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Phase II Clinical Chemoprevention Trial of Weekly Erlotinib before Bladder Cancer Surgery

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SCHEMA

Phase II Clinical Chemoprevention Trial of Weekly Erlotinib before Bladder Cancer Surgery

Male and Female participants who have a bladder tumor, confirmed by cystoscopy, are candidates for TURBT or cystectomy with a calculated Creatinine clearance (Cockcroft Gault) of ≥ 30 mL/min and normal liver function, 18 years and older, and Karnofsky Performance Status (KPS) of ≥ 60%.

↓

Baseline safety assessments, plasmapharmacokinetics, I-PSS evaluation.

↓

Participants will be randomized on a 1:2 ratio to placebo vs erlotinib with stratification for planned use of agents which significantly decrease erlotinib bioavailability and by planned surgery (TURBT vs. cystectomy)

Placebo 4 tablets weekly for 3 doses	Erlotinib 4 tablets (150 mg tablets=total dose 600 mg) weekly for 3 doses

↓

Weekly for 3 doses preceding bladder surgery*
(*If the planned day 16 surgery is going to be delayed to either day 17-22 the day 15 dose should be held and administered on the evening prior to the new surgery date; if the planned day 16 surgery is delayed to day 23-28 the day 15 dose should be administered as planned and a 4th dose administered on the evening prior to the new surgery date. If surgery is delayed further than 28 days (4 weekly doses) the participant will be considered not evaluable for the primary endpoint.)

↓

Day 8 Visit*
Day 8 safety assessments, plasma pharmacokinetics
(*Day 8 clinic visit will be optional; there will be a required phone contact for safety assessment)

↓

The day after the third dose (Day 15 dose or, for surgical delays beyond the 16th day but less than the 23rd day)
or
The day after the fourth dose of study medication for surgery delayed to day 23 – day 28

End-of-study safety assessments, plasma pharmacokinetics, I-PSS evaluation, TURBT or Cystectomy, tissue biomarkers.

<u>Primary Endpoint</u>
Determine if there is a difference in EGFR phosphorylation in normal appearing bladder epithelium adjacent to tumor approximately 9-18 hours post study dose, between patients randomized to erlotinib weekly as compared to placebo.

<u>Secondary Endpoints</u>

Assess the tolerance of high dose weekly erlotinib compared to placebo; assess limited pharmacokinetics of weekly erlotinib; and assess the expression of EGFR, e-cadherin, Ki67, ERK, p53 and let-7 in normal and abnormal urothelium, exploratory assessment of urination symptoms in men.

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1. OBJECTIVES

1.1 Primary Objectives – to determine if there is a difference in EGFR phosphorylation in normal appearing bladder epithelium adjacent to tumor approximately 9-18 hours post-study dose, between patients randomized to erlotinib weekly as compared to placebo.

1.2 Secondary Objectives –

- Assess the tolerance of high dose weekly erlotinib compared to placebo
- Assess the expression of phosphorylated EGF receptor in tumor tissue when available
- Assess the expression of e-cadherin and Ki67 in normal and abnormal urothelium
- Assess the expression of phosphorylated ERK in normal and abnormal urothelium
- Assess limited pharmacokinetics of weekly erlotinib
- Assess the expression of p53 in normal and abnormal urothelium
- Assess the expression of let-7 in normal and abnormal urothelium
- Exploratory assessment of urination symptoms in men

2. BACKGROUND

2.1 Study Disease

Bladder cancer is the second most common malignancy of the genitourinary tract. During the year 2012 alone, approximately 73,510 new cases will be diagnosed with an estimated 14,880 deaths occurring in the United States as a result of this disease (Siegel 2012). Urothelial carcinoma of the bladder may present as either superficial cancer or muscle-invasive cancer, which is associated with considerable morbidity and mortality. Muscle-invasive bladder cancer, a major source of morbidity and mortality, is initially diagnosed in as many as 30% of patients. These patients generally undergo radical cystectomy, and often neoadjuvant or adjuvant chemotherapy, for locally advanced disease. However, the remaining 70% of patients with bladder cancer are initially diagnosed with superficial bladder tumors. Superficial bladder cancer is often characterized by multifocal and recurrent disease that may appear anywhere in the bladder over relatively long intervals, thereby requiring long-term surveillance (Raghavan 1990; Gee 2002). Superficial bladder cancer includes non-invasive papillary tumors (Ta), carcinoma in situ (CIS/Tis), and tumors that invade through the lamina propria (T1). Patients diagnosed with superficial tumors are usually reevaluated at frequent intervals to detect recurrent disease (Forseman and Messing 1997). Repeated examination entails regular cystoscopic evaluation and monitoring of urine cytology and/or other diagnostic markers. As such, this closely monitored group of patients at risk for tumor recurrence and progression represents an ideal cohort for the evaluation of chemopreventive agents.

In general, 30%–80% of people with superficial bladder cancer will develop recurrent tumors (Bono 1994). A higher risk of tumor recurrence is associated with multifocal disease observed at the time of initial diagnosis, high tumor grade, depth of invasion, and cystoscopic findings 3 months after diagnosis. It has been reported that 70% of patients with multiple bladder tumors will have recurrent disease by one year, whereas approximately 50% of patients diagnosed with a solitary bladder tumor will experience disease recurrence by 4 years. Up to 10% of recurrent bladder tumors progress to muscle-invasive disease. The risk of tumor progression is lowest for individuals with stage Ta papillary tumors in that only 4% of individuals with Ta tumors will progress to muscle-invasive disease as compared with a 30% progression rate for T1 tumors within 3 years (Grossman 1996).

Bladder cancer is thought to evolve along one of two phenotypic pathways: superficial (papillary) or invasive (Koss 1992). These pathways are characterized by specific genetic defects. The

superficial/papillary pathway genotype is characterized by alterations in chromosome alleles 9p and 9q, while the CIS/invasive pathway is characterized by dysfunction of p53 or pRb (Dalbagni 1993; Rosin 1995; Spruck 1994; Wagner 1995). It is unlikely that these specific genetic derangements alone are sufficient to trigger malignant transformation of normal cells, suggesting that other genetic events or environmental exposure may contribute to their malignant potential as well.

Epidermal growth factor receptor (EGFR) is synthesized from a 1210-residue polypeptide precursor, after cleavage of the N-terminal sequence, an 1186-residue protein is inserted into the cell membrane (Jim 2006). Over 20% of the receptor is N-linked glycosylation and this is required for translocation of the EGFR to the cell surface and subsequent acquisition of function (Slieker 1986). EGFR is a 170-kDa transmembrane protein that is a member of a family of related receptor protein tyrosine kinases (PTKs) that also includes the proteins encoded by the c-erbB-2 (neu), c-erbB-3, and c-erbB-4 genes (Kumar 1995). The EGFR receptor regulates the intracellular effects of ligands such as EGF and transforming growth factor α (TGF α). (Carpenter 1990, Wells 1999, Yarden 2001). Upon ligand binding to the EGFR extracellular domain (collectively called the ectodomain), there is an increase in the proportion of dimerized receptor and the enzymatic activity of its intracellular tyrosine kinase domain increases greatly (Cohen 1982, Yarden 1987).

The EGFR kinase catalyses the transfer of the ϒ-phosphate of bound ATP to the tyrosine residues of exogenous substrates and the C-terminal domains of the EGFR (Powis & Workman 1994, Kumar 1995). The EGFR also interacts with its three known homologues, ErbB2 (also called Neu or HER2), ErbB3 (HER 3), and ErbB4 (HER4), in a ligand-dependent fashion to form heterodimers (Yarden 2001, Olayloye 2000) The sequence identity of the EGFR family varies from 37% (53% similarity) for EGFR and ErbB3 to 49% (64% similarity) for the EGFR and ErbB2.

Activation of EGFR can occur via autocrine, paracrine or juxtacrine mechanisms. On ligand binding, EGFR dimerizes with neighboring receptors and is autophosphorylated at three major tyrosine residues (Chinni 2003). EGFR, subsequently interacts signaling transduction pathways, including phospholipase C ϒ, phosphatidylinositol-3'-kinase, growth factor receptor-binding protein 2 (Grb-2), Src family kinases, and components of the Jak/STAT pathway (Kim 2009, Sliva 2008). Deregulated expression of EGFR and its ligands has been associated with the development of neoplasia in both animals and humans. At physiological receptor levels, EGF binding results in phosphorylation of Src homology 2 domain-containing proteins, which is sufficient to induce a normal mitogenic response (Kelloff 1996). In addition, an increase in EGFR expression, other substrates such as phospholipase C ϒ, and Ras-GAP, become phosphorylated. This might explain in part, how EGFR overexpression contributes to carcinogenesis.

Two general patterns have been recognized in aberrant EGFR-mediated signal transduction. The first pattern is a trend toward increased expression of EGFR during the early stages of carcinogenesis followed by receptor down-regulation, often subsequent to increased ligand production. This pattern has been observed for example in the lung, cervix and prostate. The second recurring pattern observed is the expansion of receptor and/or ligand expression from a subset of cells in normal tissue (usually in the basal layer) to extended cellular layers during neoplastic progression. This pattern has been observed in head and neck, bladder and cervix.

Lubet et al. (Lubet 2010) using an in vivo bladder cancer model analyzed three different agents to determine the optimal agents to consider studying in clinical prevention trials. Using Harlan rat model animals were treated with naproxen (400mg/kg diet), aspirin (low dose – 300mg/kg diet, high dose – 3,000 mg/kg diet), Iressa® (10mg/kg gefitinib body weight daily) or resveratrol (1,000mg/kg diet) using 1 of 3 protocols. Protocol 1 involved drug administration one week after chemically induced bladder

cancer and continued for 7 months, Protocol 2, drug administration 3 months after chemically induced bladder cancer with microscopic lesions visible and agent continued for 3 months and Protocol 3 (drug administered one week after chemically induced bladder cancer- OH-BBN and drug continued for 4 months. In animals treated under protocol number 1 naproxen, Iressa, and both doses of aspirin decreased the formation of large bladder tumors by 87% 90% 6% and 60% respectively. Tumors increased in size by 3% for animals treated with resveratrol. In protocol 2, both Iressa and naproxen were both highly effective and in protocol 3 only Iressa caused a significant decrease in microscopic bladder cancers (63%). The investigators concluded that the two most promising agents in this study were naproxen and gefitinib/Iressa. Gefitinib/Iressa was effective both in preventing large tumor formation plus effective when administered after microscopic lesions were already established in the bladder. It seems plausible based on this research that EGFR inhibitors (erlotinib) should be explored for bladder cancer prevention either as monotherapy or a combinatorial approach. Data with gefitinib and erlotinib strongly imply that small molecule inhibitors of EGFR have the potential to be effective bladder cancer preventive agents therefore we propose to test erlotinib.

2.2 Study Agent

Erlotinib HCl (Tarceva) is an orally available, highly selective, reversible inhibitor of epidermal growth factor receptor (HER1/EGFR) tyrosine kinase. Inhibition of tyrosine kinase activity prevents HER1/EGFR phosphorylation, the associated downstream signaling events, and may block tumorigenesis mediated by inappropriate HER1/EGFR signaling. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the EGFR. The recommended dosing in adults is a daily oral dose of 150 mg continuously or until dose-limiting toxicity leads to an interruption and possible reduction in daily dosing.

Erlotinib pharmacokinetic analyses have been characterized by the following observations; a relatively long half-life (10-12 hours), predominant metabolism via P450 metabolism with some correlation to hepatic function, and increasing AUC values with repeated daily dosing (White-Koning 2011, Hamilton 2006). Also multiple studies have correlated an increasing AUC of erlotinib or gefitinib with the occurrence of skin toxicity (White-Koning 2011, Thomas 2009) while there are other studies, which have not confirmed this association (Calvo 2007). Current smokers have been observed to tolerate erlotinib and gefitinib better than non-smokers but also to have less benefit observed. Consistent with these observations Hamilton et al (Hamilton 2006) performed a comparison pharmacokinetic study of erlotinib in current smokers and non-smokers at doses of 150 and 300 mg. They observed that current smokers had AUC and Cmax values approximately half of non-smokers or smokers at 300 mg had AUC values similar to non-smokers at 150 mg daily. It is theorized the likely explanation of this is the known contribution of CYP1A1 and CYP1A2 to the metabolism of erlotinib and their induction by cigarette smoking.

Over 50 Astellas (formerly OSI Pharmaceuticals, Inc.)-sponsored phase 1, 2, and 3 clinical studies of erlotinib have been initiated or completed. Various doses and schedules of erlotinib as a single agent and in combination with conventional chemotherapy agents have been studied. Twelve phase 1 studies have been conducted in healthy volunteers to determine the safety, tolerance, pharmacology, and pharmacokinetics of erlotinib (n = 268). The phase 1 healthy subject experience is based on the use of different oral erlotinib doses and schedules ranging from single-dose administration of 1–1000 mg to administration of 200 mg twice daily (bid) compared with placebo. Early tolerability studies showed that 200 mg erlotinib bid was associated with dose-limiting rash and diarrhea in addition to reversible liver transaminase elevation. Subsequent single- or multiple-dose pharmacology studies of 100 or 150 mg erlotinib daily did not reveal any new safety findings; however, the characteristic acneiform rash was unacceptable in healthy subjects receiving 150 mg erlotinib daily for approximately 1 week or longer. The phase 1 experience in cancer patients includes studies with different erlotinib doses and schedules. The

maximum tolerable dose (MTD) of single-agent erlotinib was determined to be 150 mg daily, with diarrhea being the dose-limiting toxicity (DLT) despite supportive antidiarrheal treatment. Weekly dosing of erlotinib up to 1600 mg did not define an MTD; however, severe drug-related skin disorders were reported for patients receiving 1400 and 1600 mg weekly.

There is limited published data with weekly erlotinib which has been tried as a delivery schedule to potentially lessen the toxicity observed with daily erlotinib. Grommes et al (Grommes 2011) retrospective assessed 9 lung cancer patients with brain metastases treated with weekly erlotinib (900 - 1500 mg). Two patients developed grade 1-2 rash and fatigue. Of note, all had prior daily treatment with erlotinib or gefitinib potentially leading to selection bias and it is possible concomitant steroids and anti-seizure medications could alter erlotinib metabolism. Sangha et al. (Sangha 2011) performed a phase 1/2 dose escalation trial of weekly or daily erlotinib with docetaxel in lung cancer patients. Arm A (weekly erlotinib) patients were started at 1200 mg of Erlotinib weekly for 3 doses with concomitant docetaxel. Due to significant neutropenia/infection the maximum tolerable dose was considered 600 mg of Erlotinib (weekly) and 70 mg/m2 docetaxel; but this regimen was not considered clinically viable. No grade 3/4 skin toxicities were reported but they did not detail the incidence of grade 1-2 skin toxicity for arm A, other than to imply it was common (>70%). Milton et al. (Milton 2006) performed a dose-escalation study in advanced lung cancer patients. Fourteen patients received doses of 1200, 1600 and 2000 mg weekly. Rash and diarrhea were the most frequent toxicities. Eleven of 12 evaluable Phase I patients experienced Grade 1 or 2 rash. The rash generally persisted but improved with continued weekly dosing. Of the 5 patients who developed Grade 2 rash in the Phase I portion of the trial, most did so within 2 weeks of starting erlotinib. The rash lasted 1 or 2 weeks in 3 patients and >4 weeks in 2 patients. These 5 patients were given topical clindamycin and/or oral minocycline. Similarly, 11 of 12 patients experienced Grade 1 or 2 diarrhea. Diarrhea generally was experienced within 24 to 48 hours of drug administration and was controlled well with loperamide therapy given on an as-needed basis. Thirteen additional patients were enrolled at 2000 mg weekly, again the vast majority experienced grade 1-2 rash and diarrhea. Grade 2 rash with weekly erlotinib was more frequent numerically with dose escalation and developed in 42% of patients who received 2000 mg and in 17% of patients who received 1200 mg or 1600 mg. The frequency of Grade 2 diarrhea was 26% in the 2000-mg weekly group and 33% in the 1200-mg weekly and 1600-mg weekly groups. Of 6 patients at 1200 and 1600 mg dose levels, all six developed at least grade 1 rash or diarrhea.

