lapatinib/capecitabine combination treatment, 3 experienced Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTC 3.0).

QT Prolongation

The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses of lapatinib ranging from 175 mg/day to 1,800 mg/day. Serial ECGs were collected on Day 1 and Day 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of the 81 subjects were found to have either QTcF (corrected QT by the Friedericia method) > 480 msec or an increase in QTcF > 60 msec by automated machine-read evaluation of ECG. Analysis of the data suggested a relationship between lapatinib concentration and the QTc interval.

Interstitial Lung Disease/Pneumonitis: Lapatinib has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies

Warning and Precautions:

Decreased Left Ventricular Ejection Fraction

Lapatinib has been reported to decrease LVEF. In the randomized clinical trial, the majority (> 60%) of LVEF decreases occurred within the first 9 weeks of treatment; however, data on long-term exposure are limited. Caution should be taken if LAPATINIB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with LAPATINIB to ensure that the patient has a baseline LVEF that is within the institution's normal limits. LVEF should continue to be evaluated during treatment with LAPATINIB to ensure that LVEF does not decline below the institution's normal limits.

Hepatotoxicity

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

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

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

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

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

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents

All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT >3 × ULN **and** bilirubin[a] >2 × ULN (35% direct)	24 hours	CRF	24 hours	CRF

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

Patients with Severe Hepatic Impairment

If Lapatinib is to be administered to patients with severe pre-existing hepatic impairment, dose reduction should be considered. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with lapatinib.

Diarrhea

Diarrhea, including severe diarrhea, has been reported during treatment with lapatinib. Proactive management of diarrhea with anti-diarrheal agents is important. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of therapy with LAPATINIB.

Interstitial Lung Disease/Pneumonitis

Lapatinib has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease or pneumonitis. Lapatinib should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are ≥ Grade 3 (NCI CTCAE).

QT Prolongation

QT prolongation measured by automated machine-read evaluation of ECG was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic

medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration. The prescriber should consider baseline and on-treatment electrocardiograms with QT measurement.

Pregnancy

Pregnancy Category D

LAPATINIB can cause fetal harm when administered to a pregnant woman. In a study where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC), 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human clinical exposure based on AUC).

Lapatinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib, and precocious ossification) occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

There are no adequate and well-controlled studies with LAPATINIB in pregnant women. Women should be advised not to become pregnant when taking LAPATINIB. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Supplier: This drug is supplied by GSK as investigation drug.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Subject registration

Screening studies will be performed as described in the "*Required Data for registration and follow up work flow*" table in Section 10.0. Informed consent will be obtained and an eligibility checklist will be completed prior to subject registration.

5.2 Inclusion Criteria

1. Histologically or cytologically confirmed transitional cell carcinoma of the urothelium (also called urothelial cancer). Mixed histologies are allowed as long as the predominant histology is TCC. In addition, tumor tissue must be available for evalautuon for EGFR and HER2/neu status.
2. Locally recurrent or advanced, non-resectable or stage IV transitional cell carcinoma.
3. Patient must have had prior platinum salt-based chemotherapy for TCC. Other prior systemic chemotherapeutic or investigational treatment regimens for TCC are allowed. The patient may have had up to three lines of chemotherapy for advanced disease. Patients may have had paclitaxel provided their cancer did not progress while on it; and it

was part of an adjuvant or neoadjuvant regimen. Prior targeted or biological therapy is permitted except for drugs targeting EGFR and/or HER2.
Specifically, subjects must meet one or more of the following criteria:

a. Progression after treatment with a regimen that includes a platinum salt (e.g. – carboplatin or cisplatin) for Stage IV or recurrent disease.
   OR
b. Disease recurrence within two years (from the date of last dose of chemotherapy or surgery until day the informed consent is signed) of neoadjuvant or adjuvant treatment with a regimen that includes a platinum salt.

4. Measurable or evaluable disease, as defined by RECIST 1.1 (detail in section 6). If all sites of measurable or evaluable disease have been irradiated, one site must have demonstrated growth after irradiation.
5. A left ventricular ejection fraction (LVEF) within normal range as measured by echocardiogram or MUGA scan.
6. Adequate contraceptive method for subjects with reproductive potential (females with reproductive potential must have a negative serum pregnancy test within 7 days of study entry).
7. ECOG performance status 0 or 1 (ECOG criteria are listed in Appendix A)
8. A signed written informed consent (Informed consent form is attached with protocol)
9. Age > / = 18 years old
10. Due to the experimental nature of lapatinib, female subjects must be one year postmenopausal, surgically sterile, or using an acceptable method of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation.) Male subjects must be surgically sterile or using an acceptable method of contraception during their participation in this study.

5.3 Exclusion Criteria

1. History of treatment of TCC (in any setting – neoadjuvant, adjuvant or for metastatic disease) with Docetaxel.
2. History of treatment with an EGFR or HER2 targeted agent.
3. Laboratory results:
   a. Serum bilirubin > 1.5 x the upper limit of normal (ULN) except in patients with diagnosis of Gilbert's disease.
   b. Creatinine clearance < 20 mL/minute (calculated by the Cockcroft-Gault formula or other formulas on the basis of serum creatinine levels.), Patient is not eligible if on hemodialysis, or clinically symptomatic due to uremia.
   C. Potassium, less than institutional normal level despite supplementation; serum calcium (ionized or adjusted for albumin,) or magnesium below lower limits or normal despite supplementation.
   d. Baseline liver function test including SGOT (AST) or SGPT (ALT) > 2.5 x institutional upper limits of normal.
   If the patient has bone metastases (which may result in serum alkaline phosphatase elevation independent of liver function) then the patient will be ineligible if the AST or ALT exceed 5 times the upper limit of normal (ULN).
   e. ANC < 1500/uL
   f. Platelets < 100/uL
4. Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol.

5. An abnormal left ventricular ejection fraction (LVEF) as measured by echocardiogram or MUGA scan or other suitable technique.
6. Clinically significant cardiac event such as myocardial infarction; New York Heart Association (NYHA) classification of heart disease >2 (see Appendix F) within 3 months before entry; or presence of cardiac disease that, in the opinion of the Investigator, increases the risk of ventricular arrhythmia.
7. History of arrhythmia (multifocal premature ventricular contractions (PVCs), bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation controlled on medication is not exclusion nor are infrequent or unifocal ectopic beats.
8. Current QTc prolongation as a result of medication will require discontinuation of that medication. The patient can be reassessed after discontinuation, provided this is medically appropriate, after 2 weeks or five half-lives of the drug have past which ever is longer.
9. Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age.
10. Presence of left bundle branch blocks (LBBB.)
11. QTc with Bazett's correction that is unmeasurable, or exceeds 480 msec on screening ECG. If a subject has QTc > 480 msec on screening ECG, the screen ECG may be repeated twice (at least 24 hours apart). The average QTc from the three screening ECGs must be <480 msec in order for the subject to be eligible for the study.
12. Any concomitant medication that may cause QTc prolongation, induce Torsades de Pointes (see Appendix D) or induce CYP3A4 function (see Appendix E)
13. Hypertension not controlled by medical therapy.
14. Currently active diarrhea.
15. Women who are currently pregnant or breast feeding.
16. Receipt of any investigational agent, chemotherapy or radiation therapy within 21 days prior to Study Day 1
17. Any unresolved non-hematologic toxicity greater than CTCAE grade 1 from previous anti-cancer therapy (other than alopecia)
18. Major surgery within 4 weeks or incompletely healed surgical incision before starting study therapy
19. Grade 2 or greater peripheral neuropathy
20. Previous or current malignancies within the last 3 years, with the exception of in situ carcinoma of the cervix, adequately treated carcinoma of the skin, small renal masses, and adequately treated localized prostate cancer. Other cancers that are highly likely to be cured (cure rate of 75% or greater) may be included at the discretion of the Principal Investigator.
21. History of severe hypersensitivity reaction to drugs formulated with polysorbate 80.
22. Patients with brain metastasis can only be included if they were treated > 4 week prior to enrollment. Subjects with treated brain metastases must have a post treatment brain MRI showing no further progression of prior lesions AND no new metastatic lesions. Subjects will be ineligible if they have any ongoing symptoms from brain metastases or if there continues to be radiographic evidence of cerebral edema

5.4 Restrictions

Subjects who are blood product donors should not donate blood products during the trial and for 3 months following their last dose of trial treatment.

5.5 Criteria for discontinuation from the study:

Subjects may discontinue from the study at any time, for any reason. Other reasons may include (but are not limited to):

- Disease progression
- Death
- Unacceptable toxicity
- Physician decision
- Subject decision
- Inability to follow protocol-based guidelines
- Study closure

The reason for study discontinuation must be documented if possible. All subjects will be followed for PFS at 12 weeks, PFS and OS after discontinuation. This includes patients who choose to discontinue the study and change chemotherapy regimens. The only exception to this is if the subject specifically chooses to withdraw consent in which case the patient will be censored at last contact.

6.0 DESCRIPTIVE FACTORS and STRATIFICATION SCHEME

For the purposes of this study, subjects should be evaluated initially after 6 weeks (2 cycles), then 2 cycles later at 12 weeks from commencement then every 9 weeks (3 cycles) thereafter with appropriate imaging studies for response evaluation. Response will be monitored as per the RECIST 1.1 criteria, described below. Patients will have a bone scan or suitable alternative to assess for metastatic osseous involvement. If the baseline bone assessment is negative it need not be repeated at each re-imaging session but should be repeated if clinically indicated.