2.3 Rationale

The strategy of targeting specific PTKs such as EGFR seems plausible due to the redundancy of growth factor networks and EGFR is overexpressed in a subset of cancers (bladder, breast, cervix, colon, esophagus, lung, prostate, and head and neck). The development of novel therapies remains an area of unmet need in the treatment of both superficial and muscle invasive bladder cancer. One of the most important targets for chemo-preventive intervention and drug development are deregulated signal transduction pathways (Kelloff 1996). Key components of these pathways are the protein tyrosine kinases (PTKs), which catalyze the transfer of the γ-phosphate of ATP to the hydroxyl group of tyrosine on numerous proteins (Chang 1992). Loss of PTK regulatory mechanism has been implicated in neoplastic growth and numerous oncogene codes for PTKs (Powis 1994, Powis and Workman 1994). The strategy of targeting specific PTKs such as EGFR seems plausible due to the redundancy of growth factor networks and EGFR is overexpressed in a subset of cancers (bladder, breast, cervix, colon, esophagus, lung, prostate, and head and neck).

In bladder cancer, EGFR/ERBB2 is frequently overexpressed (> 75% of transitional cell carcinomas) and the level of overexpression has been directly correlated with tumor grade/stage, tumor recurrence and overall survival (Neal 1990, Messing 1990, Mellon 1995, Chow 2001). Experimental evidence in bladder

cancer has also suggested that the EGFR pathway plays a critical role in cell proliferation, apoptosis, differentiation, migration and angiogenesis (Bellmunt 2003, Black 2007, MacLaine 2008). The distribution of EGFR differs between normal and neoplastic urothelium. For example, Messing and Reznikoff (Messing and Reznikoff 1992) noted in the normal bladder EGFR is only expressed on cells of the basal layer, whereas in malignant or dysplastic urothelium, along with histologically normal urothelium from bladder cancer patients, EGFR is equally expressed on cells of the urothelial layers, including those directly in contact with urine. In bladder cancer patients, the percentage of EGFR-expressing cells is lowest in tissue distant from the tumor, but increases in tissue adjacent to the tumor and is highest in the tumorous tissue (Rao 1993). Superficial bladder cancers (pTa, pT1, pTis/pCis) that express EGFR are significantly more likely to progress toward muscle invasive disease (Neal 1990). Because high levels of EGF are excreted in the urine, expression of EGFR in the premalignant and malignant bladder transitional epithelium could have a significant impact on proliferation of these cells (Messing and Reznikoff 1992).

Chaux et al. demonstrated EGFR protein overexpression to occur in 74% of urothelial carcinomas of the bladder (Chaux 2012). Fifty percent of tumors had high levels of EGFR, 22% low levels of EGFR and 28% of tumors were negative for EGFR. In the adjacent urothelium, 22% low levels of EGFR and 78% were negative for EGFR (Chaux 2012). The protein overexpression of EGFR has not been shown to be associated with mutations within tyrosine kinase domains (exons 19 and 21) of the EGFR gene (Chaux 2012). With the exception of non-small cell carcinomas and glioblastomas, the overall prevalence of EGFR activating mutations in solid malignancies is very low. To date, neither gene amplification nor point mutations of EGFR have been reported in bladder tumors (Blehm 2006).

Although mutations in the coding region of EGFR are rare, in invasive bladder tumors, differential sensitivity to erlotinib was recorded by Jacobs et al. (Jacobs 2007) in a panel of cell lines in the absence of EGFR mutations. Jacobs and colleagues analyzed DNA from 112 invasive bladder tumors, investigating exons 18-21, which represent the catalytic domain of the receptor. Five point mutations (A839T, A859T, A864Q, Y869C and K875R) were identified (Jacobs 2007). All mutations found were located within exon 21 of the EGFR gene. No mutations were found in exons 18-20 of the EGFR gene. Cell lines whose sensitivity profile to erlotinib was established were included in their study. Loss of pAKt was most significant in bladder cancer cell lines sensitive to erlotinib (cell line 5637), moderate decrease in moderately sensitive cell lines (CUBIII) and no decrease in pAkt in two erlotinib insensitive cell lines (UM-UC-3 and J82). Epthelial-mesenchymal transition (EMT) has been linked as a phenotypic indicator of sensitivity to erlotinib (Thomson 2005 ref21). The EMT phenotype linked to decrease drug sensitivity included loss of E-cadherin expression with concomitant expression of vimentin and fibronectin. Jacobs et al. reported the epithelial-mesenchymal transition (EMT) in erlotinib insensitive cells lines (MGHU1, TCCSUP, UM-UC3, J82) (Jacobs 2007). In bladder cancer cell lines sensitive to erlotinib, the phosphorylation status of Akt is primarily regulated via the EGFR signaling pathway. In cell lines insensitive to erlotinib, uncoupling of the EGFR signaling pathways has been reported with different levels of Akt phosphorylation suggesting the role of other molecular events such as H-ras mutations, and loss of PTEN function. The investigators concluded that even in the absence of EGFR mutations erlotinib shows potential as a therapeutic agent for bladder cancer to decrease neoplastic progression. Molecular hallmarks of erlotinib insensitivity include EMT and phosphorylation status of Akt.

In a phase II clinical trial erlotinib (Pruthi 2010) was given neoadjuvantly (150mg once daily for 4 weeks) in 20 patients with clinical stage T2 disease prior to undergoing radical cystectomy. The primary endpoint of this phase II trial was to determine the effect of neoadjuvant erlotinib before cystectomy on the pathological complete response rate (pT0 rate) in cystectomy specimens. Of the 20 patients receiving erlotinib neoadjuvantly, 15 developed grade 1 to 3 (4 subjects with grade 3) skin toxicity during the 28 day schedule. Five had their dose reduced or held because of skin toxicity. Results of operative pathology

showed that five (25%) of 20 patients had a complete response (pT0) at the time of cystectomy, and in total seven (35%) had pathologic down staging at the time of cystectomy. Interestingly, all pT0 and pTis/T1 patients had a rash.

EGFR transcript in peripheral blood has been proposed as a marker for circulating bladder cancer cell detection (Sun 2011). Antoniewicz and colleagues (Antoniewicz 2012) analyzed 51 patients who underwent transurethral resection of bladder tumor (TURBT) to determine if circulating urothelial cells in the peripheral blood increased after TURBT. While none of the 4 studied genes using RT-PCR demonstrated any significant increase in the number of PCR-positive transcripts after TURBT, only EGFR was significantly less frequent 30 days following surgery compared to results obtained prior to surgery (Antoniewicz 2012). At baseline the percent of positive RT-PCR signal for EFGR was 27% and decreased to 20%, 14%, 10% and 4% on postoperative days 1, 3, 7 and 30 respectively.

Actin remodeling has been proposed as a marker of malignant-associated field defect and a potential surrogate biomarker for chemoprevention trials. Erlotinib testing in a bladder carcinogenic model consisting of untransformed HUC-PC cells and transformed MC-T11 cells, both derived from the same normal human urothelial clone immortalized by SV40. At higher doses, erlotinib induced a decrease in cell adhesion and anoikis (detachment-associated apoptosis). This inhibitory effect was not seen with a MAPK (P44/P42) inhibitor suggesting that other pathways may be responsible for erlotinib induced actin remodeling (Jin 2006 ref22). CD34+ fibrocytes are constitutive elements of the connective tissue and play a role in matrix synthesis and tumor associated stromal remodeling. Secreted protein, acidic and rich in cysteine (SPARC) is a pivotal mediator of stromal remodeling precipitated by invasive carcinomas. In contrast to the tumor free urinary bladder, including chronic cystitis, invasive urothelial carcinomas reveal complete loss of CD34+ fibrocytes in the lamina propria, increased expression of SPARC and the appearance of alpha-smooth muscle actin (α-SMA) myofibroblasts in the superficial lamina propria (Nimphius 2007).

In addition to the concept of EGFR antagonism as a target for bladder cancer prevention, another topic we plan to explore is the concept of intermittent dosing for prevention. More often than not, this concept is pursued for patient compliance or tolerance issues. A current example in preventive health is the use of bisphosphonates (e.g. Fosamax) for prevention of osteoporosis and its complications. Fosamax is approved as a daily oral agent, but toxicity and tolerance has led to many clinicians prescribing it weekly rather than daily (Lee 2011). Intermittent dosing for cancer prevention has also been proposed and explored in animal models with supporting data (Lubet 2008, Lubet 2013 unpublished). As described above there are supporting data from lung cancer therapy studies that weekly erlotinib could achieve equal or greater dose intensity (as compared to daily) with less skin and GI toxicity (Milton 2006).

3. SUMMARY OF STUDY PLAN

Protocol chairperson: Tracy M. Downs, MD FACS, University of Wisconsin

Primary Endpoint: The primary objective is to determine if there is a difference in EGFR phosphorylation in normal appearing bladder epithelium adjacent to tumor approximately 9-18 hours post-study dose, between patients randomized to erlotinib weekly as compared to placebo.

The prioritized secondary objectives are: 1) to assess the tolerance of high dose weekly erlotinib compared to placebo. 2) to assess the expression of phosphorylated EGFR in tumor tissue when available. 3) to assess the expression of e-cadherin and Ki67 in normal and abnormal urothelium. 4) to assess the expression of phosphorylated ERK in normal and abnormal urothelium. 5) to assess limited

pharmacokinetics of weekly erlotinib. 6) to assess the expression of p53 in normal and abnormal urothelium. 7) to assess the expression of let-7 in normal and abnormal urothelium. 8) perform an exploratory assessment of men on whether urination symptoms alter while on study.

Study Schema:

This is a multi-center, phase IIa randomized, double-blind, placebo-controlled study. Participants will be randomized on a 1:2 ratio to placebo vs. active study agent and stratified according to planned surgery (TURBT vs. cystectomy) and use of agents that significantly decrease Erlotinib bioavailabiltity (tobacco, protein pump inhibitors). Fifteen participants will be enrolled on the placebo arm. A maximum of 30 participants will be enrolled on the active intervention arm. The accrual goals account for an anticipated dropout rate of 5-10%. Total anticipated accrual is therefore 45 participants.

There will be six sites participating in the study. Each randomized patient will be treated with study medication weekly x 3 doses. We will allow for study duration of approximately 3 years.

- Placebo or
- Erlotinib (with allowance for a 50% dose reduction for adverse events as specified in section 5.6)

Participants for this protocol will be accrued from a population of males and females 18 years of age and older who have a confirmed or suspected bladder tumor which will be treated with TURBT (or planned cystoscopy with biopsies) or cystectomy (total or partial). Eligible participants will be randomly assigned to either 600 mg erlotinib PO or matching placebo once weekly for 3 doses preceding their scheduled bladder surgery. The study will be terminated when all participants have completed study dosing, their scheduled surgical treatment, and a 7-14 day post-surgery follow-up period.

There is no run-in period specified for this protocol. Potential study participants will be identified from the population of patients being evaluated and treated for bladder tumors at each of the participating institutions. After being presented with information about the protocol, patients interested in participating will be scheduled for a screening/baseline study visit. After completion of the informed consent process, the following assessments/procedures will be conducted:

Screening/Baseline visit (within 30 days of first dose of study agent):

- eligibility assessment
- medical/surgical history and baseline symptoms
- physical exam/vital signs (including performance status assessment)
- clinical safety labs (including pregnancy testing for females of childbearing potential)
- plasma pharmacokinetics
- request for randomization
- International Prostate Symptom Score (I-PSS)

Study agent and topical ointment (topical clindamycin, topical hydrocortisone) dispensing: (within 30 days of baseline assessments) either in clinic or study agent will be mailed to the participant via overnight courier with a phone contact prior to dosing. Ointment instructions will be included (See Appendix B).

- study agent dosing instructions
- ointment instructions
- concomitant medication review and adverse event assessment

Pre Day 8 Phone contact (approximately 24-72 hours prior to Day 8 Visit):
- instruct participant on dose and time of Day 8 study drug administration

Day 8 Visit*:
- physical exam/vital signs (including complete assessment of any rash per CTCAE criteria)
- clinical safety labs
- plasma pharmacokinetics
- Day 8 Study dosing after plasma pharmacokinetics
- concomitant medication review, compliance and adverse event assessment

*The day 8 clinic visit will be optional; if the participant opts out then a post day 8 phone contact (within 48 hours of taking dose) will be required for a concomitant medication review, compliance and adverse event assessment.

Pre-Surgery reminder Phone contact (approximately 24-72 hours prior to Surgery):
- instruct participant on dose and time of pre-surgical study drug administration

Surgery visit: (Day 15-16):
- physical exam/vital signs
- clinical safety labs
- plasma pharmacokinetics
- concomitant medication review, compliance and adverse event assessment
- International Prostate Symptom Score (I-PSS)
- collection of paraffin-embedded blocks or slides after standard pathology processing

Post-Surgery phone contact (7-14 days post-surgery):
- concomitant medication review and adverse event assessment

Duration of study participation will range from 29-56 days depending upon how long before the day 1 study agent dosing occurs after the screening/baseline assessments.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Participants must have a confirmed or suspected invasive or non-invasive bladder tumor (initial or recurrent) discovered on cystoscopy or radiologic imaging performed within 120 days of randomization.

4.1.1.1 Patients with muscle invasive bladder cancer (MIBC) must have never received and currently be ineligible for cisplatin-based neoadjuvant chemotherapy due to any of the following:

1) calculated creatinine clearance of < 60 ml/min
2) KPS < 80
3) solitary kidney or
4) patient refusal to undergo neoadjuvant chemotherapy.

4.1.2 The participant may have prior treatment for bladder tumor (excluding radiation therapy) provided that treatment:

- Was completed greater than 30 days prior to the first dose of study agent

4.1.3 Participants must be a candidate for a trans-urethral resection of the bladder tumor (TURBT), cystectomy (partial or radical) or cystoscopy with biopsy at a participating organization.

4.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of high dose weekly erlotinib in patients less than 18 years of age, children are excluded from this study but will be eligible for future pediatric trials, if applicable.

4.1.5 Karnofsky ≥60%; see Appendix A

4.1.6 Participants must have normal * organ and marrow function as defined below:

4.1.6.1 Hematologic:
WBC ≥ 3000/mm3;
platelets ≥ 100,000mm3,
hemoglobin >10 g/dL

4.1.6.2 Hepatic:
alkaline phosphatase ≤ 1.5 X upper limit of normal
bilirubin ≤ 1.5 X upper limit of normal
AST ≤ 1.5 X upper limit of normal
ALT ≤ 1.5 X upper limit of normal
Bilirubin for Gilbert's ≤ 3.0 mg/dl

4.1.6.3 Renal:
A calculated Creatinine clearance (Cockcroft Gault) of ≥ 30 ml/min

4.1.6.4 Electrolytes:
Sodium ≥ 130 mg/dl and ≤ upper limit of normal
Potassium ≥ 3.0 mg/dl and ≤ upper limit of normal

*Normal limits are defined as the normal range appearing on the results report for the clinical laboratory providing the clinical laboratory testing.

4.1.7 The effects of erlotinib on the developing human fetus at the scheduled weekly dose are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

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

4.2 Exclusion Criteria

4.2.1 Any treatment for the bladder tumor other than intravesical therapy between the pre-study cystoscopy or radiologic imaging which identified the suspected bladder tumor and the scheduled surgical removal or cystoscopy-guided biopsy of that tumor.

4.2.2 Any chemotherapy and/or radiation therapy received ≤ 3 months of study entry and any immunotherapy received ≤ 6 months of study entry (with the execption of BCG treatment).

4.2.2.1 Any prior external beam radiation to the pelvis.

4.2.3 A concurrent skin rash or skin condition requiring treatment with a prescription medication.

4.2.4 The following medications may not be taken within 24 hours of the first dose of study agent or at any time while a participant is taking study agent due to the risk of significant drug-drug interaction.

- Coumadin
- Strong CYP3A4 inhibitors (which lead to decreased erlotinib metabolism/increased erlotinib levels) including ketoconazole, atazanavir, boceprevir, ceritinib, clarithromycin, cobicistat, darunavir, dasabuvir, idelalisib, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice.
- CYP3A4 inducers (which lead to increased erlotinib metabolism/decreased erlotinib levels) including rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, primidone, enzalutamide, fosphenytoin, lumacaftor, mitotane, and St. John's Wort.
- Agents which decrease gastric acid are allowed but should be avoided if possible.
- Participants may resume inhibitors or inducers of CYP3A4 > 14 days after their last dose of study agent

4.2.5 Participants requiring daily use of non-steroidal anti-inflammatory drugs (NSAIDs), with the exception of ≤81 mg aspirin per day. During study participation, acetaminophen is preferred for treatment of pain; the use of NSAIDs, as needed for pain, is discouraged.

4.2.6 Participants may not be receiving any other investigational agents.

4.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib or clindamycin (topical agent for potential skin toxicity).

4.2.8 An underlying predisposition to rectal or gastrointestinal bleeding or uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.9 Females who are pregnant or lactating may not participate in this study. Females of child-bearing potential must have a negative pregnancy test before starting study agent. Patients who have had a bilateral oophorectomy, hysterectomy, or are greater than 1 year since their last menses are not considered to be of child-bearing potential.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. Because of the demographics and incidence history at our consortium sites we expect a predominance of white males, which reflects the incidence of bladder cancer. The University of Wisconsin Chemoprevention consortium sites see an average of 76% male patients and 89% white patients. However, many of our consortium sites serve ethnically diverse areas. Urology San Antonio has shown successful recruitment with Hispanic and Latino patients (25% of diagnoses, 49.1% of the population), and Johns Hopkins University serves communities that are much more diverse with populations between 25-40% African-American. Johns Hopkins University and the Carolina Urologic Research Center of Myrtle Beach, SC both of which serve a more diverse patient population are recent additions to the Consortium. The Carolina Urologic Research Center has one of the largest bladder cancer populations in the country.

The UWCCC continues to look for innovative ways to increase the minority participation in our own clinical trials, despite the demographic profile of our community. This is the focus of several initiatives of the UWCCC Cancer Control Program. In addition to devising more effective means of reaching local minority populations, the UWCCC's affiliate minority recruitment has been strengthened through affiliated research networks, examples being the Wisconsin Oncology Network or the Wisconsin Network for Health Research (both started by the Consortium PI/Bailey) which includes multiple clinical sites in Milwaukee county where underserved populations approach 20% compared to <10% in UWCCC's catchment area. Another underserved population that our affiliated research networks help with is the rural poor and the elderly poor. This is especially true with the Wisconsin Network for Health Research which has many clinic sites in rural defined areas with median incomes at or near the poverty line. In addition, the UWCCC has multiple ongoing initiatives to encourage underrepresented communities participation in health care research including efforts by Study PI/Chair, Tracy Downs, MD, who performs monthly outreach to local African-American churches for cancer and clinical research awareness.

4.4 Recruitment and Retention Plan

In an attempt to address participant concerns about extra visits, missed work, and transportation expenses, we have minimized the number of study visits in this protocol. After the consent form is signed, all baseline/screening procedures and examinations will be done at one visit, including research blood sample collection (Urine sample collection will be collected only as pregnancy test option for women of child bearing potential). Participants found to be screen failures, will not be randomized and the research samples will be destroyed on-site. Eligible participants will have two additional study visits, one at Day 8* and one on the day of their surgery.

*The Day 8 clinic visit is optional; a Day 8 phone contact will be required if clinic visit doesn't occur

Study brochures, posters, protocol fast fact sheets, pocket cards, and other recruitment materials will be developed at the CLO (Consortium Lead Organization, University of Wisconsin) and made available to the participating sites for use or modification. The CLO will coordinate with the other sites to develop comprehensive site-specific recruitment plans.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

There will be two treatment groups for this trial:

Treatment Group 1) Active study agent erlotinib 600 mg administered as four 150 mg tablets by mouth once weekly for 3 doses. (30 participants)

Treatment Group 2) Placebo as administered as 4 placebo tablets by mouth weekly for 3 doses (15 participants)

Randomization to each treatment group will be stratified by planned surgery (TURBT vs. cystectomy) and planned use of agents that significantly decrease erlotinib bioavailability. For this study this is defined as tobacco use (current smoker) or daily scheduled use of proton pump inhibitors A smoker is defined as an individual who has smoked ≥ 100 cigarettes in their lifetime and who currently smokes ≥ 1 cigarette per day).

5.2 Study Agent Administration

The study agent (erlotinib or placebo) will be dispensed by an investigational pharmacist or appropriate study staff at the participating organization (PO) and then self-administered by the participant at home. A single bottle containing 16 tablets of study agent will be dispensed If the participant is unable to return to the institution to pick up their study agent, the agent will be mailed to them via courier.

The study agent must be taken on an empty stomach (at least two hours after last eating). After taking their dose of study agent the participant must wait an hour before eating anything.

On Day 1, the participant will take one dose, 600 mg erlotinib or placebo in the form of four 150 mg erlotinib or matching placebo tablets by mouth in the evening (unless otherwise directed) on an empty stomach. All 4 tablets comprising a single dose of study agent will be taken together at the same time.
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On Day 8, the participant will take their second dose of study agent (600 mg erlotinib or placebo in the form of four 150 mg erlotinib or matching placebo tablets) on an empty stomach as instructed either in the clinic following the collection of blood samples for pharmacokinetics or at home. Prior to the Day 8 Optional Visit/Mandatory Safety Assessment Phone call, the participant will receive a reminder phone contact instructing the participant when to take the Day 8 dose.

On Day 15 the participant will take their third dose of study agent approximately 9-18 hours before their scheduled surgery (600 mg erlotinib or placebo in the form of four 150 mg erlotinib or matching placebo tablets). The participant will receive a reminder phone contact prior to their final study dosing day instructing them when to take this final dose.

If surgery is delayed beyond the 16th day but less than the 23rd day, delay administration of the third dose until approximately 9-18 hours prior to the surgery. If surgery is delayed to day 23 through day 28, administer the third dose at day 15, and the fourth dose approximately 9-18 hours before surgery. If

surgery is delayed beyond day 28 (four weekly study drug doses), the patient will be considered not evaluable for the primary endpoint.

5.2.1 Supportive Medications

All study subjects will receive, along with study medication, 30 gm tube of topical Clindamycin (1%) gel and a 30 gm tube of topical Hydrocortisone (1%) cream. They will be instructed that at the first signs of painful or red acneiform skin lesions to apply twice daily (AM and PM) topical clindamycin to the aforementioned concerning skin lesions. If these lesions do not improve (less redness or pain) they will be instructed to also start applying topical hydrocortisone twice daily (AM and PM) at time points two hours apart from application of topical clindamycin. If red or painful skin lesions continue or worsen, study participants will be instructed to call study personnel to both report the toxicity and receive additional instructions. Examples of additional instructions include increased frequency of topical application, consideration of systemic antibiotics, avoiding alcohol-based skin products, etc.

Subjects should be directed that if they experience diarrhea likely to be attributable to study drug they should use loperamide (Imodium) 2 mg (1 dose) with the first loose, watery stool, and with each watery stool therafter. If the patient has 3-4 watery stools per day, they should contact their research doctor or coordinator.

5.3 Run-in Procedures

There is no run-in phase for this study.

5.4 Contraindications

While taking the study agent the participant should be instructed not to take any:

- Strong CYP3A4 inhibitors including: ketoconazole, atazanavir, boceprevir, ceritinib, clarithromycin, cobicistat; darunavir, dasabuvir, idelalisib, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ombitasvir, paritaprevir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice.
- CYP3A4 inducers including: rifampicin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, primidone, enzalutamide, fosphenytoin, lumacaftor, mitotane, and St. John's Wort. Avoid the use of other antacids if possible.NSAIDs with the exception of ≤81 mg aspirin per day. Acetaminophen may be used as needed.
- Participants should be instructed not to consume grapefruit or drink any beverages containing grapefruit juice.

5.5 Concomitant Medications

Erlotinib is protein bound (92–95%) in humans and metabolized in the liver by CYP3A4 and, to a lesser extent, CYP1A2, and in the lungs by CYP1A1. A potential for drug-drug interaction exists when erlotinib is coadministered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors/inducers. Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations, while strong CYP3A4 inhibitors increase exposure to erlotinib. For patients who are being concomitantly treated with a strong CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe AEs. For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered.

Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Coadministration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure and maximum concentration by 46% and 61%, respectively(Kletzl 2015); therefore, participants that use proton pump inhibitors concomitantly with erlotinib will be stratified to account for the decreased erlotinib exposure.

Altered coagulation parameters and infrequent reports of bleeding events, including gastrointestinal and non-gastrointestinal bleeding, have been reported in patients in erlotinib clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumadin-derivative anticoagulants should be closely monitored for changes in prothrombin time and International Normalized Ratio (INR).

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include start and stop dates, dose frequency and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included. Medications given in the hospital as part of the standard surgical protocol will not be documented as concomitant medications. However, any medications given to treat an adverse or unexpected event following surgery will be documented.

5.6 Dose Modification

Study drug will be dose reduced (by 50%) from 4 tablets to 2 tablets for any of the following events:

- A grade 1 rash or diarrhea that the study subject finds unacceptable and desires the 50% dose reduction.
- A grade 2 skin toxicity
- A grade 2 diarrhea that does not respond to Imodium
- Any toxicity or adverse event $\geq$ grade 3
- MD discretion for side effects assessed as at least possibly related to the study drug and for which the study subject finds unacceptable and desires the 50% dose reduction

Subjects that meet the above dose modification criteria even after a dose reduction will not receive any further doses. At the first report of grade 1 or 2 skin toxicity, subjects should be instructed on using the dispensed topical ointments (1% Clindamycin, 1% hydrocortisone): apply twice daily (not at the same time) each ointment to the affected area only. Subjects who report grade 1 or 2 diarrhea likely to be attributable to study drug should be instructed to use loperamide (Imodium) 2 mg after each loose stool. Provide participants with a copy of Appendix B.

5.7 Adherence/Compliance

5.7.1 Compliance (tablet ingested/tablet instructed to take) will be assessed, but only subjects who take all study drug weekly for 3 doses (or 4 doses due to surgery delay) will be evaluable for the primary endpoint.

5.7.2 Compliance will be assessed via subject questioning, returned tablet count and planned drug levels.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent (IND # 64,808: IND Sponsor: NCI, DCP)

Clinical studies investigating the chemopreventive efficacy of erlotinib are conducted under IND 64808 sponsored by NCI, DCP. Erlotinib (Tarceva®) is an epidermal growth factor receptor (EGFR) inhibitor approved by the FDA as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. It is also indicated as first-line therapy for treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer in combination with gemcitabine.

Erlotinib drug product will be supplied as the hydrochloride (HC1) salt by Astellas Pharma Global Development, Inc. Erlotinib is currently formulated as conventional, immediate-release tablets in 25 mg, 100 mg, and 150 mg strengths. For the purpose of this study, the 150 mg strength tablet will be used. Erlotinib drug substance is an off-white to pale yellow powder. Conventional excipients in the formulation include lactose monohydrate, hypromellose, hydroxypropyl cellulose, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, magnesium stearate, and titanium dioxide.

Matching placebo tablets will be manufactured containing lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

6.2 Reported Adverse Events and Potential Risks

Over 50 Astellas (formerly OSI Pharmaceuticals, Inc.)-sponsored phase 1, 2, and 3 clinical studies of erlotinib have been initiated or completed. Various doses and schedules of erlotinib as a single agent and in combination with conventional chemotherapy agents have been studied. Twelve phase 1 studies have been conducted in healthy volunteers to determine the safety, tolerance, pharmacology, and pharmacokinetics of erlotinib (n = 268). The phase 1 healthy subject experience is based on the use of different oral erlotinib doses and schedules ranging from single-dose administration of 1–1000 mg to administration of 200 mg twice daily (bid) compared with placebo. Early tolerability studies showed that 200 mg erlotinib bid was associated with dose-limiting rash and diarrhea in addition to reversible liver transaminase elevation. Subsequent single- or multiple-dose pharmacology studies of 100 or 150 mg erlotinib daily did not reveal any new safety findings; however, the characteristic acneiform rash was unacceptable in healthy subjects receiving 150 mg erlotinib daily for approximately 1 week or longer. The phase 1 experience in cancer patients includes studies with different erlotinib doses and schedules. The maximum tolerable dose (MTD) of single-agent erlotinib was determined to be 150 mg daily, with diarrhea being the dose-limiting toxicity (DLT) despite supportive antidiarrheal treatment. Weekly dosing of erlotinib up to 1600 mg did not define an MTD; however, severe drug-related skin disorders were reported for patients receiving 1400 and 1600 mg weekly.

The phase 1b studies were designed to evaluate the MTD and pharmacokinetics of erlotinib when combined with standard doses of common chemotherapy regimens. The patient populations in these trials in general consist of advanced, refractory cancer patients with limited therapeutic options. As expected, patients who received concomitant chemotherapy in each of these trials experienced more hematological toxicities including anemia, neutropenia, and thrombocytopenia than patients who received erlotinib as a single agent therapy.

In a phase 2 trial of neoadjuvant erlotinib at 150 mg daily in invasive bladder cancer patients undergoing radical cystectomy, rash was the most common AE, observed in 15 patients (75%).

Other adverse events (AEs), including fatalities, have been reported in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer, or other advanced solid tumors, based on the safety evaluations

of erlotinib in more than 1200 cancer patients who received erlotinib as monotherapy, more than 300 patients who received 100 or 150 mg erlotinib plus gemcitabine, and 1228 patients who received erlotinib concurrently with other chemotherapies.

The most common AEs in patients receiving single-agent erlotinib at 150 mg for treatment of NSCLC in the 2nd/3rd line study were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, of erlotinib-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of erlotinib-treated patients. Dose reduction for rash and diarrhea was needed in 6% and 1% of patients, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days. Liver function test abnormalities (including elevated ALT, AST, and bilirubin) were also observed. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5–5.0 × ULN) ALT elevations occurred in 4% and <1% of erlotinib- and placebo-treated patients, respectively. Grade 3 (>5.0–20.0 × ULN) elevations were not observed in erlotinib-treated patients.

In the NSCLC maintenance study, the most common adverse reactions in patients receiving single-agent erlotinib at 150 mg were also rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 6% and 1.8%, respectively, of erlotinib-treated patients. Rash and diarrhea resulted in study discontinuation in 1.2% and 0.5% of erlotinib-treated patients, respectively. Dose reduction or interruption for rash and diarrhea was needed in 5.1% and 2.8% of patients, respectively. In erlotinib-treated patients who developed rash, the onset was within two weeks in 66% and within one month in 81%. Liver function test abnormalities (including elevated ALT, AST, and bilirubin) were also observed. Grade 2 (>2.5–5.0 × ULN) ALT elevations occurred in 2% and 1%, and grade 3 (>5.0–20.0 × ULN) ALT elevations were observed in 1% and 0% of erlotinib- and placebo-treated patients, respectively. The erlotinib treatment group had grade 2 (>1.5–3.0 × ULN) bilirubin elevations in 4% and grade 3 (>3.0–10.0 × ULN) in <1% compared with <1% for both grades 2 and 3 in the placebo group.

The most common AEs in pancreatic cancer patients receiving 100 mg erlotinib plus gemcitabine were fatigue, rash, nausea, anorexia, and diarrhea. In the erlotinib/gemcitabine arm, grade 3/4 rash and diarrhea were each reported in 5% of patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients and resulted in study discontinuation in up to 1% of patients receiving erlotinib/gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific AEs including rash and required more frequent dose reduction or interruption.