Biomarkers study:
Tissue must be available for analysis of EGRF and HER2 at trial commencement. This tissue will be sourced from formalin fixed parrrfin embedded archival sources from transurethral resection of bladder tumor (TURBT), fine needle biopsy with tissue block or cystectomy or nephrectomy or other biopsy. If the patient has a malignant lesion that is readilty amenable to FNA biopsy and tissue block production without imaging guidance then the physician and patient may decide to undertake this to provide tissue for analysis only if it is deemed clinically diagnostically appropriate for the patients' general cancer care. Expression of EGFR and HER2 will be evaluated by immunohistochemistry (IHC). All samples with a 2+ or 3+ HER2 over-expression are evaluated by fluorescent in situ hybridization (FISH). We will then analyze the patient groups based on these markers for non-progression at 12 weeks.

As an exploratory evaluation, HER2 expression on CTC will be analysed before treatment. CTC counts will be monitored and compared before and during treatment at day 1, Day 7, week 7, week 10, and at progression, in an attempt to evaluate an association with response to treatment. The molecular effects of lapatinib on human target cells will be evaluated by measuring the phosphorylation activity of the AKT/ERK on pathway (targets of lapatinib) in CTC captured before and during treatment with lapatinib.

Over-expression of EGFR and HER-2 will be categorized into 3 groups: both positive, one positive, both negative. The CTC counts will be classified into 2 categories, <5 and ≥5 /7.5 mL. We hypothesize that patients with both EGFR and HER-2 over-expression are more likely to benefit from the treatment, and patients with CTC ≥5 per 7.5 mL of

bood after first cycle (3 weeks) of treatment are less likely to benefit. About 35% of patients with TCC have both EGFR and HER-2 over-expression. Approximately 30% of patients are projected to have CTC ≥5 7.5 mL after one cycle of treatment. The association between overexpression of EGFR and HER-2, CTC, and tumor response will be tested using Fisher's exact test at a significance level of 0.05. The association between overexpression of EGFR and/or HER-2, CTC, and PFS and OS will be examined using the Kaplan Meier curves and the log-rank test at a significance level of 0.05. With a small sample size in this Phase II trial, we will not have 80% power to detect small or moderate differences in the endpoints by EGFR and HER-2 over-expression and CTC. The molecular effects of lapatinib on human target cells by measuring the phosphorylation activity of the AKT/ERK on pathway (targets of lapatinib) in CTC captured before and during treatment with lapatinib will be evaluated by descriptive data.

The purpose of including the biomarkers in this trial is to generate the hypotheses and to suggest which biomarkers will be tested in future trials of similar regimens.

At the first stage, we will recruit 14 patients, and then analyze the patient groups based on HER2 or EGFr expression for non-progression at 12 weeks. We will continue to recruit 6 more patients (2 per 4 weeks) during the 12 weeks until the interim analysis for the 14 patients (first stage) is done. If 7 or more patients of the first 14 are alive with non-progression at 12 weeks then we will continue to acrrue until a total of 40 assessible patients. If one group or groups based on biomarker expression appear to benefit more relative to the recent historial contol group treated with docetaxel alone, which is from the randomized phase II trial of testing docetaxel and vandetanib led by colleagues at the Dana Farber Cancer Center, we will consult GSK to determine the value of accruing an additional cohort of around 26 patients with that marker profile as a further stage. Otherwise we will recruit all eligible patient regardless EGFR/HER2 status. It is intended to examine the EGFr /HER2 at this point for subsequent planning. It is exceeding unlikely that accrual will be curtailed or defined based on the profile at the first interim assessment. A more likely scenario is that patterns of disease control and response are defined based on the current two-stage cohort. If all 40 patients are accrued and a marker profile suggests benefit in a given group discussion with the sponsor, GSK is planned to determine whether accrual of further subjects might be beneficial to explore the marker – therapy link.

7.0 STUDY AGENTS ADMINISTRATION AND TOXICITY MANAGEMENT PLAN

Docetaxel

Docetaxel will be given once every 21 days intravenously, starting at a dose of 75 mg/square meter. It should be given over approximately one hour. Premedication the day prior to infusion and the day of infusion is recommended (dexamethasone 8 mg PO 12 hours prior to treatment, 1-3 hours prior to treatment, and 4-6 hours after treatment, although other similar institutional regimens are acceptable). The patients will all receive premedication with 5HT-3 modulator such as ondansetron, granisetron or dolasetron before docetaxel admininstration. Longer acting agents should not be used because of the risk of QT prolongation. Other premedications may be administered as per the institutional standard.

In the early part of the trial, six patients were treated and assessable with a reduced dose of docetaxel 60mg/m^2 for the first cycle and did not experience unacceptable toxicity as defined in Section 13.0 of the protocol. Therefore, as of Amendment dated 5/9/2013 all patients will commence on docetaxel 75mg/m^2 intravenously and

lapatinib 1250mg daily orally every 3 weeks from cycle 1 onwards an then be subject to the dose modifications detailed in Section 8.0 of this protocol.

Dose reduction instruction for docetaxel after full dose due to toxicity is list in section 8.0.

Lapatinib
Lapatinib: 1250 mg per day continuously, each and every day.

Concomitant therapy
Concomitant therapy with other chemotherapy and radiopharmaceuticals is not allowed.
If clinically indicated, concomitant radiation therapy may be allowed after discussion with the Principal Investigator.
Therapy with bisphosphonates is allowed at the discretion of the investigator.
Use of hematological growth factors is permitted but G-CSF will not be given prophylactically on the first cycle. If a patient develops febrile neutropenia then G-CSF may be used and subsequent prophylaxiz should be consistent with ASCO guidelines. To maintain dose intensity, if the patient has absolute neutrophil count <=1000 on any day 1 then recovery should be waited until ANC > 1000, and the next cycle supported with G-GSF. Erythropoeitin may be used within institutional and ASCO guidelines. Transfusion with blood products is allowed.
Premedication the day prior to docetaxel infusion and the day of docetaxel infusion are recommended. The preferred regimen is dexamethasone 8 mg PO 12 hours prior to treatment; 1-3 hours prior to treatment, and 4-6 hours after treatment, but other similar alternatives are acceptable.
Nausea, vomiting, or both may be controlled with antiemetic therapy. 5HT-3 antagonists may prolong QTc interval risk. Increased monitoring is suggested and discussed below.
Concomitant uses of the known potent **inducers and inhibitors** of CYP3A4 (see E) are not allowed during the study.
Oral and IV glucocorticoids (e.g. – dexamethasone) are allowed as part of a pre-medication strategy for docetaxel infusion.
Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see Appendix D) are not allowed during study.
The following medications can be taken by subjects, but require additional monitoring:
Co-administration of drugs that in some reports might be associated with Torsades de Pointes, but at this time lack substantial evidence, should be avoided if possible (see Appendix D). However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the subject must be closely monitored including regular checks of QTc and electrolytes. The ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the subject remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no ECG prolongation has been noted during 4 weeks of coadministration of a drug from Appendix D Table 2. Electrolytes should be maintained within the normal range using supplements if necessary.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

There are several general guidelines for toxicity management that apply to all specific toxicities:
1. Neither docetaxel nor lapatinib should be re-escalated if reduced.

2. If dose reduction for docetaxel is mandated below dose level –2 or if docetaxel is held for more than 3 weeks from its scheduled date, docetaxel should be permanently discontinued (the subject should stay on lapatinib until disease progression or unacceptable toxicity related to lapatinib).
3. If dose reduction for lapatinib below dose level –1 is mandated or lapatinib is held for more than 6 weeks (or 3 weeks, in the case of QTc prolongation), Lapatinib should be permanently discontinued (The subject should stay on docetaxel until disease progression or unacceptable toxicity of docetaxel).

Dose Reduction for docetaxel and Lapatinib/Placebo

Dose Levels for Docetaxel	
Dose Level	**Dose (mg/m2), given q 3 weeks**
0	**75**
-1	**60**
-2	**48**

Dose Levels for Lapatinib		
Dose Level	**Dose (mg)**	**Tablets per Dose**
0	**1250, given every day**	**5**
-1	**1000, given every day**	**4**

Hematologic toxicities
Blood counts on Day 1 of each cycle:

ANC/uL		**Platelets/uL**	**Docetaxel**	**Lapatinib**
>/= 1000	**And**	**>/ = 100,000**	**No change**	**No change**
< 1000	**OR**	**< 100,000**	**Hold ***	**No change**

* Hold docetaxel. Repeat counts weekly and resume therapy when ANC >/= 1000/uL and platelets >/= 100,000/uL. For platelet < 100,000/uL, resume docetaxel at one reduced dose level for subsequent cycles. For ANC < 1000/uL, if therapy is held for one week or less, please institute growth factor support with the subsequent cycle. If therapy is held for more than one week (or growth factor support has already been instituted), resume docetaxel at reduced one dose level.

Febrile neutropenia
The occurrence of febrile neutropenia (Grade 4 neutropenia associated with an oral temperature of >/= 38.5 degrees Celsius) should result in the institution of growth factor support with subsequent cycles. If growth factor support has already been initiated (prior to the febrile neutropenia) please resume docetaxel at reduced one dose level.
No Lapatinib dose or schedule change for hematologic toxicities.

Hepatic toxicities
Docetaxel should not be administered to subjects with a serum total bilirubin >1.5x ULN. If serum total bilirubin is >1.5x ULN, hold docetaxel until serum total bilirubin is </= 1.5x ULN, then retreat with docetaxel at a dose which is reduced by one dose level. Lapatinib should not be held or dose adjusted for a Grade 1 total bilirubin elevation. For Grade 2, 3 or 4 total bilirubin elevation, Lapatinib should be held until resolution to Grade 1 or below, and then restarted at a reduced dose level.

Dose adjustments for abnormal liver function tests in the absence of bone metastases:
If AST or ALT > 2.5 upper limit of normal range, will reduce Docetaxel one dose level, no change in Lapatinib. If AST or ALT > 5.0 upper limit of normal range we will hold both Docetaxel and Lapatinib.

* Hold both means hold docetaxel and lapatinib until subject's liver function tests meet the eligibility criteria; then resume docetaxel at reduced dose level. No change to lapatinib.

If the patient has bone metastases, then the docetaxel should be held if the AST or ALT exceed 5 times the upper limit of normal until resoulation to <5x ULN and the dose of docetaxel should be reduced one level.

Neurotoxicity
For Grade 3 or 4 neurotoxicity, hold docetaxel until resolved to </= Grade 2, then resume at decreased one dose level. Do not hold or change lapatinib.

Management of diarrhea
Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation.
□ No dose modifications will be made because of grade 1 or 2 diarrhea.
□ If grade 3 diarrhea develops, docetaxel and lapatinib should be withheld until diarrhea resolves to grade 2 or below. The following actions should be instituted:

- Subjects who are clinically unstable because of diarrhea or other intercurrent medical illness must be admitted and evaluated using telemetry, until clinically stable.
- If study therapy is held due to diarrhea for 3 weeks or less, Lapatinib should be dose reduced one level. Docetaxel can be reinstituted at same dose level.
- If study therapy is held for greater than 3 weeks, but less than 6 weeks, Lapatinib can be reinstituted at reduced dose level after consultation with the Overall Principal Investigator. Docetaxel can be reinstituted at same dose level.
- If grade 3 or 4 diarrhea recurs after dose reduction and appropriate supportive therapy, the subject must permanently discontinue Lapatinib. Docetaxel treatment can be reinstituted at same dose level. In this situation, docetaxel should be withheld until diarrhea resolves to Grade 1 or below, and then restarted at a same dose level.
- If study therapy is held for more than 6 weeks, subject should be removed from study.

Management of other Gastrointestinal (GI) Toxicity
Nausea, vomiting, or both may be controlled with antiemetic therapy. 5HT-3 antagonists may prolong QTc interval risk. Increased monitoring is suggested and discussed in section 5.0. For Grade 3 or 4 oral ulceration, dysphagia, nausea or vomiting, hold both docetaxel and Lapatinib. Upon recovery to Grade 1 or below, treatment may resume at a reduced dose level of both docetaxel and Lapabinib

Management of fluid retention
There is no dose or schedule change to either treatment for fluid retention. Fluid retention should be managed with diuretics.

Management of Skin Toxicity

It is strongly recommended that all subjects follow a program of sun protective measures while receiving study therapy and for 3-4 weeks after discontinuing study therapy. The aim is to reduce the risk of development of skin rash, minimize the severity of skin rash, and to minimize the requirement for dose reduction of study therapy.

If a subject develops a skin rash, the following actions are recommended to the Investigator for the management of this reaction:

- A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.
- The rash should be graded/assessed by a physician as soon as possible according to the CTCAE cutaneous toxicity criteria and documented accordingly.
- If a rash of CTCAE grade 2 or higher is detected, immediate symptomatic treatment should be provided.
- If a rash of CTCAE grade 3 or higher is detected, Lapatinib and docetaxel should be withheld until recovery to grade 2 or below.

The following actions should be instituted:

a. If study therapy is held due to severe skin toxicity for 3 weeks or less, Lapatinib should be dose reduced one level. Docetaxel can be reinstituted at same dose level.

b. If study therapy is held for greater than 3 weeks, but less than 6 weeks, Lapatinib can be reinstituted at reduced dose level after consultation with the Overall Principal Investigator. Docetaxel can be reinstituted at same dose level.

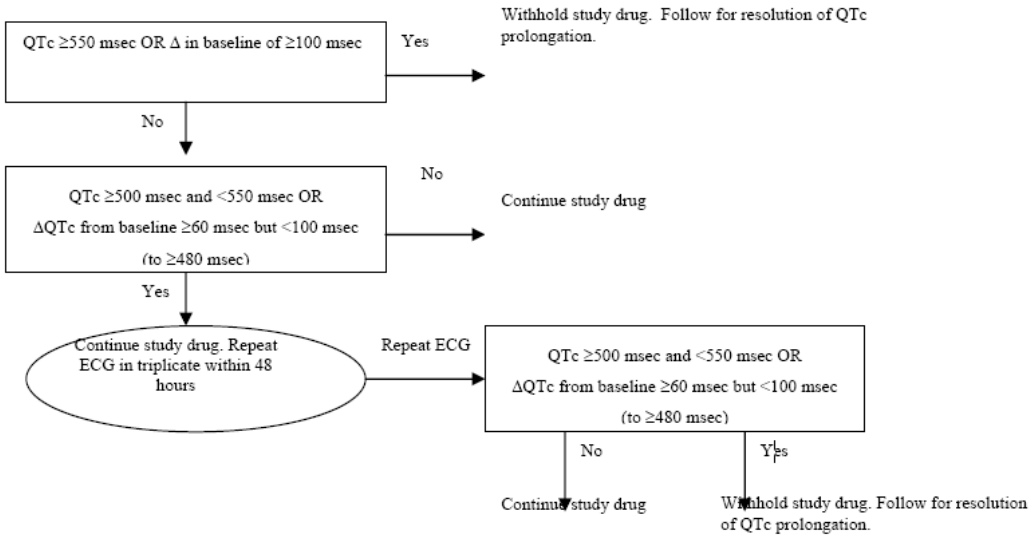
c. If severe cutaneous toxicity recurs after this dose reduction, the subject must permanently discontinue Lapatinib. Docetaxel treatment can be reinstituted at same dose level. In this situation, docetaxel should be withheld until skin toxicity resolves to Grade 2 or below, and then restarted at a same dose level.

d. If study therapy is held for more than 6 weeks, subject should be removed from study.

QTc Prolongation

Subjects will have ECGs performed to monitor QTc interval (using Bazett's correction, Appendix G) as outlined in the study plan.

Figure 1 Flowchart detailing management of QTc prolongation



For this study, QTc prolongation is defined as:
A single QTc value of > = 550 msec or an increase of > = 100 msec from baseline;
OR
Two consecutive ECG measurements, within 48 hours of one another, in which either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):

A QTc interval > = 500 msec but <550 msec OR
An increase of > = 60 msec, but <100 msec, from baseline QTc to a QTc value > = 480 msec. The baseline will be the average of the screening and Day 1 pre-dose QTc values.

Management of Subjects with QTc Prolongation
For a single QTc value of ≥550 msec or an increase of ≥100 msec from baseline,
Lapatinib must be withheld. ECGs and electrolytes should be followed 3 times a week until QTc falls below 480 msec or baseline, whichever is higher. Lapatinib treatment may be resumed at a lower dose level after the QTc recovers to <480 msec or baseline.

For a QTc interval ≥500 msec, but <550 msec, or an increase of ≥60 msec but <100 msec from baseline QTc to a QTc value ≥480 msec, Lapatinib may be continued but a repeat ECG (in triplicate) must be obtained within 48 hours. If QTc prolongation is confirmed, Lapatinib should be withheld. ECGs and electrolytes should be checked 3 times a week until QTc falls below 480 msec or baseline, whichever is higher.Lapatinib treatment may be resumed at a lower dose level after the QTc recovers to <480 msec or baseline. If the subject does not meet the criteria for QTc prolongation at the repeat ECG, then the subject should continue treatment and resume the ECG schedule as outlined in the Study Plan.

If Lapatinib is restarted after the QTc prolongation has resolved, ECGs should be performed 1, 2, 4, 7, 10 weeks and then every 3 months after treatment is restarted. If Lapatinib must be withheld for >3 weeks to allow for QTc prolongation to recover to <480 msec or baseline, the subject will not be restarted on Lapatinib. If QTc prolongation

recurs after the dose reduction as detailed, the subject must permanently discontinue treatment with study medication.
There are no changes to the dose and schedule of docetaxel due to QTc prolongation.

Management of Decreased left ventricular ejection
Lapatinib should be discontinued in patients with a decreased left ventricular ejection fraction (LVEF) that is grade 2 or greater by NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF that drops below the institution's lower limit of normal. Lapatinib may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks if the LVEF recovers to normal and the patient is asymptomatic.

Concomitant admistration of strong inhibitors or inducers of CYP3A4:
Concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly. Dose adjustment of lapatinib should be considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes: Lapatinib will not be adjusted by AUC without inhibitors/inducers. Lapatinib dosage without inhibitors/inducers was decided by phase I studies as mentioned in this protocol.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit may also increase plasma concentrations of lapatinib and should be avoided. If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the lapatinib dose is adjusted upward to the indicated dose.

Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day based on tolerability. This dose of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the lapatinib dose should be reduced to the indicated dose.

Management of hypersensitivity reactions
Subjects who experienced Grade 3 or 4 of hypersensitivity which felt due to docetaxel should permanently discontinue docetaxel. These patients may be eligible for continue Lapatinib alone.
Management of Grade 1 or 2 hypersensitivity reactions secondary to docetaxel should be managed as per local standard of care.

Surgery

For subjects who require surgery while on study, it is recommended that all study treatment be discontinued at least 3 weeks prior to surgery. Re-initiation of protocol therapy should be discussed with primary investigators, Dr. David Quinn and Dr. Sujie Tang.

Management of all other toxicities
Docetaxel and Lapatinib should be held for any other CTCAE Grade 3 or 4 toxicity (other than alopecia, hemoglobin, and fatigue or if covered above) until resolved to Grade 2 or less (or the subject's baseline). If the toxicity is felt to be related to study treatment; that treatment can be reduced one dose level.