In the pancreatic carcinoma trial, 10 patients in the erlotinib/gemcitabine group developed deep venous thrombosis (incidence 3.9%), compared with three patients in the placebo/gemcitabine group (incidence 1.2%). The overall incidence of grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for erlotinib/gemcitabine *vs*. 9% for placebo/gemcitabine. No differences in grade 3 or 4 hematologic laboratory toxicities were detected between the erlotinib/gemcitabine group compared with the placebo/gemcitabine group. AEs ≥ grade 3 in the erlotinib/gemcitabine group with incidences <5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency. Liver function test abnormalities (including elevated ALT, AST, and bilirubin) were also observed. The erlotinib/gemcitabine treatment group had grade 2 (>2.5–5.0 × ULN) ALT elevations in 31% and grade 3 (>5.0–20.0 × ULN) elevations in 13% compared with 22% for grade 2 and 9% for grade 3 in the placebo/gemcitabine group.

There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC study the incidence of ILD-like events was the same

in both the placebo and erlotinib groups (0.8%). In the pancreatic cancer study (in combination with gemcitabine) the incidence of ILD-like events was 2.5% in the erlotinib/gemcitabine group *vs*. 0.4% in the placebo/gemcitabine group. The overall incidence of ILD-like events in approximately 32,000 erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 1.1%. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome, and lung infiltration. Symptoms started from five days to more than nine months (median 39 days) after initiating erlotinib therapy. In the lung cancer trials most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metatstatic lung disease, or pulmonary infections.

During the NSCLC and the combination pancreatic cancer trials, infrequent cases of gastrointestinal bleeding have been reported, some associated with concomitant warfarin or NSAID administration. These adverse events were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena, and hemorrhage from possible colitis. Cases of acute renal failure or renal insufficiency, including fatalities, with or without hypokalemia have been reported. Cases of grade 1 epistaxis were also reported in both the single-agent NSCLC and the pancreatic cancer clinical trials. Corneal ulcerations or perforations have been reported in patients receiving erlotinib. Abnormal eyelash growth, including in-growing eyelashes, excessive growth, and thickening of the eyelashes have been reported and are risk factors for corneal ulceration/perforation. Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving erlotinib therapy in the NSCLC and pancreatic cancer clinical trials. Hepatic failure has been reported in patients treated with single-agent erlotinib or erlotinib combined with chemotherapy in clinical studies and during post marketing use of erlotinib.

Bullous, blistering, and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis. In patients who develop skin rash, the appearance of the rash is typically erythematous and maculopapular and it may resemble acne with follicular pustules, but is histopathologically different. This skin reaction commonly occurs on the face, upper chest, and back, but may be more generalized or severe (grade 3/4) with desquamation. Skin reactions may occur or worsen in sun-exposed areas; therefore, the use of sunscreen or avoidance of sun exposure is recommended. Associated symptoms may include itching, tenderness, and/or burning. Also, hyperpigmentation or dry skin with or without digital skin fissures may occur. Hair and nail disorders, including alopecia, hirsutism, eyelash/eyebrow changes (mentioned above), paronychia, and brittle and loose nails have also been reported.

In the pancreatic carcinoma trial, six patients (incidence 2.3%) in the erlotinib/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, three patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction. In the same trial, six patients in the erlotinib/gemcitabine group developed cerebrovascular accidents (incidence 2.3%). One of these was hemorrhagic and was the only fatal event. In contrast, there were no cerebrovascular accidents in the placebo/gemcitabine group. In the same trial, two patients in the erlotinib/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence 0.8%), compared with no patients in the placebo/gemcitabine group.

Cases of hepatorenal syndrome, acute renal failure (including fatalities) or renal insufficiency with or without hypokalemia have been reported. Some were secondary to severe dehydration due to diarrhea, vomiting, and/or anorexia while others were confounded by concurrent chemotherapy use. Asymptomatic increases in liver transaminases have been observed in erlotinib-treated patients. Rare cases of hepatic failure (including fatalities) have been reported during post marketing use of erlotinib. Confounding

factors for severe hepatic dysfunction have included pre-existing liver dysfunction from cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

Erlotinib can cause fetal harm when administered to a pregnant woman; therefore, women should avoid becoming pregnant while being treated with erlotinib. Adequate contraceptive methods should be used during therapy and for at least two weeks after completing therapy. There are no adequate and well-controlled studies in pregnant women using erlotinib; however, studies in animals have shown some reproductive toxicity. Breastfeeding should be discontinued during erlotinib therapy. While it is not known whether erlotinib is excreted in human milk, in animals erlotinib and/or its metabolites were excreted in milk.

Please see Concomitant Medications Section.

6.3 Availability

Erlotinib and matching placebo are manufactured and supplied to NCI/DCP by Astellas Pharma Global Development, Inc. (Northbrook, IL).

6.4 Agent Distribution

Drug Shipment Authorization allowing study agent to be shipped to a participating organization will only be provided by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

Requests for shipment of study agent will be made by the CLO. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the CLO must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
425 Volker Blvd.
Kansas City, MO 64110
Phone: (816) 360-5369
FAX: (816) 753-5359
Email: NCI.DCP@mriglobal.org
Emergency Telephone: (816) 360-3800

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received DCP using the NCI "Investigational Agent Accountability Record". The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. This responsibility has been delegated to investigational pharmacist or study coordinator at each site. Include on receipt record from whom the agent was received and to

whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

Erlotinib and matching placebo will be packaged and labeled by the DCP agent repository contractor, MRIGlobal. For the treatment period, participants will be supplied with bottles containing identically appearing tablets containing either 150 mg erlotinib or placebo, according to the dose cohort. Investigational products will be supplied in bottles containing 16* tablets each of study agent (*pending repackaging, we will continue to dispense bottles containing 24 tablets with specific instructions to only take 600 mg as four 150 mg tablets per dose). Each bottle will be labeled with the following content: protocol number, storage information, investigational use language (Caution: New Drug Limited by Federal Law to Investigational Use Only. Keep out of reach of children"), and instructions to take as directed. Prior to dispensing investigational product, trial personnel will attach a label containing the participant identification number, randomization number, and dispensing date.

6.7 Storage

Erlotinib and placebo tablets are supplied in high density, polyethylene bottles and should be stored in a secure location. Storage will be maintained at 25° C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). See USP Controlled Room Temperature.

6.8 Registration/Randomization

Participants will be considered registered on the trial when they sign the consent form. All patients who sign a consent form will be assigned a Participant Identification (PID) number. A set of unique sequential PID numbers will be provided to the PO in the form of a Study Registration Log. This log will be provided to the PO by the CLO at the study initiation.

Randomization
Participants will be randomized according to the scheme outlined in section 3. The study statisticians will provide the CLO with a stratified list of randomization numbers. The DCP Drug repository will also be provided with the list along with the treatment assignment that corresponds to each randomization number.

When an eligible participant is identified at the screening/baseline visit, the site will request randomization of the participant by faxing the appropriate documentation as outlined in the Study Visit Guides to the CLO at 608-265-3287.

The CLO will verify eligibility and confirm that the correct version of the informed consent was signed. Once this information is verified, the CLO will assign the next available randomization number from the stratification that applies to the participant (TURBT vs. cystectomy and use of agents which significantly decrease erlotinib bioavailability). The CLO will then fax an Investigational Agent Request form to the DCP drug repository requesting that the bottle of study agent corresponding to the randomization number

assigned the participant be shipped to the site's (investigational) pharmacy by overnight delivery. The site will follow local procedures to have the study agent dispensed to the participant once it is received at the pharmacy.

For next day delivery of study agent, the request for randomization must be received at the CLO office by 2:30 PM Eastern Time (1:30 PM Central Time) on the business day before the drug is needed. Per NCI policy, drug cannot be shipped on a Friday or the day before a holiday. There may be instances where a five-day turn-around is needed (holidays or unusual circumstances). If possible, please randomize a week before the drug is needed.

As soon as a subject has been randomized, the CLO will email a confirmation of randomization to the study coordinator at the PO. If a confirmation is not received within two hours, the coordinator should contact the CLO to confirm that randomization documents were received.

6.9 Blinding and Unblinding Methods

Unblinded study personnel will be the study statisticians, and the DCP Drug repository staff. No staff involved in patient care or assay performance and interpretation will be unblinded. All participants will be administered identical drug, so the study staff will be blinded to both the treatment and dose level. All drug will be dispensed and reordered according to kit number, and so the pharmacy staff will all remain blinded to treatment.

All requests to unblind treatment assignment will be funneled to the Consortium Principal Investigator [Howard H. Bailey, (608) 263-8624, hhb@medicine.wisc.edu]. Dr. Bailey will determine if disclosure of treatment assignment is required after consultation with the NCI/DCP medical monitor (Howard Parnes, MD) and/or the protocol chair (Dr. Downs) or the Data and Safety Monitoring Board. Except in cases of emergency, decisions regarding unblinding of the treatment group of a randomized subject will be made in consultation with the NCI/DCP medical monitor, Dr. Howard Parnes. If disclosure of the treatment would affect important medical decisions in a subject experiencing an adverse event, unblinding might be allowed. Other circumstances might warrant breaking the blind but the decision will be left to the Dr. Bailey and the DSMB. Authorization for unblinding of randomized treatment will come from Dr. Bailey or the DCP Medical Monitor. If disclosure is warranted, the site will be directed to the product label found in the subject's CRF binder or other designated research record. The label has a scratch off area that will disclose the treatment. The site will complete an Unblinding Disclosure Form and send it to the CLO [K4/643, 600 Highland Avenue, Madison, WI 53792-6164 or Fax (608) 265-3287]. Each site will document the unblinding process in the patient chart.

The NCI Medical Monitor and/or Scientific Monitor will be notified that the blind has been broken.

Howard Parnes, MD
Prostate and Urologic Cancer Research Group
Division of Cancer Prevention, National Cancer Institute, NIH, DHHS
Shady Grove Campus
9609 Medical Center Dr., Suite 5E-302
Rockville, MD 20850
Phone: (240) 276-7045;
parnesh@mail.nih.gov

6.10 Agent Destruction/Disposal

All returned drug will be maintained at the site until a representative from the CLO has verified all pharmacy records. Once the CLO representative has reviewed the drug records, he or she will authorize the return of the drug to the DCP Repository. The site may then return the drug to the DCP repository for destruction.

At the completion of the study, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Pre-Study Evaluation/ Baseline (≤30 days)	Randomize / Dispense Study Agent	Phone Contact (24-72 hours Prior to Day 8 Visit)	Day 8 Visit[7]	Pre-surgery phone contact (24-72 hours prior to surgery)	Surgery Visit (day 15-16)	Post-surgery Phone Contact (7-14 days after surgery)
Informed Consent	X						
Assess Eligibility	X						
Medical History	X						
Physical Exam	X[2]			X[2]		X[2]	
Baseline Symptoms	X						
Vital signs (temp, pulse, BP, Ht and Wt)	X			X		X	
Hgb, Hct, WBC, Plt	X			X		X	
Na, K, CO2, Cl	X			X		X	
BUN,Creat	X			X		X	
AST, ALT, Alk Phos	X			X		X	
T Bili	X			X		X	
Urine or Serum Pregnancy Test	X						
Blood for PK	X			X		X	
Tissue Blocks/slides						X	
Concomitant Meds	X			X[7]		X	X
Dose of study agent		X[1]		X[3]	X[4,5]		
Dose reminder call			X		X		
Dispense 1% clindamyacin & 1% hydrocortisone		X[6]					
I-PSS (men only)	X					X	
Compliance				X[7]		X	
Adverse Events				X[7]		X	X

1. The date of the Day 1 dose equals the date of the surgery minus 15 days. For example, if the surgery was on the 23rd of the month, 23-15= 8, therefore the participant would take their 1st dose of study agent on the 8th of the month.
2. Physical exam should include evaluation for rash. If a rash is noted, document the extent of the rash per CTCAE grading criteria
3. The Day 8 dose of study agent should be taken during the clinic visit after the pharmacokinetic blood draw is completed or at home as instructed by study staff.
4. The pre-surgical dose of study agent should be taken in the evening prior to the day of surgery and within approximately 9-18 hours of the time of the pre-surgery pharmacokinetic blood draw.
5. If surgery is delayed beyond the 16th day but less than the 23rd day, delay administration of the third dose until the evening prior to the day of surgery. If surgery is delayed to day 23 through day 28, administer the third dose at day 15 and the fourth dose in the evening prior to day of scheduled surgery. If surgery is delayed beyond day 28 (four weekly study drug doses), the patient will be considered not evaluable for the primary endpoint. A reminder phone contact should be made 72 – 24 hours prior to the day of the re-scheduled surgery.

6. Dispense to all study participants when dispensing medication per NCI requirements. Instruct participant to use these agents for skin toxicities.
7. Day 8 clinic visit will be optional; if participant opts out a mandatory phone call to review safety assessments will be required within 48 hours of taking the Day 8 dose.

All participants who sign a consent form will be assigned a registration number. The consent form must be signed before any research procedures may be performed. The assigned registration number will be tracked using the registration log provided by the CLO. Registered participants need to be entered into the OnCore database.

7.2 Baseline Testing/Prestudy Evaluation

Baseline Evaluations
Baseline evaluations determine if the participant is a fit candidate for study participation and establish the participant's health status before entering the study. Standard-of-care labs or procedures done prior to signing consent will qualify for these baseline evaluations (i.e. physical exams, routine labs, vital signs) provided they were obtained within 30 days of the participant's Day 1 dose of study agent. All baseline evaluations (including labs) must be completed before requesting randomization and dispensing study drug. An Eligibility Checklist will be provided by the CLO at study initiation to help determine if the participant is eligible for the trial. This document will need to be signed and submitted to the CLO at the time of randomization.

Baseline **cystoscopy** demonstrating a bladder tumor. The physician should assess if the bladder tumor is invasive or non-invasive. The baseline cystoscopy must be completed within 120 days of randomization.

At the screening/baseline visit, blood for pharmacokinetics may be collected before eligibility has been confirmed. However, if the participant is later found to be ineligible, the sample may not be used. If the participant is found to be ineligible, clearly document the destruction of the pharmacokinetic blood sample in the participant's research chart.

A review of the participant's **medical history** will be done within 30 days of randomization.

A **physical examination** must be performed within 30 days of randomization.

Performance Status, using the Karnofsky must be assessed

A review of **concomitant medications** will be done within 30 days of randomization.

Laboratory tests needed for eligibility are: WBC, platelets, hemoglobin, total bilirubin, AST, ALT, alkaline phosphatase, creatinine, sodium and potassium. All of these laboratory analyses must be completed within 30 days before randomization.

Women of child-bearing potential must have a negative pregnancy test within 30 days of randomization.

Plasma Pharmacokinetics - Levels of erlotinib and metabolites will be assessed for all participants.

International Prostate Sympyom Score (I-PSS) – The participant will complete the survey within 30 days of randomization

Review of Study Participation and Study Calendar - The research staff should review the upcoming

study visits and procedures with the participant. The participant should be provided a study calendar to record any side effects and the time the participant takes their study medication. The participant should be strongly encouraged to contact the research staff with questions about study participation.

Randomization and Drug Request
Once the eligibility evaluations have been completed and the participant meets all of the inclusion criteria in section 4.1 and meets none of the exclusion criteria in section 4.2, then the participant may be randomized to the trial. Before the participant may be randomized, the Eligibility Checklist must be completed and signed. Refer to section 6.8 for specific instructions on participant randomization.

7.3 Evaluation During Study Intervention

Special Drug Dosing Procedures
The participant must be instructed to take the medication in the evening on an empty stomach (no food within two hours before ingestion and within one hour post-ingestion) on day 1, 8 and 15 with the scheduled surgery on day 16. To ensure compliance, participants will be instructed verbally and in writing to take 4 tablets from their dispensed bottle on the scheduled evenings (study days 1, 8, and 15).

Drug Dispensing
Study agent will be shipped to the PO on a per participant basis. The request to ship study agent will be sent by the CLO once a request for participant randomization has been received from the site and eligibility has been verified by the CLO (refer to section 6.8). The bottle of study agent shipped to the PO will be identified with the randomization number assigned to the participant. When the participant's study agent arrives at the PO it may be dispensed to the participant. If the institution requires a prescription for investigational agents, the site coordinator or pharmacy staff must clearly document that all prescription procedures were followed before drug was dispensed to the participant.