9.0 Adverse Event Reporting
Quality Assurance Committee (QAC) in USC will monitor the safety/toxicity from the chemotherapy (Lapatinib + Doxetaxel) in this study. USC financial supporter, GSK, will monitor safety/toxicity as well. Primarily, the monitoring will come from the QAC.

Definitions
The definitions of Adverse Events (AEs) and Serious Adverse Events (SAEs) are given below. It is of the utmost importance that all staff involved in the study be familiar with the content of this section. The Principal Investigator is responsible for ensuring this.
Adverse Event
An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.
Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.
Serious Adverse Event
A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Life-threatening: Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more sever form.
- Require or prolong inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned). Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment

in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care

Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

Procedures for AE and SAE Recording

Adverse events will be assessed at each study visit. CTCAE Version 4.0 will be used to assess and describe AEs. AEs will be collected and reported from the time of beginning study treatment. The following adverse events will be recorded on the case report forms:

1. All SAEs
2. All Grade 3 and 4 adverse events, including Grade 3 and 4 laboratory AEs.
3. All adverse events resulting in a treatment interruption, dose reduction, or withdraw from the study.

Should a pregnancy occur during study participation, it must be reported to the principal investigator. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Reporting Responsibilities

The conduct of the study will comply with FDA and all local safety reporting requirements. Each participating investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" as defined above or according to local reporting requirements are present.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Principal Investigator on the toxicity Case Report Forms.

Serious Adverse Events Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Overall Principal Investigator. This includes events meeting the definition of Serious Adverse Events as defined above, as well as the following:

- o Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are Unexpected and Possibly, Probably or Definitely Related/Associated with the intervention.
- o ALL Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- o ALL Grade 5 (fatal) Events – When participant is enrolled and actively participating in the trial OR when occurs within 30 days of the last study intervention.

  Note: If participant is in Long Term Follow Up, death is reported at the time of continuing review.

All SAEs, regardless of "expectedness" or "causality" must be reported to the Overall Principal Investigator within 24 hours of learning of the event. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. All SAEs should be recorded on a MedWatch 3500a form. Please fax all supporting documentation as it becomes available.

If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be provided to Principal Investigator.

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Reporting to the Institutional Review Board (IRB)

All serious adverse events will be reported directlyto the Human Research Studies offices.

Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

Reporting to FDA

As the sponsor-investigator, the Principal Investigator is required to notify the FDA of any serious adverse event that is unexpected and assessed by the investigator to be possibly related to the study treatment in accordance with the reporting obligations of 21 CFR 312.32.

SAE reports of fatal or life-threatening events must be telephoned or faxed to the FDA within 7 calendar days of first learning of the event. SAE reports of unexpected events (not fatal or life-threatening) must be telephoned or faxed to the FDA within 15 calendar days of first learning of the event.

IND Safety Reports

In accordance with 21 CFR 312.32, GSK shall be responsible for notifying the
Overall Principal Investigator via an IND Safety Report of the following information:

1. Any AE associated with the use of the study drug in this study or other studies that is both serious and unexpected.
2. Any finding from tests in the laboratory animals that suggests a significant risk to human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
3. Serious adverse events that do not require expedited reporting to the FDA will be reported to GSK on a monthly basis and under no circumstance less frequently than quarterly.

Report to GSK:

All serious adverse events, in addition to being reported to the FDA by the investigator, must be reported by facsimile within 24 hours to GlaxoSmithKline.
Oncology MDC Fax: (610) 917-6715
For medical emergencies contact:
Yasir Nagarwala, MD, Director,
Office: 610-917-6068
Mobile: 610-906-5035
or
Michael Arbushites; Assistant Director
Office: 610-917-4039
Mobile: 610-331-9395
Toll Free Number: (800) 877-7074, ext. 5731 or 6862
After Hours or Weekends: (800) 366-8900, ask for physician on call
GlaxoSmithKline UP4420
1250 S. Collegeville Road,
P.O. Box 5089
Collegeville, PA 19426-0989

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

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

10.0 CLINICAL AND LABORATORY EVALUATIONS

Required Data for registration and follow up work flow

Cycle (21 days in length)	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3**	**Cycle 4**		**Cycle 5**		**Cycle 6**	**Cycle 7**	**Cycle 8**	**Follow up**
Week		**Week1**	**Week2**	**Week4**	**Week6**	**Week7**	**Week10**	**Week 12**	**Week 13**	**Week15**	**Week 16**	**Week 19**	**Week 22**	
Day	**-28 to -1**	**1 C1D1**	**8[a] C1D7**	**22[a] C2D1**		**43[a] C3D1**	**64[a] C4D1**		**85[a] C5D1**		**106[a] C6D1**	**127 [a] C7D1**	**148 [a] C8D1**	
Informed consent	X													
Medical history	X													
Inclusion/ exclusion Criteria	X													
Physical examination	X			X		X	X		X		X	X	X	
Vital signs	X	X		X		X	X		X		X	X	X	
ECG c, d (see Section 7.0) c, d And MUGA Scan	X[b]	X[c]	X[d]				X[bd]		X[d]			X[d]		
Hematology clinical Chemistry[g]	X[i]	X		X		X	X		X		X	X	X	
Pregnancy test	X[l]													
Blood for CTCs and tissue collection[h]	X[h]	X[h]	X[h]	X[h]			X[h]							X[h]
ECOG Performance Status	X[m]			X		X	X		X		X	X	X	
Imaging[e,]	X[e]				X[f]			X[f]				X[f]		
Lapatinib dispensing		X		X		X	X		X		X	X	X	
Docetaxel infusion		X		X		X	X		X		X	X	X	
AE reporting	X	X		X		X	X		X		X	X	X	X[j]
Survival														X[k]

a. +/- 3 days
b. 12-lead ECG must be performed within 28 days before first dose. Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility. MUGA scan (or echocardiogram, or other suitable technique) must be performed within 28 days before first dose and at week 10. Additional MUGA scan (or echocardiogram or other suitable technique) will be done if clinically suspect that patient develops heart failure during treatment.
c. On day 1, cycle 1, 12-lead ECGs are to be performed pre-dose. Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on day 1. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary on day 1.
d. ECGs must be performed at week 2 (C1D8), week 10 (C4D1), week 13 (C5D1), then every 4 cycles. When possible, ECGs should be performed at the same time throughout the study (performed 4-8 hours after the subject takes their oral medication lapatinib, - therefore patients may take their Day 1 dose of drug in the morning to ensure the ECG is appropriately timed. If patient is on the schedule for blood draw for CTC, patient may draw blood in the morning, take the oral medication lapatinib right after blood draw, then perform ECG 4-8 hours later).
Moreover, increased ECG monitoring is needed in the setting of certain concomitant medications that may prolong the QTc (see Appendix D and Section 5.0). The ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the subject remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no ECG prolongation has been noted during 4 weeks of co-administration of a drug from Appendix D Table 2.
e. Screening imaging must be performed within 35 days before first dose Must include chest/abdominal /pelvic CT scans (with IV and PO contrast if not contraindicated). MRI may be substituted for CT scan. Bone scan or other bone maging modality will be performed, subsequent restaging bone imaging only it there are bone metastases at baseline or if clinically indicated.
f. Imaging to be performed prior to cycles 3 and 5 (6 week intervals) then prior to cycle 8 and 11 (9 week intervals).
g. To include electrolytes, BUN, creatinine, liver function tests, calcium, magnesium, phosphorus, and CBC with differential.
h. CTC will be captured and analyzed from patient blood before the treatment on cycle 1, day 1, and during treatment at cycle 1 day 1 (4-6 hours after treatment (patient takes lapatinib in the morning, Docetaxel infusion needs to schedule in the morning as well)), Day 7 (before lapatinib dose, (patient may take the lapatinib right after the blood draw for CTC in the morning)), cycle 2 day 1 (before lapatanib dose (patient may take the lapatinib right after the blood draw for CTC in the morning)), cycle 4 day 1 (before lapatanib dose (patient may take the lapatinib right after the blood draw for CTC in the morning)), and at progression, in an attempt to evaluate an association with response to treatment.
Evaluate tissue from previous TURBT or tumor biopsy for correlative studies at study entry. This will be in the form of actual frozen tissue, blocks, or unstained slides. See section 17.0 for processing and handling of research tissue.
i. Baseline labs performed within 3 days of start date will not need to be repeated.
j. During Follow-up, AE reporting must continue for 30 days following last dose of study drug (please see section 8.0 for AE reporting guidelines).
k. Follow for survival information every 6 months (±1 month) until death, up to 2 years after discontinuing therapy, or patient lost to follow-up
l. Pregnancy test is required for woman of childbearing potential.
m. ECOG performance status evaluation is requried at screening. Re-evaluation within 72 hour before treatment is needed if the ECOG performance stautus screening is out of the 72 hours window.

11 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

11.0 RECIST 1.1 Evaluation

11.0.1 Measurability of Tumors at Baseline

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
10mm by CT scan (irrespective of scanner type) and MRI (*no less than double the slice thickness and a minimum of 10mm*)
10mm caliper measurement by clinical exam (when superficial)
20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

11.0.2 Non-measurable Lesions

Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

11.0.3 Assessment of Lymph Nodes

Definitions provided for

Normal: short axis < 10 mm
Measurable (Target): short axis ≥ 15 mm
Non-measurable: short axis 10 to < 15 mm

Target nodes measured in the short axis (perpendicular to longest diameter) :

More reproducible and predictive of malignancy

Short axes of target nodes to be added to the sum of longest diameters

11.0.4 Bone Lesion Measurability

Lytic bone lesions, with an *identifiable soft tissue component*, evaluated by CT or MRI, *can be considered as measurable lesions* if the soft tissue component otherwise meets the definition of measurability previously described.