Reminder Phone Contact Before Day 8 Visit
Approximately twenty four to seventy two hours before the Day 8 Visit, the participant will be contacted by phone and reminded about their Day 8 appointment time. The participant will also be reminded about study dose (timing, any dose modifications, how to take it, etc.).

Day 8 Visit*
Participants will be seen and evaluated by research staff on day 8 prior to ingesting their day 8 study dose. The evaluation includes vital signs, review any adverse events that took place including an assessment of toxicities (especially skin toxicity and diarrhea) and concomitant medications. Blood for safety labs and pharmacokinetics will be obtained. The coordinator should collect and calculate study drug compliance. If dose modifying toxicity (as described above) has occurred, study staff will instruct the participant on their modified study dose (3 tablets) for day 8 and 15. After completion of this assessment the day 8 study dose will be taken as instructed.

*Day 8 clinic visit is optional. If participant decides to opt out; a Day 8 phone call to evaluate safety assessments will be required. This phone call should occur after the day 8 dose is taken and within 48 hours of the dosing. The call should include an evaluation of toxicities, a review of concomitant medications and compliance.

Reminder Phone Contact Before Surgery
Approximately twenty four to seventy two hours before surgery or cystoscopy with biopsy, the participant will be contacted by phone and reminded about their last study dose (timing, any dose modifications, how to take it, etc.) and returning any leftover study medication and study medication bottles to the research

staff. The participant will also be reminded about the appointment(s) on the day of surgery with study staff.

7.4 Evaluation at Completion of Study Intervention

At the end of study participation, the participant will have research blood work and evaluations for toxicity. The results of these analyses will be compared to the baseline results. At the end of study intervention the following procedures must be completed. The end of study visit has some critical timing requirements to allow for accurate pharmacokinetic measurements in the blood. The final dose of study drug should be taken on the day before surgery on an empty stomach. The participant should be instructed to take this final dose in the evening prior to the day of their surgery. The end-of-study pharmacokinetic blood work must happen approximately 9-18 hours after the last dose of study drug was taken. Please document the date and hour: minute of the last study dose along with the date and hour: minute of the pharmacokinetic blood draw.

Laboratory analyses for safety: **WBC, platelets, hemoglobin, Hct, BUN, total bilirubin, AST, ALT, alkaline phosphatase, creatinine, sodium, potassium, chloride and bicarbonate**.

The participant's **vital signs**, including weight, blood pressure, pulse rate, respiration rate and temperature will be taken.

A review of **concomitant medications** focusing on any changes to the medication list since study initiation and any new medications started since study initiation. Participants should be questioned about medications that have been discontinued prior to surgery.

The coordinator should collect and calculate study **drug compliance**.

International Prostate Sympyom Score (I-PSS) – would be completed prior to surgery and the coordinator would collect this.

The participant and coordinator should review any **adverse events** that took place during study participation. The coordinator should record the relevant details about the adverse events as outlined in protocol section 11.

To insure consistency in pharmacokinetic evaluations, all participants should have their end-of-study pharmacokinetic blood work and biomarkers within approximately 9-18 hours after the final dose of study medication. See section 10.2.2 for instructions on drawing and processing the end-of-study pharmacokinetics and biomarkers. Record the date and time of the pharmacokinetic blood draw and the date and time of the last dose of study drug.

Interventions at Time of Surgery
At the time of the study surgery (TURBT or cystectomy) biopsies from tumor (if available and may be invasive or non-invasive neoplasm) and adjacent normal appearing urothelium should be performed. Unstained slides or blocks relative to tumor and adjacent normal urothelium will be obtained. Detailed instructions for collection are found in section 10.2.

7.5 Post-intervention Follow-up Period

Surgery and pathology reports from the surgical procedure should be added to the participant chart. Samples of paraffin-embedded bladder tissue/unstained slides need to be requested from pathology for

immunohistochemical analysis. See section 10.2.4 for more details. If the tissue blocks are required for future diagnostics or care, the request for tissue blocks may be delayed up to 2 months after surgery to provide adequate time for evaluation.

Phone Contact after Surgery
Approximately 7-14 days after surgery, subjects will be called by research staff to assess any toxicity related to the day 15 study drug dose and when it has resolved.

7.6 Methods for Clinical Procedures

There are no special clinical procedures that require additional instructions in this protocol.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

The primary goal is assessing whether there is sufficient tissue delivery and duration of effect to justify the continued testing of weekly administered erlotinib. Because erlotinib is a targeted tyrosine kinase inhibitor of EGFR phosphorylation measuring that is the best way to assess tissue effects. Multiple studies have shown inhibition (from moderate to complete) of EGFR phosphorylation in skin and less consistent inhibition in tumor (Perez-Soler 2011, Calvo 2007). Of note, this measured inhibition has not always correlated with positive or negative biological effects (effectiveness/toxicity). Because we aren't trying to determine effectiveness, but rather any biological effect in bladder epithelium without clinically limiting toxicity for prevention, EGFR phosphorylation in bladder epithelium is the ideal marker. Our primary tissue of interest is the normal appearing urothelium adjacent to bladder neoplasia since we are very interested in preventing the field cancerization effect seen in progressive, high grade superficial bladder cancer. We intend to examine EGFR phosphorylation in tumor as well. We are assessing biological effects of intermittent, high dose erlotinib therefore our premise is that intermittent inhibition of EGFR phosphorylation should be of sufficient duration (≥ 24 hours) to have a reasonable likelihood of perturbing bladder carcinogenesis. For this initial pilot study assessing intermittent erlotinib in a bladder prevention study we will assess bladder urothelium approximately 9-18 hours post-dosing of study drug. Methodology Summary - three primary antibodies will be simultaneously stained and detected on patient tissue samples [cytokeratin AE1/AE3 (black), anti-EGFR(brown) and anti-EGFR phosphor (red]. Multispectral immunohistochemstry will be used to detect these two targets simultaneously (phosphorylated EGFR and EGFR). Hematoxylin will be used as counterstain. Since phosphorylated EGFR and EGFR are located on cell membrane including cytoplasmic membrane, endoplasmic reticulum membrane, Golgi apparatus membrane, nucleus membrane and endosome membrane. We will acquire quantitative measurement (mean optical density per pixel area) from tumor epithelium and adjacent normal urothelium. Please see Section 9 for additional detail.

8.2 Secondary Endpoints

Tolerance. The recommended dosing in adults of erlotinib is a daily oral dose of 150 mg continuously or until dose-limiting toxicity leads to an interruption and possible reduction in daily dosing. Since the advent of phase 1 and 2 studies of erlotinib and gefitinib, the dose-limiting toxicity has been painful rash or less commonly diarrhea. Grade 1 or 2 rash which is relatively common even at the lowest daily doses, approximately 50 mg, and is reluctantly tolerated even by patients with advanced cancer (Perez-Soler 2011). The cutaneous toxicity is an inflammatory follicular rash in the face and, less frequently, in the torso and extremities (Perez-Soler 2011). The pathophysiology of this new dermatologic entity has not

been fully elucidated, but the leading hypothesis is that the keratinocytes of the basal layer of the epidermis reacts to EGFR inhibition by secreting cytokines that trigger an inflammatory response that eventually causes loss of skin barrier protection and secondary skin infections involving mainly the hair follicles (Perez-Soler 2011). Attempts to ameliorate this skin toxicity have been of questionable effectiveness and there is no standard procedure other than symptomatic treatments and dose discontinuation (Perez-Soler 2011). Clinicians and researchers have attempted to ameliorate the frequency and severity of cutaneous toxicity through intermittent dosing, which is the premise behind this study. Milton et al. (Milton 2006) performed a dose-escalation study in 14 advanced NSCLC patients who received doses of 1200, 1600 and 2000 mg once weekly. Rash and diarrhea were the most frequent toxicities. Eleven of 12 evaluable Phase I patients experienced Grade 1 or 2 rash. The rash generally persisted but improved with continued weekly dosing. Of the 5 patients who developed Grade 2 rash in the Phase I portion of the trial, most did so within 2 weeks of starting erlotinib. The rash lasted 1 or 2 weeks in 3 patients and >4 weeks in 2 patients. These 5 patients were given topical clindamycin and/or oral minocycline. Similarly, 11 of 12 patients experienced Grade 1 or 2 diarrhea. Diarrhea generally was experienced within 24 to 48 hours of drug administration and was controlled well with loperamide therapy given on an as-needed basis. Thirteen additional patients were enrolled at 2000 mg weekly, again the vast majority experienced grade 1-2 rash and diarrhea. Grade 2 rash with weekly erlotinib was more frequent numerically with dose escalation and developed in 42% of patients who received 2000 mg and in 17% of patients who received 1200 mg or 1600 mg. Pertinent to this study, of the 6 patients treated at 1200 and 1600 mg dose levels, all six developed at least grade 1 rash or diarrhea. Therefore, assessing the tolerance of weekly erlotinib in a bladder cancer patient population will help determine the clinical viability of intermittent weekly erlotinib as a potential bladder cancer preventive agent either alone or in combination.

Urothelial tissue markers. EGFR phosphorylation will also be assessed in neoplastic urothelium where our prior studies, like others, have shown increased expression of phosphorylated EGFR. Our ability to assess all the proposed tissue markers from blocks means we will have the opportunity in some participants (those undergoing cystectomy for invasive disease should have blocks available from their initial diagnostic cystoscopy; and participants with high grade non-invasive bladder neoplasm undergoing a 6 week post-TURBT surveillance cystoscopy and biopsies will also have their initial TURBT tissue blocks) to assess the proposed tissue biomarkers before and after study drug exposure.

There are numerous “downstream” biomarkers associated with EGFR phosphorylation/activation with examples being PI3Kinase, STAT3 or MAPKinase pathways (Bellmunt 2003, Black 2007, MacLaine 2008). We are choosing to focus on pathways that have recently been observed to correlate with prevention modeling in animal models of breast and bladder cancer examining the effects of erlotinib administered either continuous or intermittently (weekly). Studies from Lubet et al. (Lubet, submitted 2013) have observed decreased Ki67 expression in response to weekly erlotinib in the MNU mouse breast cancer model as well as a significant decrease in phosphorylated ERK expression. The limited clinical efficacy of EGFR inhibitors suggests that identification of resistance mechanisms may identify new pathways for targeting. Studies also showed that the extent of loss of E-cadherin was in associated with the depth of urothelial carcinoma invasion (Sun 2002), and that E-cadherin plays a central role in modulation of EGFR response in urothelial carcinoma (Black 2008). Recent collaborative work involving extramural and intramural NCI-funded researchers examined the effects of gefitinib in a rat bladder cancer model suggested gefitinib exhibits its preventive efficacy on bladder tumorigenesis by upregulating let-7 and inhibiting the cell cycle (Lu 2011). Cell culture study confirmed that the increased expression of let-7c decreases gefitinib-treated bladder tumor cell growth. An identified hub gene, like let-7 may be able to serve as pharmacodynamic or efficacy biomarkers in clinical trials of chemoprevention in human bladder cancer. Micro (mi)RNAs are emerging as important regulators of cellular differentiation, their importance underscored by the fact that they are often dysregulated during

carcinogenesis. Let-7, a conserved family, regulates key differentiation processes during development. Loss of let-7 in cancer results in reverse embryogenesis and dedifferentiation (Peter 2009). Let-7 alterations have been reported in various malignancies (Osada and Takahashi 2011, Childs 2009, Nadiminty 2012, Quesne 2012).

In addition to the above biomarkers directly associated with erlotinib/EGFR, we will also examine expression of p53. Mutations of the p53 gene are the most common genetic defect in human tumors. The p53 gene functions as a tumor-suppressor gene and more specifically as a cell-cycle regulator. Levels of p53 protein increase in response to damage to DNA, arresting the cell cycle and allowing time for the repair of DNA (Esrig 1994). P53 has been studied extensive in the past decade. Many studies showed that P53 overexpression was associated with bladder cancer progression (Shariat 2009, Sarkis 1993, Grossman 1998).

Methodology Summary - For all protein marker detection and quantification a mask antibody – pancytokeratin (panCK) will be used to define the epithelial compartment including benign urothelium and urothelial tumor. A horse radish peroxidase (HRP) conjugated secondary antibody and Deep Space Black chromogen (DSP, Biocare Medical) will be used as the detecting system. A state-of-the art morphometrical system-Vectra™ (PerkinElmer) will be used for quantitation of the biomarkers. For miRNA detection (let-7 miRNA is located in the cytoplasm) and quantification a state-of -the-art technology – RNAscope™ (Advanced Cell Diagnostics) will be used. This technology has a claimed sensitivity of detecting single copy of mRNA. Briefly, a cocktail of let-7 specific probes will be designed to detect let-7 from patient tissue samples and a HRP-labeled amplification system will be used for visualization (www.acdbio.com). Vectra system will be used to quantify let-7 miRNA expression in the cytoplasmic compartment of tumor and normal urothelium. (Please see Section 9 for details).

Pharmacokinetics. Pharmacokinetic parameters have been associated with erlotinib toxicity, an important consideration in chemoprevention trials and will be assessed as part of this trial (White-Koning 2011, Lu 2006). Erlotinib and its principal metabolite OSI-420 will be evaluated by high-performance liquid chromatography as previously described (Hamilton 2006).

International Prostate Symptom Score (I-PSS). Hyperplasia and inflammation are directly or indirectly linked to carcinogenesis. Thusly, we are interested in prostatic hyperplasia. Little is known about the role of EGFR in benign prostatic hyperplasia. Recently, fibrosis has been implicated as a major player in benign prostatic hyperplasia (Ma 2012, Macoska 2012, Rodriguez-Nieves 2013). Fibrosis of the urinary tract has largely been assessed in kidney disease (Chen 2012) and EGFR appears to be a key mediator of fibrosis. However, less is known about the role of EGFR in fibrosis of the prostate and BPH. Our unpublished findings have identified that when the EGFR ligand, TGF-alpha, is force expressed in mice, prostatic fibrosis and increased rates of lower urinary tract dysfunction ensue. Additionally, we have demonstrated that EGFR-phosphorylation promotes collagen type 1 expression in prostatic stromal cells grown in vitro and the EGFR inhibitor, erlotinib, decreased prostatic collagen gene expression in these cells. These preliminary findings suggest that EGFR inhibitors may positively affect lower urinary tract symptoms.

As a part of our preliminary study of erlotinib in participants at risk of bladder neoplasia, we would like to perform an exploratory assessment of men randomized onto the study whether urination symptoms alter while on study. A well documented survey (IPSS) of urination symptoms which correlates with prostatic hyperplasia in men will be filled out by men at baseline and end of study.

8.3 Off-Agent Criteria

All subjects will be off agent on or before day 28 of administration. Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event that would compromise the surgery, inadequate agent supply, noncompliance, concomitant medications or medical contraindication. Being off agent does not imply being off study. Unless a patient meets the off study criteria in the next section, a patient will still be considered on study.

8.4 Off-Study Criteria

Participants may go off study for the following reasons: the protocol intervention and any protocol required follow-up period is completed, AE/SAE, lost to follow-up, participant withdrawal, physician decision, protocol violation, or death. Off study will mean that the investigator will not be able to or does not need to follow the patient to complete any measurements. If the reason is reversible (e.g., lost to follow-up), a patient may be placed back on study. Unless a patient specifically requests it (which may or may not happen with a withdrawal of consent), even though a patient goes off study, available data will still be used for analyses subject to compliance and exclusion requirements (refer to section 13.4).

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the investigation at any time. If not stopped early, the study will be considered terminated when the final report is written. The Consortium's data and safety monitoring board will be reviewing interim safety data, and will make recommendations as to study continuation after considering the safety data.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

Erlotinib Pharmacokinetics. Pharmacokinetic parameters have been consistently associated with erlotinib toxicity, an important consideration in chemoprevention trials and will be assessed as part of this trial. (White, 2011, Lu 2006)

Blood samples will be collected prior to starting therapy, prior to dosing on day 8 (if available), and on the day of surgery, approximately day 16. Erlotinib and its principal metabolite OSI-420 will be evaluated by high-performance liquid chromatography as previously described (Hamilton 2006).

EGF receptor. EGF receptor (EGFR) is upregulated in most epithelial cancers where signaling through EGFR contributes to cancer cell proliferation and survival. The limited clinical efficacy of EGFR inhibitors suggests that identification of resistance mechanisms may identify new pathways for therapeutic targeting. E-Cadherin. Studies have shown that the extent of loss of E-cadherin was associated with the depth of urothelial carcinoma invasion (Sun 2002), and that E-cadherin plays a central role in modulation of EGFR response in urothelial carcinoma (Black 2008). Ki67. Antigen KI-67 is a nuclear protein that is associated with and may be necessary for cellular proliferation. Lubet et al. (Lubet 2013 submitted) observed decreased Ki67 expression in response to weekly erlotinib in the MNU mouse breast cancer model as well as a significant decrease in phosphorylated ERK expression. ERK. Extracellular regulated kinase (ERK) is an important downstream factor of EGFR in MAP kinase pathway. Its activation (phosphorylation) plays a key role in carcinogenesis and cancer progression of many cancers (Lujan 2010, Chou 2010)including urothelial carcinoma (Lee 2013, Ling 2011). Study showed that aberrant ERK activation causes resistance to some EGFR kinase inhibitors (Ercan 2012).

Let 7. Micro (mi)RNAs are emerging as important regulators of cellular differentiation, their importance underscored by the fact that they are often dysregulated during carcinogenesis. Let-7, a conserved family, regulates key differentiation processes during development. Loss of let-7 in cancer results in reverse embryogenesis and dedifferentiation (Peter 2009). Let-7 alterations have been reported in prostate and lung cancers and other malignancies (Osada and Takahashi 2011, Childs 2009, Nadiminty 2012, Quesne 2012). P53. Mutations of the p53 gene are the most common genetic defect in human tumors. The p53 gene functions as a tumor-suppressor gene and more specifically as a cell-cycle regulator. Levels of p53 protein increase in response to damage to DNA, arresting the cell cycle and allowing time for the repair of DNA (Esrig 1994). P53 has been studied extensive in the past decade. Many studies showed that P53 overexpression was associated with bladder cancer progression Shariat 2009, Sarkis 1993, Grossman 1998).

Assay Performance: Immunohistochemistry (IHC) and Biomarker Quantitation (W. Huang, U of Wisc): Chromogenic multiplex IHC assay will be used, so the spatial variation of the biomarker expression in the tissue can also be analyzed and compared. Tissue slides will be deparaffinized and stained following standard protocol (Warren 2009, Huang 2009, Huang 2012). Target markers will be detected with specific antibodies. Horse radish peroxidase (HRP) conjugated secondary antibody and 3,3'-Diaminobenzidine (DAB) substrate, and alkaline phosphatase conjugated secondary antibody and Warp red substrate (Biocare Medical, Concord, CA) will be used as detecting system. The Hematoxylin will be used as counterstain.

Vectra™ (Caliper Life Sciences, Hopkinton, MA) will be used for quantitation of the biomarkers. This system includes an automated slide scanner and state-of-the-art softwares (NuanceTM and inFormTM). Vectra™ is the most advanced instrument for extracting proteomic and morphometric information from tissue microarray or intact tissue sections. Vectra merges automated slide-handling, multispectral imaging technology, and unique pattern-recognition-based image analysis into a powerful system for discovery and clinical studies. This system accurately measures protein or mRNA/DNA targets and morphometric characteristics in distinct tissue regions of interest on whole slides or tissue microarray (TMA). Sections can be labeled with either immunofluorescent (IF) or immunohistochemical (IHC) stains, or in situ hybridization (ISH) or with conventional stains such as H&E and trichrome. With IF or IHC or ISH, single or multiple proteins or mRNA/DNA targets can be measured on a per-tissue, per-cell, and per-cell-compartment (eg. nuclear, cytoplasmic) basis, even if those signals are spectrally similar, are in the same cell compartment or are obscured by autofluorescence. Vectra™ processes up to 200 slides in a single run or analyze every spot in a TMA. Pathology Tissue Imaging Laboratory (PTI), directed by W. Huang, has been using the Vectra system for two years. The process to quantitate target proteins using the Vectra™ is briefly described as follows:

Image acquisition: Briefly, the stained slides will be loaded onto the Vectra slide scanner. A scanning protocol including a spectral library will be created based on the tissue size, areas of interest and staining complexity (single or multiple staining in a single section). 8-bit image cubes will be acquired for analysis. For setting up the spectral library, three control prostate tissue slides with one dye only (DAB dye, Warp red and hematoxylin, respectively) will be prepared and scanned.

Analysis: Each chromogen has its unique spectral characteristics (curve), which is the basis for building the spectral library. First, we will use the Nuance software and image cubes acquired from the control slides to create a spectral library – defining the spectral curve for each chromogen (DAB, Warp red and hematoxylin) used in this experiment. The spectral library will then be used to unmix the signals on the test slides triple-stained with DAB, Warp red and hematoxylin by recognizing their unique spectral curves for quantitation. By such, signal noises and cross-talk are eliminated (Figure 1). Then, using the created spectral library and inForm software to do tissue (epithelium vs. stroma, etc.) and cell (nucleus vs.

cytoplasm) segmentations. Then the target signals will be quantitated within the selected subcellular compartment(s) of interest. Continuous signal intensity data will be generated.

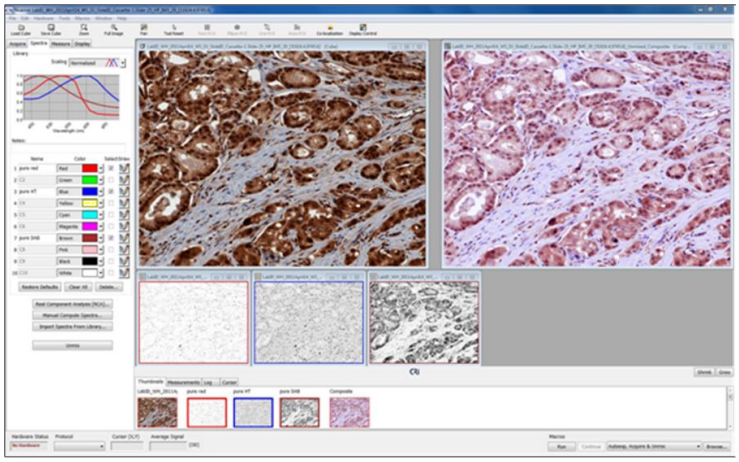

Figure 1. Nuance work area: Left pane shows the spectral library created with pure DAB, pure Warp red and pure hematoxylin slides. Right pane shows an image (top left panel) of prostate adenocarcinoma (PCa) dual immunostained with anti-p27 (brown) and Ki-67 (red)and counter stained with and hematoxylin (blue), three unmixed gray images of PCa (DAB, Warp red and hematoxylin, respectively) using the spectral library (3 middle panels) and a composite image (top right panel) of unmixed DAB, Warp red and hematoxylin. Target markers (p27 and Ki-67) are quantitated with unmixed pure signals.

Endpoint-specific Methodology.

For all protein marker detection and quantification:
A mask antibody – pancytokeratin (panCK) will be used to define the epithelial compartment including benign urothelium and urothelial tumor. A horse radish peroxidase (HRP) conjugated secondary antibody and Deep Space Black chromogen (DSP, Biocare Medical) will be used as the detecting system. A state-of-the art morphometrical system-Vectra™ (PerkinElmer) will be used for quantitation of the biomarkers. (Please see methodology p33-34 for details).

Phosphorylated EGFR detection and quantification: Antibody specific for EGFR (anti-EGFR, mouse monoclonal (mmAB), Abcam) and EGFR autophosphorylation (anti-EGFR phospho Y1092, rabbit monoclonal antibody (rmAb), Abcam) will be used to detect and quantitate EGFR and phosphorylated EGFR. A horse radish peroxidase (HRP) conjugated secondary antibody and 3,3'-Diaminobenzidine (DAB) substrate (brown), and an alkaline phosphatase conjugated secondary antibody and Warp red substrate (Biocare Medical, Concord, CA) will be used as the detecting system, respectively. So, totally three primary antibodies will be simultaneously stained and detected on patient tissue samples [cytokeratin AE1/AE3 (black), anti-EGFR(brown) and anti-EGFR phosphor (red]. Multispectral immunohistochemstry will be used to detect these two targets simultaneously. Hematoxylin will be used as counterstain. Since phosphorylated EGFR and EGFR are located on cell membrane including cytoplasmic membrane, endoplasmic reticulum membrane, Golgi apparatus membrane. nucleus membrane and endosome membrane. We will acquire quantitative measurement (mean optical density per pixel area) from tumor epithelium and adjacent normal urothelium. And then we will compare phophorylated EGFR expression levels in tumor to adjacent normal urothelium, and also compare the ratios of phosphorylated EGFR (detected by anti-EGFR phosphor, rmAb) to total EGFR (detected by anti-EGFR mmAb) in tumor and adjacent normal urothelium.

Ki-67, p53 and E-cadherin detection and quantification: Antibodies specific for Ki-67, p53 and E-cadherin will be used to detection and quantitation. Three sets of double immunostaining will be performed for each sample (Ki-67 and panCK, p53 and panCK, and E-cad and panCK)

(Biocare Medical). An alkaline phosphatase conjugated secondary antibody and Warp red substrate (Biocare Medical) will be used to detect the target antibodies (Ki-67, p53 and E-cad). Hematoxylin will be used as counterstain. Since Ki-67 and p53 are located in the nucleus and E-cad is located in the cytoplasmic membrane, nuclear Ki-67 and p53 and membranous E-cadherin expression will be quantitated using Vectra system.

Method for miRNA detection and quantification:
Let-7 quantification: let-7 miRNA is located in the cytoplasm. A state-of -the-art technology – RNAscope™ (Advanced Cell Diagnostics) will be used. This technology has a claimed sensitivity of detecting single copy of mRNA. Briefly, a cocktail of let-7 specific probes will be designed to detect let-7 from patient tissue samples and a HRP-labeled amplification system will be used for visualization (www.acdbio.com). Vectra system will be used to quantify let-7 miRNA expression in the cytoplasmic compartment of tumor and normal urothelium.

Erlotinib Pharmacokinetics (J Kolesar, U of Wisc): Blood samples will be collected prior to starting therapy, on day 8, and on the day of surgery (day 16). Plasma will be separated by centrifugation and stored at -70C or colder until analysis. Erlotinib and its principal metabolite OSI-420 will be evaluated by high-performance liquid chromatography as previously described (Hamilton 2006).

9.2 Comparable Methods

For the analysis of erlotinib, both LCMSMS and HPLC assays are available methodologies. LCMSMS is usually preferred over HPLC due to its improved sensitivity although both methods are standard for quantitative analysis of drug levels. For expression of tissue biomarkers the options of assessing message RNA or DNA levels exists in addition to gene product levels (protein expression). Our goal is to assess direct and indirect effects of erlotinib upon bladder urothelium and based on this goal and the convenience of examining protein expression from paraffin blocks or unstained slides, we have chosen protein expression (with the exception of let-7 which is microRNA expression). The increased sensitivity and ability to also examine cellular localization of protein expression has led us to use the multispectral analysis of the VECTRA system rather than standard qualitative expression of macro or micro array immunohistochemistry.

10. SPECIMEN MANAGEMENT

10.1 Laboratories

The University of Wisconsin Comprehensive Cancer Center's 3P Laboratory (Pharmacodynamics, Pharmacokinetics, Pharmacogenomics Lab) will serve as the central repository for all research specimens. The UWCCC 3P Laboratory will prepare sample kits for each subject enrolled on the study. Each site will receive one kit as they activate the study. The 3P lab will send additional kits to the sites as needed based on the rate of accrual. All tissue biomarkers will be done in the University of Wisconsin Translational Research in Pathology (TRIP) Laboratory under the direction of Wei Huang, MD (Study Pathologist).

10.2 Collection and Handling Procedures

10.2.1. Methods for drawing and processing the pharmacokinetics of blood:

At each pharmacokinetic time point draw one 3ml green top tube. Centrifuge the tube for 10 minutes to separate plasma. Divide the plasma into 2 cryovial tubes. Label the 2 cryovial tubes with the labels provided in the kit. Make sure to add the participant number, initials, date, and hour: minute of the pharmacokinetic blood draw to the labels. Freeze the cryovial tubes at –70°C, and save for transport to the UWCCC 3P Laboratory. The 3P Laboratory has purchased a software system to track samples.

10.2.2 Tissue Handling:

Biopsy tissues will be sent to Surgical Pathology for routine fixation, processing and embedding. Each site will provide tissue blocks of normal appearing bladder urothelium adjacent to tumor and tumor OR 10 unstained slides representing normal appearing bladder urothelium adjacent to tumor and 10 unstained slides representing tumor tissue (when available).

10.3 Shipping Instructions

10.3.1 Shipping to UWI

Once a patient has completed the study and all laboratory samples have been collected, ship the carton containing all of the samples for one patient to the address below. If multiple patients are completing the study, samples from multiple patients can be combined in one shipment.

3P Lab
K4/559 CSC, 600 Highland Avenue
Madison, WI 53792-5666

Call the 3P Lab to inform them of a shipment (608) 263-5369 or email the 3P lab mailing list 3plab@lists.medicine.wisc.edu

Use the express courier service indicated by the shipping label contained in the kit. Closely follow all special shipping instructions outlined in the kit instruction packet.

Ship only on Monday, Tuesday or Wednesday to ensure safe arrival during the week. Do not ship the day before a holiday.

Fill the styrofoam cooler with dry ice and put all of the blood samples into the cooler. Place the cooler into the shipping box in which you received the kit.

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

11. REPORTING ADVERSE EVENTS

DEFINITION: An adverse event (AE) is any untoward medical occurrence in a study participant. An AE does not necessarily have a causal relationship with the treatment or study participant. An AE can

therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or
disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6.2, Pharmaceutical Information as well as the Investigator Brochure.

11.1 Adverse Events

11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE CRC (paper and/or electronic) whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for adverse event reporting.

- AE verbatim term
- System Organ Class (SOC)
- Common Terminology Criteria for Adverse Events v4.0 (CTCAE) AE term
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (SAE)
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade	Severity	Description
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Fed. Reg. 75, Sept. 29, 2010 defines SAEs as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (*Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP form found at http://prevention.cancer.gov/files/clinical-trials/SAE_form.doc.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

Howard Parnes, MD
Prostate and Urologic Cancer Research Group
Division of Cancer Prevention, National Cancer Institute, NIH, DHHS
Shady Grove Campus
9609 Medical Center Dr., Suite 5E-302
Rockville, MD 20850
parnesh@mail.nih.gov
(240) 276-7045

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug and expectedness

11.2.2.3 The Lead Organization and all Participating Organizations will FAX written SAE reports to the DCP Medical Monitor within 48 hours of learning of the event using the paper SAE form. The written SAE reports will also be Faxed (650-691-4410) or emailed (safety@ccsainc.com) to DCP's Regulatory Contractor, CCS Associates (phone: 650-691-4400).

11.2.2.4 The DCP Medical Monitor and regulatory staff will determine which SAEs require FDA submission.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE form in the appropriate format. Follow-up information should be sent to DCP as soon as available. SAEs related to study agent will be followed until resolution.

12. STUDY MONITORING

12.1 Data Management

All of the procedures outlined in the University of Wisconsin Chemoprevention Consortium standardized Data Management Plan (DMP approval 6/3/2013) will be followed in this protocol. There are no supplementary Data Management procedures for this protocol.

This study will report clinical data using the CLO database OnCore which is a web-based clinical trials/database. OnCore will be the database of record for the protocol and subject to NCI and FDA audit. All OnCore data entry will be performed at the CLO where staff is trained in OnCore per our DMP and applicable regulatory requirements such as 21 CFR; Part 11.

In order to standardize the collection of information, the CLO will provide POs with preprinted study-specific source documents.