Blastic bone lesions are non-measurable

11.0.5 Cystic Lesions

Lesions that meet radiographic criteria for simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable)

Radiographically indeterminate, complex "cystic" lesions should be considered non-measurable lesions

"Cystic Lesions" thought to be cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. However, if non-cystic lesions are present in the same patient, these should be preferably selected for assessment.

11.0.6 Prior Local Treatment of Lesions

Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Study protocols should detail the conditions under which such lesions would be considered measurable.

11.0.7 Baseline Documentation of Target Lesions

All lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions

It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

11.0.8 Documentation of Non-target Lesions

It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”)

11.0.9 Definition of CR

Target Lesions: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes)

Non-target Lesions: disappearance of all non - target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

11.0.10 Definition of PD

Target Lesions: > 20% increase in the SLD taking as reference the smallest SLD recorded since the treatment started (nadir) and minimum 5 mm increase over the nadir

When sum becomes very small, increases within measurement error (2-3 mm) can lead to 20% increase

11.0.11 Definition of Unequivocal Progression

Unequivocal progression of existing non-target lesions defined as:

Overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy

In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread

11.0.12 Too Small to Measure

All target lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm)

However, if target lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure' and a default value of 5mm should be assigned

11.0.13 Lesions that Split or Coalesce

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum

Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'

11.0.14 New Lesions

Finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. This is particularly important when patient's baseline lesions show PR or CR

When in doubt, subsequent timepoint should be evaluated

Lesion seen in anatomical region which was not imaged at baseline = new lesion

11.0.15 PET

PET scanning will not be used routinely in this study as it is not standard of care for patients with ruothelial cancer.

11.0.16 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response

11.0.17 Overall Response Table, Subjects With Measurable Disease

RECIST 1.1:

Target	Non-target	New	Overall Response
CR	CR	No	CR

CR	Non-CR / non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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11.0.18 Best Overall Response

Overall Response First Timepoint	Overall Response Subsequent Timepoint	BEST overall response
CR	CR	CR
CR	PR	SD, PD, OR PR
CR	SD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD

		duration are met. Otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
NE	NE	NE

11.0.19 Lesion Reappearance

In the setting of PR (or SD), if a lesion disappears and reappears at a subsequent time point it should continue to be measured. Response will depend upon the status of his/her other lesions. The lesion should simply be added into the sum.

In the setting of CR, reappearance of a lesion would be considered PD.

Most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

11.1 Outcome Parameters / Analytical Endpoints

The primary endpoint is progression-free survival (PFS) rate at 12 weeks. PFS is defined as the time period from the start of treatment and documented progression or death without documentation of progression; patients who are alive and without evidence of progression will be censored at the date of last response evaluation. The binary endpoint the PFS at 12 weeks is defined as yes if patients have progressed or died within 12 weeks (PFS $\leq$ 12 weeks) or no if patients are alive and free of progression at 12 weeks (PFS > 12 weeks) since starting treatment. Patients who have progressed or died within 12 weeks of treatment (PFS $\leq$ 12 weeks) will be counted in the number of patients with PFS $\leq$ 12 weeks. Patients who remain alive and progression-free at 12 weeks (PFS > 12 weeks) will be counted in the number of patients with PFS > 12 weeks. Patients who discontinue treatment due to toxicity prior to 12 weeks without documented progression will be counted in the number of patients with PFS $\leq$ 12 weeks. Patients who withdraw the study or start another treatment not due to progression or toxicity prior to 12 weeks (follow-up $\leq$ 12 weeks) will not be counted in the decision of continuing or stopping the trial.

Secondary endpoints are: PFS; objective response rates, with response defined as a confirmed overall PR or CR; overall survival, defined from date of starting treatment to date of death or censored at the date the patient was last known alive; and toxicity.

The primary and secondary endpoints of all patients registered in this study, will be reported. Patients who complete the first course of treatment and receive at least 50% of the doses, or who have experienced a DLT, will be evaluable for toxicity. All patients who complete the first cycle of treatment will be included in the assessment of response; patients who do not complete the first cycle of treatment for reasons of toxicity due to the treatment or early progression, will also be included in the assessment of response.

Patient baseline demographic and clinical characteristics will be described.

Toxicities observed will be summarized in terms of type (organ affected, laboratory determination), severity (by CTC and nadir or maximum values for the laboratory measures), time of onset, duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects by cycle of therapy.

The overall response rate will be calculated as the ratio of the number of evaluable patients who experienced a confirmed CR or PR (by RECIST) divided by the total number of evaluable patients; 95% confidence intervals will be constructed. Progression-free survival and overall survival will be summarized with Kaplan-Meier curves. The median PFS and OS will be estimated using a non-parametric method.

12.0 DATA COLLECTION AND MONITORING

12.1 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from a patient or a patient's legal representative before any study related procedures are performed. The Investigator will provide an informed consent in compliance with ICH GCP and U.S. FDA guidelines (21 CFR 50). A summary of these guidelines can be found in Appendix C. The informed consent document must clearly describe the potential risks and benefits of the trial and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. The informed consent must be approved by the IRB prior to being presented to a potential patient.

12.2. Use and completion of case report forms (CRFs)

The Investigator will prepare and maintain adequate and accurate CRFs to record all observations and other data pertinent to the clinical investigation. All CRFs will be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the information to be modified must not be overwritten or erased. The corrected information will be transcribed next to the previous value, initialed and dated by the authorized person. The investigator is to maintain an up to date sheet bearing an example of the signatures of all persons authorized to enter data on the CRF.

12.3. Confidentiality

It is the responsibility of the Investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms must never contain the name of a trial patient. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial. Personal medical information may be reviewed by representatives of the IRB or of regulatory authorities in the course of auditing the trial. Every reasonable effort will be made to maintain such information as confidential.

12.4 Confidentiality Agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigator by GlaxoSmithKline (or any company acting on their behalf), including the Investigators' Brochure are the exclusive property of GSK. They may not be given or disclosed by the Investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of GSK.

12.5 Record Retention

The Investigator must maintain all study records, patient files and other source data for the duration of the trial and as per FDA and institutional requirements.

13.0 STATISTICAL CONSIDERATIONS

This is a single arm two-stage phase II trial to assess the efficacy of 1250 mg lapatinib daily given in combination with docetaxel with regard to the 12-week progression-free survival rate.

Study Design

There are no standard regimens of chemotherapy for patients with TCC who have progressed after receiving a first line therapy. We do not consider a randomized phase II design to compare the efficacy between docetaxel alone vs. the combination of docetaxel and lapatinib because a multi-center randomized study of docetaxel +/- ZD6474 in metastatic TCC has completed recently. Dana Farber Cancer Institute colleagues have submitted an abstract to the 2011 Genitourinary Cancers Symposium (Feb 17-19, 2011). The results of PFS from both groups, docetaxel only group and docetaxel + vandetanib group, will be presented at the 2011 Genitourinary Cancers Symposium. The data and the result of PFS at 12 weeks and median PFS of the docetaxel only group from DFCI study will be available before this proposed study starts. The patients in control arm of the trial receive docetaxel 75 mg/m2 q 3 wks + placebo. Based on the published previous studies for patients on second line chemotherapy, the progression-free survival rate at 12 weeks after starting treatment (a binomial outcome) will be the primary endpoint. The landmark time of 12 weeks is selected because tumor response is evaluated every 2 cycles (6 weeks). A two-stage Phase II design (Simon 1989) will be used to estimate a progression-free survival rate at 12 weeks (36). The median progression-free survival in patients with chemotherapy-refractory TCC treated with chemotherapy was around 8-10 weeks. Therefore, 60% patients remain alive and free of progression at 12 weeks (translates to a median progression-free survival of around 16 weeks) will be considered important and indicative that this regimen warrants further study; a progression-free rate of 40% or less at 12 weeks (translates to a median progression-free survival of 9 weeks) would be considered background and disappointing.

In the first stage, we will enroll and treat 14 patients. If ≤ 6 of the first 14 evaluable patients treated with the combination of docetaxel and lapatinib are alive and free of progression at 12 weeks or ≥ 8 patients have progressed within 12 weeks, then accrual will be terminated with conclusion that the regimen is not promising. If ≥ 7 patients are alive and remain free of progression at 12 weeks, then accrual will continue until a total of 40 evaluable patients have been treated and are followed. If ≤ 19 of the 40 patients are alive and free of progression at 12 weeks or ≥ 21 patients have progressed within 12 weeks, then we will conclude that no activity is observed for this regimen in these patients. 20 or more patients are alive and free of progression at 12 weeks will be taken as evidence that this regimen has some activity in these patients.

Primary Endpoint Evaluation

The primary endpoint is progression-free survival (PFS) rate at 12 weeks. PFS is defined as the time period from the start of treatment and documented progression or death without documentation of progression; patients who are alive and without evidence of progression will be censored at the date of last response evaluation. The binary endpoint the PFS at 12 weeks is defined as yes if patients have progressed or died within 12 weeks (PFS $\leq$ 12 weeks) or no if patients are alive and free of progression at 12 weeks (PFS > 12 weeks) since starting treatment. Patients who have progressed or died within 12 weeks of treatment (PFS $\leq$ 12 weeks) will be

counted in the number of patients with PFS ≤ 12 weeks. Patients who remain alive and progression-free at 12 weeks (PFS > 12 weeks) will be counted in the number of patients with PFS > 12 weeks. Patients who discontinue treatment due to toxicity prior to 12 weeks without documented progression will be counted in the number of patients with PFS ≤ 12 weeks. Patients who withdraw the study or start another treatment not due to progression or toxicity prior to 12 weeks (follow-up ≤ 12 weeks) will not be counted in the decision of continuing or stopping the trial. Patients who are not evaluable for the primary endpoint will be replaced.