12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used to create the electronic CRF (eCRF) screens in OnCore. CLO staff will enter data into OnCore and transfer to Federal Security Compliant formats for transmission to DCP according to pre-established DCP standards and procedures. Amended CRFs will be submitted to the DCP Protocol Information Office for review and approval.

12.3 Source Documents

All data reported on CRFs must be documented on separate source documents found in the subject's medical record. The CLO will provide participating sites with standardized, pre-printed source documents that may be used to help ensure that all data items are collected. Participating sites are discouraged from using the CRFs for source documentation. If this practice occurs, the CRFs used as source documents must be signed and dated on the date of contact and a copy of the CRFs must be placed in the medical record as well as the research chart.

12.4 Data and Safety Monitoring Plan

The standard University of Wisconsin Chemoprevention Consortium DSMP was approved by the DCP on 9/14/2005. The UW Chemoprevention Consortium Data and Safety Monitoring Committee meet every 6-12 months to review all data from ongoing consortium studies. Members review pooled, unblinded safety data to assess ongoing human subjects safety.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records will be accessible for inspection and copying by authorized persons of the Food and Drug Administration.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

This section is not applicable for this study agent. The agent will be purchased by NCI.

12.7.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a patient participating on the study or participant's family member requests a copy of this protocol, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from the DCP website.

12.7.2 For a clinical protocol where there is an Investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-party Data").

12.7.3 NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

12.7.4 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

12.7.5 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

12.7.6 Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

12.7.7 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators of Collaborator's wish to contact them.

12.7.8 Any manuscripts reporting the results of this clinical trial must be provided to DCP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days (or as specified in the CTA) from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

Head, DCP Protocol Information Office

E-mail: NCI_DCP_PIO@mail.nih.gov

The Protocol Information Office will forward manuscripts to the DCP Project Officer for distribution to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a Phase IIa randomized, placebo-controlled, double-blind cancer chemoprevention trial of modulation of EGFR phosphorylation and other intermediate endpoint biomarkers by intermittent erlotinib in subjects with bladder cancer. Because there is a potential for a number of patients to be placed on a reduced dose of 300 mg/week because of intolerance to drug due to acne, in order to retain sufficient accrual at the 600 mg dose level, participants will be randomized in a 1:2 ratio of placebo to 600mg erlotinib administered weekly for 3 doses with the last dose approximately 24 hours of TURBT or cystectomy.

The primary endpoint for modulation of intermediate endpoint biomarkers will be the EGFR phosphorylation in normal appearing bladder epithelium adjacent to tumor 9-18 hours post-study dose; it is hypothesized that erlotinib will inhibit EGFR phosphorylation.

The secondary endpoints as prioritized include tolerance of high dose weekly erlotinib compared to placebo, EGF receptor phosphorylation in neoplastic bladder epithelium 9-18 hours post-study dose, the expression of e-cadherin and Ki67, the expression of phosphorylated ERK in normal and abnormal urothelium, limited pharmacokinetics of weekly erlotinib, the expression of p53 in normal and abnormal urothelium, and the expression of let-7 in normal and abnormal urothelium.

The primary analysis will be an as-randomized comparison of EGFR phosphorylation in bladder epithelium between the two randomized arms, based on two-sample t-test with normalizing transformation if necessary or Wilcoxon rank-sum test.

13.2 Randomization and Stratification

Randomization will be in a ratio of 1:2 in Placebo (4 tablets): erlotinib (4 tablets) by mouth once weekly, based on a permuted block of size 3 with stratification by planned use of agents that significantly decrease Erlotinib bioavailabiltity (tobacco, protein pump inhibitors) and by planned surgery (TURBT vs. cystectomy). The decision was made not to stratify by site to avoid problems with sparse data. After random permutation of numbers from 1 to 3 in each block, incoming subjects in sequence will be randomized to treatment corresponding to the permuted numbers in sequence according to the following: placebo for number 1, and erlotinib for numbers 2 and 3. This process will be repeated after every 3 subjects.

13.3 Sample Size and Feasibility

The sample size for each group is based on comparing EGFR phosphorylation in bladder epithelium as measured by quantitative Vectra assay analysis of expression between the erlotinib and placebo arms. This primary endpoint can be considered a continuous random variable. The sample size justification is thus based on a two-tailed two-sample t-test of the difference between the two groups at a significance level of 0.05. In order to detect an effect size of 1, i.e. the difference in the mean change between the placebo arm and the erlotinib arm of 1 standard deviation, with power 0.85, the trial requires an effective sample size of 14 in the placebo arm and 28 in the erlotinib arm. Assuming a random drop-out of up to 5%, 15 subjects in the placebo arm and 30 subjects in the erlotinib arm will be enrolled for a total of 45 subjects for this exploratory study.

There will be six sites participating in the study. Each randomized patient will be treated with study medication weekly x 3 doses. We will allow for study duration of approximately 3 years.

13.4 Primary Objective

The primary objective is to determine if there is a difference in EGFR phosphorylation in normal appearing bladder epithelium adjacent to tumor approximately 9-18 hours post-study dose, between patients randomized to erlotinib weekly as compared to placebo. The primary endpoint of the study is EGFR phosphorylation in bladder epithelium at the end of study (weekly for 3 doses) in subjects with bladder cancer. For the primary comparison the difference between the placebo group and the erlotinib group will be tested as-randomized using a two-sample t-test with normalizing transformation if necessary or Wilcoxon rank-sum test.

Because of the required dose modification to 300 mg for grade 2 rash or diarrhea and allowed dose modification for grade 1 rash/diarrhea if subject prefers (refer to section 5.6) there is the potential for a number of patients to reduce dose at some point in the study. In addition, prior research has shown that smokers and those that regularly take proton pump inhibitors metabolize erlotinib faster, tolerating

erlotinib better, but gaining fewer benefits, effectively receiving a reduced dose compared to non-smokers and those that are not taking proton pump inhibitors (refer to section 2). As a supporting analysis for the primary endpoint we will explore a relationship for EGFR phosphorylation with a measure of dose received, and accounting for smoking status and proton pump inhibitor use.

13.5 Secondary Objectives

For the secondary objectives, we will determine whether skin toxicity is present when erlotinib is administered weekly at 600 mg for weekly for 3 doses. We will determine if there is a difference in EGFR phosphorylation in neoplastic bladder epithelium 9-18 hours post-study dose between subjects randomized to erlotinib weekly versus placebo. We will assess erlotinib plasma concentrations in subjects taking erlotinib weekly. We will test for differences between arms in expression of phosphorylated ERK in normal and abnormal urothelium. We will examine limited pharmacokinetics of weekly erlotinib. We will determine, for normal, neoplastic tissue, and the difference between normal and neoplastic tissue, if there is a difference in the following markers of EGFR: e-cadherin, Ki-67 and p-ERK, p53, and let-7 micro RNA.

For secondary objectives, all measurements and changes in measurements of interest will be summarized by treatment arm (and, if applicable, by visit) with appropriate descriptive statistics. Compliance, in terms of the number of pills missed, will be summarized by treatment arm with descriptive statistics, and tested for imbalance using Wilcoxon rank-sum test. Patient toxicity throughout the study will be summarized in several ways; the presence or absence of any toxicity, worst CTCAE grade, and strongest investigator-defined relationship will all be examined and characterized by treatment arm, and analyzed appropriately (Wilcoxon rank-sum for ordinal data, Fisher's exact test for dichotomous data, and log rank test for time to event data). For tissue biomarkers, we will examine the differences between the groups for biomarkers in normal and neoplastic tissue, and the difference between normal and neoplastic tissue at the time of surgery; (also, for those with available paired tissue samples we will examine pre to post change) with the appropriate tests; for dichotomous data we will use Fisher's exact test, for ordinal data we will use Wilcoxon rank-sum test, and for continuous data, and a two-sample t-test with normalizing transformation if necessary or Wilcoxon rank-sum test.

13.6 Reporting and Exclusions

As the nature of this study is exploratory, intent-to-treat should not be used as a principal analysis criteria. Nevertheless, no subjects will be excluded from the analysis and reporting, except for obvious random dropouts and for those who never took the protocol treatment.

Compliance with the protocol treatment will be measured in the form of pill counts; the information will not be used for the primary analysis, but for the analysis supporting the primary endpoint. There will be no imputation of missing data for both the primary and the secondary endpoints.

13.7 Evaluation of Toxicity

All participants receiving any protocol treatment will be evaluated for toxicity from the time of their first dose of placebo or erlotinib up to the time of surgery according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. After the surgery the participants will be followed for seven to fourteen days for adverse events that are possibly, probably or definitely related to study drug. Serious Adverse Events (SAEs) related to study agent will be followed until resolution. Any adverse events that occurred before surgery and are considered possibly, probably or definitely related to study

drug will be followed after surgery until resolved or for 3 months, whichever is sooner. Adverse events that do not resolve should be referred to the participant's primary care provider.

13.8 Evaluation of Outcome/Endpoints

For the primary analysis comparing EGFR phosphorylation across the treatment groups, the as-randomized analysis will be used. All of the participants who met the eligibility criteria, with the exception of those who did not receive study agent, will be included in the main analysis. Random dropouts will be excluded.

13.9 Interim Analysis

Interim analysis will be performed at a regular schedule to document study progress and to review safety data. This will be performed by an unblinded statistician who is not connected with the day-to-day operation of the study; the regular study staff will not be unblinded. There is no plan for interim analysis for efficacy data. Results of interim analyses of safety data will be reported to the Consortium's data and safety monitoring board for review at approximately six month intervals. They will be in charge of reviewing safety information, including adverse events, serious adverse events, and death data, and making a judgment as to the advisability of continuation. There will be no hard and fast criteria set for the safety analysis.

13.10 Ancillary Studies

No ancillary studies are planned.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Signed and dated current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Protection of Human Research Subjects" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to the DCP Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates
1923 Landings Drive
Mountain View, CA 94043
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to the DCP Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

All laboratory tests and clinic visits required for study participation will be done at no cost to the participant or his/her insurance company. The cost of the cystectomy or TURBT and all follow-up visits post-operatively will be the responsibility of the subject or insurer. Although it is not expected, taking part in this study may lead to added costs to participants.

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APPENDIX A

Performance Status Criteria

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B

Information on Erlotinib (Study Drug)

Erlotinib
(Tarceva)

Description
Erlotinib is a medication used in the treatment of some cancers. This study is being done to determine the potential cancer prevention effects in bladder tissue when erlotinib is taken once a week, and to determine how well people tolerate taking erlotinib once a week. Erlotinib needs to be taken on an empty stomach, which means taking it at least 2 hours after you last ate something one hour before you next eat something.

How It Is Given
This medicine is a pill that you swallow.

When to call us: We would like to know if you experience any rash or diarrhea that continues for over 24 hours. We would also like to know if you experience any unexplained, persistent cough, fever, or shortness of breath immediately.

Common Side Effects When Taken Daily:

COMMON, SOME MAY BE SERIOUS In 100 people receiving erlotinib, more than 20 may have:
• Rash • Diarrhea • Loss of appetite • Tiredness or fatigue • Shortness of breath • Cough • Nausea • Infection • Vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving erlotinib, from 4 to 20 may have:
• Sores in mouth • Itching • Acne • Dry skin • Weight loss • Irritation (redness, swelling, warmth, and pain) or infection of the skin around fingernails or toenails • Eye infection/pink eye • Dry eyes • Stomach pain or pain in the abdomen (belly) • Red bumps on the skin that are red, sore, and possibly infected

POSSIBLE, SOME MAY BE SERIOUS The frequency of some individual side effects for people receiving erlotinib has not yet been determined:
• Shoulder pain • Change in urine color • Indigestion • Gas in the belly, burping • Irritability (easily annoyed or made angry) • Swelling of the face, hands, feet or ankles • Runny nose • Dizziness • Headache • Blood clot in the lung which may cause pain, shortness of breath • Stroke (Stoppage of blood flow to your brain which may cause paralysis, weakness, headache) • Death or injury to unborn baby • Because of the potential harm to the infant, women should be advised against breast-feeding while receiving erlotinib therapy

RARE, SOME MAY BE SERIOUS

In 100 people receiving erlotinib, 3 or fewer may have:

Although very rare, some of the side effects listed below can cause death

- Abnormal laboratory result which may indicate liver damage
- Liver damage
- Kidney damage which may cause swelling, may require dialysis
- Swelling, irritation, or scarring of the lungs, which may cause pain or difficulty breathing.
- A tear or hole in the stomach that may require surgery. More common in people with ulcers (sores in the stomach), diverticulitis (redness, pain, and swelling of part of the belly), and in people who take some types of drugs (NSAIDS, corticosteroids, chemotherapy). Talk to your study doctor about drugs to avoid.
- Severe blistering or peeling of the skin
- Patches of skin may become darker in color
- Redness, swelling, sores, or a tear or hole in eye which may cause pain or blurred vision.
- Increased bleeding (Internal bleeding, nose bleed). More common in people who take blood thinning drugs.
- Increased body hair growth, hair loss, eyelash/eyebrow changes, or brittle/loose fingernails or toenails
- Severe diarrhea or vomiting can cause an imbalance of minerals in the blood (called electrolytes) such as low potassium, with symptoms that may include weakness, fatigue, muscle cramps, or constipation.
- In people with cancer of the pancreas who took combined treatment of erlotinib plus gemcitabine: heart attack, stroke, decreased red blood cells (anemia) which may cause tiredness, or may require blood transfusion, and decreased platelets which may cause easy bleeding, or longer bleeding.

Special Concerns

Erlotinib can interact with some kinds of antibiotics, antiviral, and antifungal drugs, and warfarin (a blood thinner). You should make sure you have told your cancer doctor about all medicines you are using, and make sure your local doctor knows you are taking erlotinib if they prescribe any new ones.

Appendix C

International Prostate Symptom Score (I-PSS)-Men Only

PID:_____ **Date of birth:**_____ **Date completed**_____

In the past month:	**Not at All**	**Less than 1 in 5 Times**	**Less than Half the Time**	**About Half the Time**	**More than Half the Time**	**Almost Always**	**Your score**
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

About the I-PSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life in men. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

The questions refer to the following urinary symptoms:

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

Question eight refers to the patient's perceived quality of life.

The first seven questions of the I-PSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index which currently categorizes symptoms as follows:

Mild (symptom score less than or equal to 7)
Moderate (symptom score range 8-19) Severe
(symptom score range 20-35)

The International Scientific Committee (SCI), under the patronage of the World Health Organization (WHO) and the International Union Against Cancer (UICC), recommends the use of only a single question to assess the quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of benign prostatic hyperplasia (BPH) Symptoms or quality of life, it may serve as a valuable starting point for a doctor-patient conversation.

The SCI has agreed to use the symptom index for BPH, which has been developed by the AUA Measurement Committee, as the official worldwide symptoms assessment tool for patients suffering from prostatism.

The SCI recommends that physicians consider the following components for a basic diagnostic workup: history; physical exam; appropriate labs, such as U/A, creatinine, etc.; and DRE or other evaluation to rule out prostate cancer.

Research Subject Information and Consent Form

Study Title for Participants: Testing erlotinib to prevent bladder cancer in people with bladder cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: UWI2013-01-02 Phase II Clinical Chemoprevention Trial of Weekly Erlotinib Before Bladder Cancer Surgery

Invitation/Summary

We would like to invite you to participate in this clinical trial, a research study that we hope will help us learn more about how to prevent bladder cancer in people who are at risk for that kind of cancer. You are being asked to take part in this study because you have been diagnosed with or are suspected of having a cancerous tumor in your bladder which your doctor plans to remove with surgery. Your doctor and the research study staff will explain this study to you and answer any questions you might have about it. Participation is voluntary. Please take your time to make your decision about whether or not you want to participate. You may want to discuss this with your family, friends or other members of your health care team. Please feel free to contact us with any questions or concerns you might have.

Why is this study being done?

We are doing this study to determine the potential cancer prevention effects in bladder tissue of once a week erlotinib and how well tolerated erlotinib is once a week. In this study, you will get either erlotinib or placebo. There will be a total of about 45 people taking part in this study nationally and about *insert number* people will be enrolled here at the *insert study site*.