Interim analysis

An interim analysis will be conducted when the first 14 patients have been evaluated for the primary endpoint: PFS at 12 weeks. Patient enrollment will not been stopped (up to an additional 6 patients, for a total of 20, will be permitted) when the first 14 evaluable patients have been treated, but the decision to stop accrual is pending because of insufficient follow-up time in some patients. As soon as ≥8 of the first 14 evaluable patients have PFS ≤ 12 weeks, the accrual will be suspended for analysis.

Sample size justification

If the true progression-free survival rate at 12 weeks is 40%, there is a < 10% chance (type I error rate) that we will conclude that the regimen is promising. If the true progression-free survival rate at 12 weeks is 60% (translates to a 79% improvement in median PFS), there is an 82% chance (power) that we will observe an activity. If the true progression-free survival rate at 12 weeks is 40%, there will be a 69% chance that the accrual will be terminated early because of lack of activity. With 40 patients, we will be able to estimate the objective tumor response rate, the secondary endpoint, with 95% confidence intervals having a half-width of ±15.5% or less

Analysis of Endpoints

The initial analysis of outcome (PFS at 12 weeks, PFS, objective response rate, and OS) will include all patients who begin treatment. A secondary analysis (response rate) will include patients who have received at least one cycle of treatment and whose tumor response has been evaluated; patients whose treatment is terminated too early to have tumor response evaluated due to drug-related toxicity or disease progression will also be included in the calculations.

The secondary clinical endpoints include PFS, OS, and drug-related toxicity. PFS and OS will be summarized using the Kaplan-Meier curves. The first 6 patients accrued will be dosed with docetacel 60mg/ m^2 for cycle 1, and then escalated to 75mg/ m^2 at cycle 2 and subsequent cycles, ensuring safety and tolerability of lapatinib and docetaxel in bladder cancer. If one or fewer of the first 6 experience any Grade 4 clinical or non-hematologic abnormalities lasting more than 7 days in the first cycle, then subsequent patients will begin treatment at 75 mg/m2. Otherwise, all patients will begin treatment with a reduced dose of docetaxel on the first course. Drug-related toxicity will be summarized by starting dose, cycle, grade, and type.

<u>Analysis of Correlative Endpoints</u>
The associations between over-expression of EGFR/HER2 in tumor tissue or CTCs and PFS, objective response rate, and OS will be analyzed. If the PFS in patients with expression of Her2 in cancer cell specimens exceeds that for patients who are negative for this expression and/or that in the docetaxel only arm of the zactima trial in USC, which was led by colleagues at the Dana Farber Cancer Center as mentioned before, by more than 4 weeks then we will consider amending the protocol to further accrue only patients with HER2 expression either in tumor tissue or CTCs

to assess response parameters in that selected population, beyond the initially planned 40 unselected patients. This will likely extend accrual by 30-35 patients and would only be undertaken after discussion with GSK.

The association between circulating tumor cell number (CTC) and PFS will be analyzed.
The CTC counts will be monitored and compared prior treatment at day1, and after the treatment at day 1, Day 7, week 4, week 10, and at progression, in an attempt to evaluate an association with response to treatment. Scatterplot will be used to show the patterns of the changes in the CTC counts before and after the treatment and repeated measures ANOVA will be used to analyze the changes if the CTC counts are normally distributed. The changes in the CTC counts between prior treatment at day 1 and after treatment (the lowest count) will be categorized as an increase, a decrease, and no change. The association between the change in the CTC counts and tumor response, PFS, and OS will be analyzed using Fisher's exact test and log-rank test whenever appropriate.

The effect of lapatinib in human at molecular level by targeting the phosphorylation activity of the AKT/ERK on pathway prior and during the treatment with lapatinib will be evaluated by descriptive analysis.

We will describe the data of the EGFR and HER2 expression on the tumor blocks, and the HER-2, AKT and ERK expressions on the circulating tumor cells of this patient population, which includes the patients' data who are not eligible for treatment after screening but allow the testing on their tumor block and circulation tumor cells.

Monitoring unacceptable toxicity

The first 6 patients accrued will be dosed with docetaxel 60mg/ m^2 for cycle 1, and then escalated to 75mg/ m^2 at cycle 2 and subsequent cycles, ensuring safety and tolerability of lapatinib and docetaxel in bladder cancer. If one or fewer of the first 6 experience any Grade 4 clinical or non-hematologic abnormalities lasting more than 7 days in the first cycle, then subsequent patients will begin treatment at 75 mg/m2. Otherwise, all patients will begin treatment with a reduced dose of docetaxel on the first course. The monitoring rule of *unacceptable* toxicities will be applied to all patients regardless of their starting dose levels.

Note for Amendment dated 5/9/2013: 6 patients were intially treated with docetaxel 60mg/m^2 on cycle 1 and assessable for toxicity. They did not develop unacceptable toxicity as defined in the protocol and from 5/9/2013 all patients will be commenced at the dose level of 75mg/m^2 for docetaxel.

Although we would expect this regimen to be safe, we have established additional guidelines and criteria which will be used to flag an unexpected number of patients who experience unacceptable toxicity (TOX). **Unacceptable toxicity in this trial** will be defined as any death occurring within 30 days of treatment on this protocol that can be possibly, probably or definitely attributed to the regimen.

All toxicities will be recorded and summarized for all patients who receive any lapatinib or docetaxel treatment.

The **risk set** to be used in the safety monitoring decision (to trigger a review and possibly halt the trial) will include all patients who have either completed at least one course of treatment or been taken off treatment with a TOX event or other adverse events.

Every time a patient dies within 30 days of last treatment, this death will be reviewed to ascertain whether the death could be attributed to the treatment (possibly, probably or definitely related). If the attribution for the death is at least possibly related, then the total number of patients (X) who have experienced a TOX to date, will be compared to the number of patients (N) who are in the risk set (defined above). If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table below, then accrual will continue. If N is less than or equal to N_X, then the monitoring boundary has been crossed and a careful review of the trial data will be mandated.

Criteria for Crossing the Safety Monitoring Boundary and Evaluating Safety				
X: # pts who experienced a TOX event	2	3	4	≥5
N_x: safety boundary crossed if # patients in risk set (N) is less than or equal to N_x (if $N \leq N_x$)	≤ 9	≤ 22	≤ 35	Stop

These rules were selected to ensure a low probability that the safety boundary would be crossed, indicating excessive toxicity, if the true chance of unacceptable toxicity were less than 5% and a high probability that the boundary would be crossed if the true chance of unacceptable toxicity were about 20%. Criteria for flagging an excessive number of patients with TOX are based on the sequential probability ratio test with α=0.10, β=0.05, p_o=0.03 and p_a=0.15.

The table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval).

Probability of Crossing the Safety Boundary (i.e. too many patients have TOX)						
True Chance of a TOX	**3%**	**4%**	**5%**	**10%**	**15%**	**20%**
Probability of Crossing the Safety Boundary	0.05	0.10	0.16	0.57	0.85	0.96

14.0 REGISTRATION GUIDELINES

This is a single arm 2-stage phase II clinical trial. A total of 40 subjects will be enrolled. Informed consent, Registration Worksheet will be obtained from each patient. At the time of registration, two copies of a signed and dated patient Informed Consent form with Bill of Rights must be available (an original for patient's medical chart; one copy for the patient; and the other for the PI's file).

Study Organization

Institution:
LAC-USC Medical Center
University of Southern California University Hospital/Norris Comprehensive Cancer Center, Hospital and Clinics
Principal Investigators:
Sujie Tang, MD, MS
David Quinn, MD, PhD (Mentor)
Address: 1441 Eastlake Avenue, Room 3453
Division of Medical Oncology
Los Angeles, CA 90033

15. BIOHAZARD CONTAINMENT

Information of Lapatinib and Docetaxel (Taxotere) Handeling, Disposal, Preparation, administration, storage preparation and administration are included in the drug information, section 4.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Ethical Principles

The study should be conducted according to the principles outlined by the 18th World Medical Assembly (Helsinki, 1964, Appendix B) and all applicable amendments; the International Conference on Harmonization Guidelines for Good Clinical Practice; and FDA regulations regarding the conduct of clinical trials and the protection of human subjects. All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

Specific mechanisms to protect human subjects include:

- Potential subjects will be informed that participation in this protocol is completely elective and the patient will have the option to cancel participation at any time.
- Participants will be given the name and telephone number of the Principal Investigator and the IRB.
- Informed consent will be obtained after a discussion of risks and benefits and alternatives, which include best supportive care. This discussion will be documented in the medical record.
- To insure confidentiality of study data, each subject will be assigned a study ID number. Subjects will be identified only by this ID number in computer files used for statistical analysis and in laboratory records. All study related paperwork will be stored in locked file cabinets. Although the statistician will hold a key that will link the study ID number to the patient, this will be stored in a secure place and not made available to other project investigators. Specimens associated with the clinical trial will be de-identified, utilizing the study ID number generated by CAFÉ (the USC Cancer Center clinical trials database) so that laboratory personnel performing correlative studies will not have access to any protected health information. Published results from the study will be in the form of tabular descriptions of groups only, with no identifiable patient information or ID numbers.

16.2 Investigational Review Board (IRB) Approval

The Investigator must obtain the approval of the protocol, the informed consent document and any other material used to inform the patient about the nature of the trial from the local IRB in the form of a written letter. On the approval letter, which must be signed by the Chairperson of the IRB or the Chairperson's designee, the following items should be clearly stated: trial title, protocol number and version, study-related documents (protocol, informed consent material, advertisement when applicable), IRB review date, and IRB decision. The trial should not start until a copy of this written approval has been received by the Investigator.

Annually, or more often if stipulated by the IRB, and at the completion or termination of the study, the Investigator will report the progress of the trial to the IRB.

16.3 Data Safety Monitoring Plan **Active Monitoring Program Details**

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

b. Day-to-Day Monitoring – Eligibility: The PI will review the patient eligibility (with assistance from the Study Coordinator, who will assemble the required source documents, and do an initial review) prior to registering the patient on study.

c. Day-to-Day Monitoring – Informed Consent: Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses.

d. Day-to-Day Monitoring – Treatment: The PI is responsible for ensuring that treatment is given per protocol. If another physician administers treatment, the Study Coordinator will review the treatment orders with the PI. Regardless of who the treating physician is, there will be only one Study Coordinator for each study at each of the hospitals affiliated with the USC/Norris Cancer Center. The PI will review the status of each patient on-study, with the Study Coordinators and treating physicians, on an on-going basis.

e. Day-to-Day Monitoring - Evaluation of Safety: Generally, it is the Study Coordinator who schedules the visits to evaluate adverse events to treatment, who initially interviews the patient to discuss the symptomatic side effects of the treatment, and who initially reviews the lab results. At the USC/Norris Comprehensive Cancer Center, we have developed adverse event forms that tailor the collection of side effects and toxicity information for each protocol and allow the comparison of past adverse events with the current side effects. These are presented to the treating physician who will decide on the appropriate course of action - follow-up with additional tests or treatment. The PI (if not the treating physician) will review the adverse event assessment and changes in schedule on an on-going basis.

f. Day-to-Day Monitoring – Evaluation of Treatment Response: The Study Coordinator will schedule the tests or scans that are necessary to evaluate response to treatment. Although the treating physician will evaluate the results to establish the response, it is the responsibility of the PI to review all the scans and tests of all the patients to confirm the initial assessment of the response.

g. Data Management – Medical Records: Some study source documents are stored in the patient's medical record, which is maintained electronically or in hard copy by the Department of Medical Records at the appropriate hospital. X-rays and other images are stored electronically or in hard copy by the Department of Radiology. Physician's notes, orders, test results and pathology notes, as well as a copy of the signed informed consent, are maintained in the patients' medical records.

h. Data Management – Research Charts: To facilitate adherence to good clinical practice, protocol schedule and data management requirements, research charts are created for each patient on a study. Research charts will contain the original, signed, informed

consent and HIPAA documents. Protocol calendars, worksheets, and checklists, along with relevant notes, orders and results, are also kept in the research chart. It is the responsibility of the Study Coordinator and the Data Manager to ensure that the research chart contains all the required documents. Research Charts are maintained in the Clinical Investigation Support Office until the study is closed to follow-up/or study results have been analyzed for publication. These are then stored off-site.

i. Data Management – Case Report Forms: It is the responsibility of the Data Manager to complete the required case report forms. For NCCC investigator-initiated (in-house) trials, these are electronic CRFs that are maintained in the Cancer Center clinical trials database (CAFÉ).

Quality Assurance Committee (QAC) Monitoring

The USC PI has overall responsibility for the conduct of the clinical trial and the completeness and accuracy of the data collected regarding patients enrolled at the NCCC. The QAC monitors the progress of all clinical trials conducted at NCCC. During the **Phase II** trial, the QAC will review the trial semi-annually.

All USC-initiated and managed **Phase II** trials will be audited by the QAC. The audit results, together with the reported violations, and overall accrual rate and toxicities observed are used to evaluate the progress of the study. Failure to report adverse events in a timely fashion is considered very serious and will lead to suspension of the trial if not corrected.

Protocol Violations

Data managers and Study Coordinators coordinate the reporting of major protocol violations to the QAC. This is done by completing a computer form – thereby ensuring that the information is stored in the NCCC clinical trials database. Major violations are defined as:

(a) Deviation from protocol treatment by 10% or more of a drug dose or a 15% or greater deviation in the dose of radiation therapy, delay in treatment by 50% or more beyond the prescribed cycle length for drug therapy, 20% or more beyond the prescribed cycle length for radiation therapy, failure to hold a drug or radiation for reasons of toxicity, or inappropriate administration of a drug or radiation therapy.

(b) Departure from the follow-up schedule (i) leading to an inadequate assessment of toxicity or (ii) compromising the assessment of the outcome measures.

These reported violations are then reviewed and discussed at the next QAC meeting. Repeat violations and patterns are flagged. A memo is sent to the PI, requesting a plan to avoid these violations in the future. Sometimes the QAC will suggest a specific modification of procedures or protocol amendment. If the PI does not respond or if the violations continue, the QAC will report this to the CIC with a recommendation to either close the study or suspend accrual until the problems can be resolved. In practice, because of the close co-operation between the QAC and the CISO leadership, problems can be addressed expeditiously, on a one-to-one basis, usually in consultation with the data manager or Study Coordinator– and formal action is not required.

Violations identified early in the conduct of the trial may reveal a logistic difficulty, inadequately described protocol procedures, or a misunderstanding on the part of one of the trial staff. By monitoring violations on an on-going basis, corrective action can be taken before the integrity of the study is compromised.

16.4 Additional Responsibilities of the Investigator

The Investigator(s) agrees to perform the study in accordance with ICH Good Clinical Practice and FDA regulations. The Investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the protocol.

The Investigator should be able to recruit the required number of suitable patients and should have sufficient time to properly conduct and complete the trial. The Investigator should have available an adequate number of qualified staff and adequate facilities for the duration of the trial, and should ensure that all persons assisting with protocol therapy and trial related duties and functions comply with all appropriate regulations.

The Investigator should be responsible for all trial-related medical decisions. During and following a patient's participation in a trial, the Investigator should ensure that adequate medical care is provided to a patient for any adverse events related to the trial.

16.5 Protocol Amendments

Any changes to this protocol made by the Investigator must be in the form of a written amendment and the amendment will be appended to this protocol. Approval of amendments by the IRB is required prior to their implementation unless there are overriding safety reasons. If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval may be obtained by expedited review. When appropriate, an amendment may require a change to a written consent form as well.

17.0 Processing and handling of research blood and tissue samples

Processing and handling of research blood samples

Venous blood samples for research purposes should be collected as per the protocol.
At each collection time point, three 7.5 ml tubes of venous blood (total ~22.5 ml) should be collected in CellSave tubes provided by Dr. Amir Goldkorn lab. Total 3 tubes of 7.5ml venous blood should be collected and send to Dr. Goldkorn's lab at the same day of blood collection.
Samples will be held in Dr. Goldkorn's lab until the end of the study.

Please contact Dr. Goldkorn lab for CellSave tube and measures.
Contact information:
Dr. Amir Goldkorn lab
Contact person: Roy Lau
Email: roylau@usc.edu
Phone: 323 442-7722
Address:
1450 Biggy Street, North Research Tower 6516

USC/Norris cancer center
Los Angeles, CA 90033

With the patient's consent, please draw blood for CTC testing before the treatment at cycle 1 day 1, and during treatment at cycle 1 day 1 (4-6 hours after treatment (patient takes lapatinib in the morning, Docetaxel infusion needs to schedule in the morning as well)), Day 7 (before lapatinib dose (patient may take the lapatinib right after the blood draw for CTC in the morning)), cycle 2 day 1 (before lapatanib dose (patient may take the lapatinib right after the blood draw for CTC in the morning)), cycle 4 day 1 (before lapatanib dose(patient may take the lapatinib right after the blood draw for CTC in the morning)), and at progression, in an attempt to evaluate an association with response to treatment.

NOTE: Mr. Roy Lau or Dr. Amir Goldkorn should be notified at least 24 hours in advance via email or phone CTC collection and measures.
SPECIMENS MUST BE DRAWN AND SENT TO THE LAB ON THE SAME DAY.
1. Collection Instructions:
Blood samples should be collected using standard venipuncture technique.
Do not centrifuge the tubes. If brief storage is required, please store at room temperature out of direct sunlight.
2. Label each vial with the patient ID#, patient initials, and date and time of collection.
Information must be registered for documentation.

Processing and handling of tissue samples
Tissue from previous TURBT or tumor biopsy will be sent to Dr. Michael Press's lab to do future tissue correlative studies with the possibility of construction of tissue microarrays. Archival tissue samples will be used to evaluate EGFR and HER2 and correlate this with clinical outcome.
Dr. Michael Press's lab address:
1441 Eastlake Ave, NOR 5409
USC/Norris cancer center
Los Angeles, CA 90033
Phone: 3238650563

Paraffin-embedded tissue blocks should be shipped at room temperature while frozen tissue samples need to be kept on dry ice the entire time.
Dr. Michael Press or Ivonne Villalobos should be notified in advance via email or phone about the delivery of any material.