Definitions:

Erlotinib (also known as Tarceva) is an anticancer medication. It blocks the action of an abnormal protein that tells cells in the body to multiply more than they should. When cells multiply more than they should, they form a growth called a tumor. Erlotinib is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor.

Placebo is something that is made to look like a treatment or medicine but has no real medicine in it. In this study, placebo will be tablets that look just like erlotinib but don't have erlotinib or any medicine at all in them.

What are my other choices if I do not take part in this study?

The choice is yours. If you decide not to take part in this study, you do have other choices. For example:

- You may choose to have the surgery and any other standard treatments recommended by your doctor and not participate in this study.
- You may choose to take part in a different study, if one is available.
- Or you may choose to do nothing.

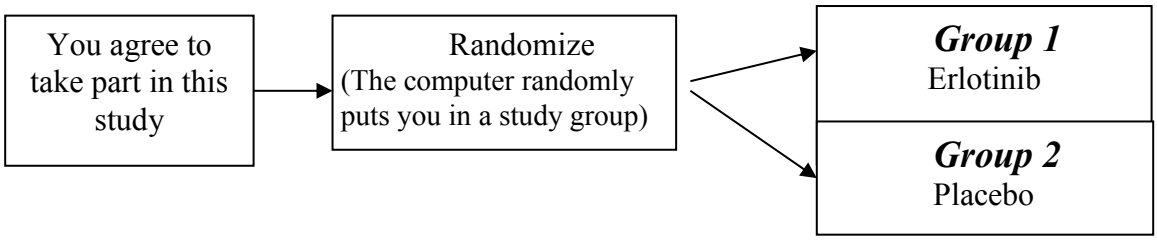
What are the study groups?

This study has two study groups.

Group 1 will receive the study drug erlotinib.
Group 2 will receive a placebo.

You will be randomly put into one of the two study groups. Being randomly put into a group is like a coin toss that is done by a computer. We do this because no one knows if one study group is better, the same, or worse than the other group. Once you are put in a group, you cannot switch to the other group. Neither you nor your doctor will know if you are receiving the erlotinib or the placebo. Your doctor cannot choose which group you will be in.

For every two people who are put into the erlotinib group, one person will be put into the placebo group. This means that you have about a 70% chance of being in the erlotinib group versus the placebo group.



How long will I be in this study?

You will receive the study drug weekly for 3 doses before your bladder surgery. If that procedure is delayed for some reason, you could receive one additional weekly treatment but that is the most you could receive. Even if you do not finish the study, your doctor will continue to watch you for side effects and follow your condition for 7-14 days after your surgery. The duration of study participation is 4-6 weeks.

What extra tests and procedures will I have if I take part in this study?

In addition to the exams, tests, and procedures you will have as part of the usual approach for your condition, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study you will have a screening/baseline visit.

At this visit the following extra tests and procedures will be done to find out if you can be in the study. If you have already had any of these tests done as part of your regular medical care within 30 days of starting the study medicine we may be able to use those results:

- Medical History: A doctor or nurse from the study will ask you about any health problems, surgeries or treatments you had in the past and any health problems or symptoms you are having now. We will also ask you about any medicines you are taking and about your smoking history.
- Physical Exam and Vital Signs: A doctor or nurse from the study will do an exam and measure your height, weight, blood pressure, pulse and temperature.
- The lead study doctor is interested in seeing if the study medicine improves urine difficulty in men. The study staff will ask men to fill out a survey about their urinary symptoms before they take the study medicine and after they take the study medicine
- Because the effects of erlotinib on the developing human fetus are unknown, if you are a woman of childbearing potential, we will do a urine or serum pregnancy test at your Baseline Visit to make sure that you are not pregnant. In addition both women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.
- Blood Tests: About 2 tablespoons of blood will be taken with a needle from a vein in your arm.
    - Most of this blood will be sent to the hospital or clinic lab and will help us find out if your health is well enough for you to participate in this study.
    - About 1/3 tablespoon of this blood will be used to help us learn more about how the study drug will work in your body.

If you are determined eligible for the study and agree to proceed with receiving the study drug you will be given two additional medications: topical clindamycin which is an antibiotic gel; and topical hydrocortisone which is an anti-inflammatory cream to be used in case a rash develops (the rash is described in the section of this consent under "What risks can I expect from taking part in this study?").

Taking the Study Medicine:

If these exams, tests, and procedures show that you can take part in the study, and you choose to, we will order study medicine for you. It will arrive in just a couple of days. You can return to pick up your study medicine or we can send it to you by UPS or FedEx overnight delivery.

The tablets in your bottle of study medicine will contain either erlotinib or placebo. You will take the study medicine only 1 time per week for 3 doses before your surgery. You will take your last dose on the day before your surgery. Along with your study medication, you will be given a calendar. The calendar will help remind you when and how to take your study medicine. We will ask you to write down the date and time you take your study medicine and to make a note of any symptoms, side effects or health changes you experience.

The study medicine needs to be taken on an empty stomach (at least 2 hours after you last ate something and one hour before you next eat something). We ask that you take your medicine in the evening at least two hours AFTER eating, take dose, and wait one hour before eating anything again. We will tell you what day to start taking your study medicine. We will call that Day 1. Day 1 will be about 15-16 days before your scheduled bladder surgery. On Day 1, you will take 4 tablets of study medicine (4 tablets = 1 dose of study medicine).

- If your tablets contain erlotinib, each tablet will have 150 mg of erlotinib (150 mg per tablet x 4 tablets = 600 mg total dose of erlotinib).

- If your tablets contain placebo, each tablet will have 0 mg of erlotinib and your total dose will be 0.

In addition to the study tablets you may be instructed to apply to any uncomfortable skin reactions (if they were to occur – please see risk section below) clindamycin gel twice a day to lessen any redness or discomfort; if this does not improve the skin reactions you may be instructed to also apply to the affected skin reactions hydrocortisone cream twice daily two hours after applying the clindamycin gel.

Please do not use these topical medications unless the study doctor specifically instructs you to use them.

One week later, on Day 8, you will take your second dose (4 tablets) of study medicine.

One week after that, on the day before your surgery, you will take your 3rd (last) dose (4 tablets) of study medicine. We call a few days before your surgery and tell you what time to take this last dose.

(Note: if your surgery or cystoscopy with biopsy is delayed for any reason, you may be asked to take one additional weekly dose of study medicine. 4 total doses of study agent are the most that you can take on this study).

During the study:

Phone Contact (approximately 24-72 Hours Prior to Day 8 Visit):
One to three days before your Day 8 Visit, we will call you to remind you of your appointment time/date. We will also give you instructions on when to take your weekly dose of study medicine.

On Day 8* (7 days after your first dose of study medicine) you will be asked to return to the clinic for another study visit. Bring your study calendar along with you to this visit.

At this visit we will do the following tests or procedures which are not part of the usual treatment for a bladder tumor:

- Physical Exam and Vital Signs: The study doctor or nurse will do a brief physical exam and measure your temperature, pulse, blood pressure, and weight. They will also ask you about any changes in your non-study medications and any symptoms, side effects or health problems you have noticed since you started the study.
- Review your Study Calendar: Study staff will review your calendar to be sure you are taking the study medicine correctly.
- Blood Tests: The same blood tests that were done at the screening baseline visit will be repeated at this visit.
- Once these blood tests have been drawn, you can take your weekly dose of study medicine and in an hour you can eat.

* The Day 8 visit is optional. If you decide to not come to clinic on Day 8 we will call you at a number you provide to us and check how you are doing. During this call we will discuss with you how you are feeling, if you are taking your study drug as instructed, and if you are taking any other drugs or supplements.

Pre-surgery Phone Call:

24 to 72 hours before the day that your bladder surgery is scheduled, we will call you to schedule your final study visit which will be on the day of your bladder surgery before you have your procedure. We will also give you instructions on when to take your last weekly dose of study medicine. This dose needs to be taken about 9-18 hours before your surgery or biopsy. Depending on what time your surgery or biopsy is scheduled to start, you may need to take this last dose at a different time than your other doses.

Day of Surgery Visit:

Your last study visit will be on the day of your surgery before you have the surgery. At this visit, we will do the following:

- Physical Exam and Vital Signs
- The study doctor or nurse will do a brief physical exam and measure your temperature, pulse, blood pressure, and weight. They will also ask you about any changes in your non-study medications and any symptoms, side effects or health problems you have noticed since you started the study.
- The study staff will ask you to fill out a survey about your urinary symptoms
- Review your Study Calendar: Study staff will review your calendar to be sure you took the study medicine correctly.
- Blood Tests: The same blood tests that were done at the screening baseline visit will be repeated at this visit.
- After your surgery, the tissue that is taken from your bladder is sent to the pathology lab at your clinic or hospital. After the pathology looks at the bladder tissue under the microscope and makes a report to your doctor, we will ask them

for a piece of the left over tissue. We will use this tissue to run some tests to tell us more about the effects of the study medicine on the bladder tissue.

Post-surgery Phone Call:

Seven to fourteen days after your surgery or biopsy, we will call you by phone to ask you about any symptoms, side effects or health problems you have noticed since you started the study.

Note: While you are participating in this study, we will watch you carefully for any side effects from the study medicine. If you develop side effects we may cut your weekly dose of study medicine in half (to 2 tablets each week) or we may ask you to stop taking the study medicine. If you stop taking the study medicine we would still like to have you come in for your surgery visit if you are willing.

What risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual.
- Be asked sensitive or private questions which you normally do not discuss.
- Have a slight discomfort from the needle stick when blood is drawn or bruising at the site of the needle stick. In rare instances some people faint during a blood draw or develop an infection at the site of the needle stick.

Reproductive Risks: You should not get pregnant, breastfeed, or father a baby while in this study. The erlotinib used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

The medicine used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- Tell the study doctor if you experience any unexplained, persistent cough.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common side effects that we know about erlotinib, some of which may be serious. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Erlotinib

COMMON, SOME MAY BE SERIOUS In 100 people receiving erlotinib, more than 20 may have:
• Rash • Diarrhea • Loss of appetite • Tiredness or fatigue • Shortness of breath • Cough • Nausea • Infection • Vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving erlotinib, from 4 to 20 may have:
• Sores in the mouth • Itching • Acne • Dry skin • Weight loss • Irritation (redness, swelling, warmth, and pain) or infection of the skin around fingernails or toenails • Eye infection/pink eye • Dry eyes • Stomach pain or pain in the abdomen (belly) • Red bumps on the skin that are red, sore, and possibly infected

POSSIBLE, SOME MAY BE SERIOUS The frequency of some individual side effects for people receiving erlotinib has not yet been determined:
• Shoulder pain • Change in urine color • Indigestion • Gas in the belly, burping • Irritability (easily annoyed or made angry) • Swelling of the face, hands, feet or ankles • Runny nose • Dizziness • Headache • Blood clot in the lung which may cause pain, shortness of breath • Stroke (Stoppage of blood flow to your brain which may cause paralysis, weakness, headache) • Death or injury to unborn baby • Because of the potential harm to the infant, women should be advised against breast-feeding while receiving erlotinib therapy

RARE, SOME MAY BE SERIOUS

In 100 people receiving erlotinib, 3 or fewer may have:

Although very rare, some of the side effects listed below can cause death

- Abnormal laboratory result which may indicate liver damage
- Liver damage
- Kidney damage which may cause swelling, may require dialysis
- Swelling, irritation, or scarring of the lungs, which may cause pain or difficulty breathing.
- A tear or hole in the stomach that may require surgery. More common in people with ulcers (sores in the stomach), diverticulitis (redness, pain, and swelling of part of the belly), and in people who take some types of drugs (NSAIDS, corticosteroids, chemotherapy). Talk to your study doctor about drugs to avoid.
- Severe blistering or peeling of the skin
- Patches of skin may become darker in color
- Redness, swelling, sores, or a tear or hole in eye which may cause pain or blurred vision.
- Increased bleeding (internal bleeding, nose bleed). More common in people who take blood thinning drugs.
- Increased body hair growth, hair loss, eyelash/eyebrow changes, or brittle/loose fingernails or toenails.
- Severe diarrhea or vomiting can cause an imbalance of minerals in the blood (called electrolytes) such as low potassium, with symptoms that may include weakness, fatigue, muscle cramps, or constipation.
- In people with cancer of the pancreas who took combined treatment of erlotinib plus gemcitabine: heart attack, stroke, decreased red blood cells (anemia) which may cause tiredness, or may require blood transfusion, and decreased platelets which may cause easy bleeding, or longer bleeding.

Will I benefit from this study?

Participating in this study is unlikely to help your condition. This study may help us learn things that could help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

We will tell you about any new information or changes in the study that could affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes.
- If the study is no longer in your best interest.
- If new information becomes available.
- If you do not follow the study rules.
- If the study is stopped early for any reason.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, *Insert your IRB's contact information or your IRB's designated Patient Relations/Rights Representative's contact information.*

What are the costs of taking part in this study?

The study medicine will be supplied at no charge while you take part in this study. The cost of study-specific exams, tests, and procedures will be paid for by the study.

Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer.

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will receive $*XX.XX* to cover the cost of travel and other expenses associated with the study baseline/screening visit. If you are found to be eligible and decide to participate in this study, you will receive an additional $*XX.XX* to cover the costs of travel and expenses associated with

participation in this study. *(This section may vary depending on how you elect to set up your participant reimbursements)*

What happens if I am injured or hurt because I took part in this study?

In the event that you are physically injured as a result of participating in this research, emergency care will be available. You will, however, be responsible for the charges for emergency care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact your study doctor or the study investigator, *Insert PI Name* at *Insert PI phone number* if you are injured or for further information.

It is important that you tell your study doctor or the study investigator, *Insert PI Name*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at *Insert PI phone number* if you are injured or wish further information.

Who will see my medical information?

Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the US, and similar organizations if other countries are involved in the study.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.
- The study sponsor and Astellas Pharma Global Development, Inc. (formerly OSI Pharmaceuticals, Inc.), the drug company providing the study drug for this study.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Personnel from the University of Wisconsin Comprehensive Cancer Center in charge of quality assurance.
- Contractors hired by the government to review study files.
- Data will be stored on computer files at the University of Wisconsin and the National Cancer Institute's statistical center.

We will ask you if you would like other doctors informed of your participation in this

research. If you do, we will inform them of your participation.

Special Concerns

Erlotinib can interact with some kinds of antibiotics, antiviral, and antifungal drugs, and warfarin (a blood thinner). You should make sure you have told your cancer doctor about all medicines you are using, and make sure your local doctor knows you are taking erlotinib if they prescribe any new ones. Also, please contact your doctor if you experience any unexplained, persistent cough.

Where can I get more information?

You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor, *Insert PI Name* at *Insert PI phone number*.

Optional Tissue Banking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from biopsies, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

We ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called “biobanking”. The Biobank is run by the National Cancer Institute.

What is involved?

If you agree to take part, any of your tissue samples remaining after we complete this study will be stored in the Biobank, along with samples and information from other people who take part.

The samples will be kept until they are used up.

1) Qualified researchers can submit a request to use the materials stored in the Biobank. A research committee at the National Cancer Institute will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
2) Neither you nor your study doctor will be notified if/when research is conducted using your samples and no information on the results of this research will be placed in your medical records.
3) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1) There is a risk that someone could get access to the personal information in your medical records or other information we have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the Biobank, no information identifying you (such as your name or social security number) will be sent. Samples will be identified by a unique study code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. The Biobank is required to keep your identity confidential.
3) Researchers to whom the Biobank sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, *Insert Study P.I. name* at *Insert P.I. phone number* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?
If you have questions about the use of your samples for research, contact the study doctor, *Insert Study P.I. name* at *Insert P.I. phone number*

Please circle your answer to show whether or not you would like to take part in each option

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any tissue banking where I circled 'yes'.

_____	_____
Participant's signature	*Date of signature*
_____	_____
Signature of person(s) conducting the informed consent discussion	*Date of signature*