18.0 TABLES AND APPENDICES

Table 2. Summary of the second line therapy outcomes in TCC

Agent	Dose	Response rate (%)	No.	Median TTP / PFS (months)	Median Survival (months)	Reference
Ifosfamide		20%		NR	NR	(37)
Gallium nitrate		18%		NR	NR	(38)
Gemcitabine*	1250 mg/m^2 D1+8 q3 weeks	11%	30		8.7	(39)

Paclitaxel	80mg/m^2 weekly	10%	31	2.2	7.2	(40)
Paclitaxel	80mg/m^2 weekly		45	3	7	(41)
Paclitaxel	200mg/m^2 every 3 weeks	7%	14	<2	NR	(42)
Docetaxel	100mg/m^2 every 3 weeks	13.3% (3.8 – 30.7%)	30	NR	9	(6)
Paclitaxel + methotrexate	175mg/m^2 every 3 weeks	32%	20		5	(43)
Paclitaxel + Gemcitabine*	200mg/m^2 every 3 weeks	47%	15		7.5	(44)
Docetaxel + Ifosfamide	60mg/m^2 every 3 weeks	25%	22		4	(45)
Pemetrexed	500mg/m2 every 3 weeks	ORR 27.7%, SD 21.3%	47	2.9	9.6	(46)
Pemetrexed + Gemcitabine	500mg/m2 day1 + 1250mg/m2 Day1 + 8, 3 weeks	ORR 20%, SD 34%	47	3.1	8.1	(47)
Pemextrexed	500mg/m2 every 3 weeks	ORR 8%	13	2.2	NR	(48)
Vinflurine + BSC	320 mg/m2 every 3 weeks	PR 8.6%, SD 46.5%, DCR 41%	25 3	3.0	6.9	(49)
Best supportive care	BSC	PR 0%, SD 27.1%, DCR 24.8%	11 7	1.5	4.6	(49)

*** Note: patients had not received gemcitabine as part of first line therapy.**

Table 3. Summaries of studies on EGFR and HER2 over-expression in patients with bladder cancer

LAB Technique	ErbB1 (epidermal growth factor	ErbB2 (HER2) expression	. Co- Expression of EGFR and HER2	Total number of patient	Reference

	receptor)				
IHC*	14/73 (19.2)	33/55 (80%)	NA	73 and 55 respectively	(50)
IHC	177 (72.2%)	109 (44.5%)	83 (33.9)	245	(51)
IHC	30 (52%)	25 (44%)	13 (22%)	59	(52)

IHC overexpression 2+ or 3+
*Chakravarti A, study was for patient with muscle invasive bladder cancer only.

APPENDICES

Appendix A. ECOG Performance Status

ECOG PERFORMANCE STATUS	
Grade	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work, etc.
2	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	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix B. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed

as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example,

access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix C. Elements of Informed Consent

The written informed consent document should explain:

1. That the trial involves research
2. The purpose of the trial
3. The trial treatments
4. The trial procedures to be followed, including all invasive procedures
5. The patient's responsibilities
6. Those aspects of the trial that are experimental
7. The reasonable foreseeable risks or inconveniences to the patient, and when applicable, to an embryo, fetus or nursing infant
8. The reasonably expected benefits.
9. Alternative procedures or courses of treatment that may be available to the patient, and their important potential benefits and risks
10. The compensation and/or treatment available to the patient in the event of trial-related injury
11. The anticipated payment, if any, to the patient for participating in the trial.
12. The anticipated expenses, if any, to the patient for participating in the trial
13. That the patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient is otherwise entitled.
14. That monitors, auditors, the IRB and regulatory authorities will be granted direct access the patient's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by law and regulations and that, by signing a written informed consent form, the patient or the patient's legal representative is authorizing such access.
15. That records identifying the patient will be kept confidential and, to the extent permitted by law and/or regulation, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
16. That the patient or the patient's legal representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
17. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
18. The foreseeable circumstances and/or reasons under which the patient's participation in the trial may be terminated.
19. The expected duration of the patient's participation in the trial.
20. The approximate number of patients involved in the trial

APPENDIX D
Medications Known To Prolong The QT Interval and/or Induce Torsades De Pointes (Tdp)

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsade de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Group 1. Drugs That are Generally Accepted by Authorities to Have a Risk of Causing Torsades de Pointes

Concomitant use of these drugs is *not allowed during* the study *or within seven days of study entry* or entry into the cross-over portion of the trial (at *least eight weeks for Amiodarone; four weeks for Levomethadyl; and two weeks for Pimozide and Chloroquine*). All Group 1 Drugs should also be avoided for *up to fourteen days following* discontinuation of study treatment:

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Albuterol (by parenteral administration)	Bronchodilator (asthma)	Inhaled Albuterol at normal doses acceptable
Amiodarone	Anti-arrhythmic (heart rhythm)	F>M, TdP Cases in Literature
Arsenic trioxide	Anti-cancer (leukaemia)	TdP Cases in Literature
Bepridil	Anti-anginal (heart pain)	F>M
Chlorpromazine	Anti-psychotic/antiemetic (schizophrenia/nausea)	TdP Cases in Literature
Chloroquine	Anti-malaria (malaria infection)	
Cisapride	GI stimulant (stimulates GI motility)	Open Prescription Restricted F>M
Disopyramide	Anti-arrhythmic (heart rhythm)	F>M
Dofetilide	Anti-arrhythmic (heart rhythm)	
Domperidone	Anti-nausea (nausea)	

Table 1 Group 1 Drugs		
Drug (Generic Names)	**Drug Class (Clinical Usage)**	**Comments**
Droperidol	Sedative/hypnotic (anaesthesia adjunct)	TdP Cases in Literature
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F>M
Halofantrine	Anti-malarial (malaria infection)	F>M
Haloperidol	Anti-psychotic (schizophrenia, agitation)	
Ibutilide	Anti-arrhythmic (heart rhythm)	F>M
Levomethadyl	Opiate agonist (narcotic dependence)	
Mesoridazine	Anti-psychotic (schizophrenia)	
Methadone	Opiate agonist (pain control/ narcotic dependence)	F>M
Pentamidine	Anti-infective (pneumocystis pneumonia)	F>M
Pimozide	Anti-psychotic (Tourette's tics)	F>M, TdP Cases in Literature
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F>M
Salbutamol (by parenteral administration)	Bronchodilator (asthma)	Inhaled salbutamol at normal doses acceptable
Sotalol	Anti-arrhythmic (heart rhythm)	F>M
Sparfloxacin	Antibiotic (bacterial infection)	
Thioridazine	Anti-psychotic (schizophrenia)	

Group 2. Drugs That in Some Reports May be Associated With Torsades de Pointes But at This Time Lack Substantial Evidence of Causing Torsades de Pointes *two weeks of entry into the cross-over portion of the trial with the exception of the following drugs:*
Granisteron, Odansetron, Levofloxacine, and Venlafaxine (not allowed within 48 hours of study entry or entry into the cross-over portion of the trial);
Citalopram, Lexapro, and Paroxetine (not allowed within four days of study entry or entry into the cross-over portion of the trial) Some Group 2 drugs may be *allowed during the study, at the discretion of the Overall Principal Investigator*, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular check of QTc and electrolytes. Increased ECG monitoring is needed in the setting of Group 2 drugs. The ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the subject remains on the medication.

The frequency of ECG monitoring could revert to the standard schedule if no ECG prolongation has been noted during 4 weeks of co-administration of a drug from Group 2.

Table 2 Group 2 Drugs		
Drug (Brand Names)	**Drug Class (Clinical Usage)**	**Comments**
Alfuzocin	Alpha 1-blocker (Benign prostatic hyperplasia)	
Amantadine	Dopaminergic/Anti-viral/Anti-infective (Parkinson's disease)	
Amitriptyline	Tricyclic anti-depressant (depression)	
Amoxapine	Tricyclic anti-depressant (depression)	
Azithromycin	Antibiotic (bacterial infection)	
Citalopram	Anti-depressant (depression)	
Clarithromycin	Antibiotic (bacterial infection)	TdP Cases in Literature
Clomipramine	Tricyclic antidepressant (depression)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Desipramine	Tricyclic anti-depressant (depression)	TdP Cases in Literature
Dolasetron	Anti-nausea (nausea and vomiting)	

Table 2 Group 2 Drugs		
Drug (Brand Names)	**Drug Class (Clinical Usage)**	**Comments**
Doxepin	Anti-depressant (depression)	TdP Cases in Literature
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Fluconazole	Anti-fungal (fungal infection)	
Fluoxetine	Anti-depressant (depression)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron	Anti-nausea (nausea and vomiting)	
Imipramine	Anti-depressant (depression, pain, other)	TdP Cases in Literature
Indapamide	Diuretic (stimulates urine & salt loss)	TdP Cases in Literature, QT in animals
Isradipine	Anti-hypertensive (high blood pressure)	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lexapro	Anti-deppressant; anti-anxiety	
Lithium	Anti-mania (bipolar disorder)	
Mexilitine	Anti-arrhythmic (abnormal heart rhythm)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	

Table 2 Group 2 Drugs		
Drug (Brand Names)	**Drug Class (Clinical Usage)**	**Comments**
Moxifloxacin	Antibiotic (bacterial infection)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nortriptyline	Tricyclic antidepressant (depression)	
Octreotide	Endocrine (acromegaly/carcinoid diarrhoea)	
Ofloxacin		
Ondansetron	Anti-emetic (nausea and vomiting)	
Paroxetine	Anti-depressant (depression)	
Protriptyline	Tricyclic antidepressant (depression)	
Quetiapine	Anti-psychotic (schizophrenia)	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	
Salmeterol	Sympathomimetic (asthma, COPD)	
Sertraline	Antidepressant (depression)	Association not clear
Solifenacin	Muscarinic receptor antagonist (treatment of overactive bladder)	
Tacrolimus	Immune suppressant	TdP Cases in Literature
Tamoxifen	Anti-cancer (breast cancer)	
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Trimipramine	Tricyclic antidepressant (depression)	

Table 2 Group 2 Drugs		
Drug (Brand Names)	**Drug Class (Clinical Usage)**	**Comments**
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

APPENDIX E
Clinically relevant inducers and inhibitors of isoenzyme CYP3A4

Drug Class	Agent	Wash-out[1]
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)	
Antiretrovirals	efavirenz, nevirapine	
Glucocorticoids (oral)	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)[2]	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir, atazanvir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant	
Other	grapefruit, **star fruit, pomegranate, papaw and their juices**	
	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennies	Excluded 1

		hour before and after dosing
Herbal or dietary supplements	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil, and St John's Wort	14 days

APPENDIX F
NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION
The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

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