Clinical Study Protocol

Protocol No.:	IRB13-0540/ 1200.171
BI Investigational Product:	Afatinib
Title:	Afatinib in advanced refractory urothelial cancer
Clinical Phase:	Phase II
Principal/Lead Investigator:	Peter H. O'Donnell, M.D.
Drug Manufacturer:	Boehringer Ingelheim Pharmaceuticals, Inc.
Sponsor:	The University of Chicago

Version, and Date of Protocol:	V. 1, June 3, 2012 V.2, August 3, 2012 V.3, September 20, 2012 V.4, January 13, 2013 V.5, April 26, 2013 V.6, May 30, 2013 V.7, August 26, 2013 V.8, February 5, 2014 V.9, June 16, 2014 V.10 March 6, 2017 (CTRC re-review submission) V.11 April 25, 2017 (revised per CTRC review comments) V.12 September 12, 2017 (Administrative change in personnel and update to registration process) V.13 March 5, 2018 (page 6 revised flow chart, page 62 add 10ml to lavender sample) V.14 July 9, 2018 (page 6 updated flow chart, page 17/section 2.2 add information to study objective, page 20/section 3.3.3 add new exclusion criteria statement, page 26section 4.2.2.1 clarify restrictions regarding concomitant treatment, page 29/section 5.1.1 update exploratory endpoints, page 39/section 6.4 updated biomarker studies, page 40. update personnel, page 44/section 7.1.2 update secondary and exploratory analysis, page 49/section 9.1 updated IB version number, page 59 update personnel and administrative changes) V.15 November 22, 2018 (Page 2: Remove text reading “Page 1 of 58”; Page 3: Update contact information for Regulatory Manager; Page 19, Section 3.3.2.4: Clarify disposition of germline genomic test results; Page 26, section 4.2: Update section heading; Page 27: Update section to clarify which subjects in whom afatinib should be used with caution.) V. 16 November 01, 2019 (Sections 3.3.2.1, 3.3.3.1, and 5.4 – clarified prior radiotherapy eligibility.)

CLINICAL STUDY PROTOCOL SYNOPSIS

Protocol date: 7/9/2018	**Protocol number:** IRB13-0540/1200.171	
Title of study:	Afatinib in advanced refractory urothelial cancer	
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Study site(s) :	This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.	
Sponsor:	The University of Chicago	
Drug Manufacturer:	Boehringer Ingelheim Pharmaceuticals, Inc.	
Clinical phase:	phase II	

Protocol date: 7/9/2018	**Protocol number:** IRB13-0540/1200.171	
Objective(s):	This trial was originally designed to test the 3-month PFS rate of molecularly unselected urothelial cancer patients receiving afatinib. We previously completed this first portion of the study. Overall, five of 23 patients (21.7%) met PFS3 (two partial response, three stable disease). Results indicated a signal of activity for afatinib in a portion of patients with specific molecular alterations. Specifically, among the 21 patients whose tumors were available, pre-specified analysis of *ERBB* family molecular alterations showed that five of six patients (83.3%) with *HER2* and/or *ERBB3* alterations achieved PFS3 (PFS = 10.3, 7.0, 6.9, 6.3, and 5.0 months, respectively) versus none of 15 patients without alterations ($P < 0.001$). Three of four patients with *HER2* amplification and three of three patients with *ERBB3* somatic mutations (G284R, V104M, and R103G) met PFS3. One patient with both *HER2* amplification and *ERBB3* mutation never progressed on therapy, but treatment was discontinued after 10.3 months as a result of depressed ejection fraction. The median time to progression/discontinuation was 6.6 months in patients with *HER2/ERBB3* alterations versus 1.4 months in patients without alterations ($P < 0.001$). Based on these data, the study is now being amended to determine the 6-month progression free survival (PFS) rate in metastatic urothelial cancer patients receiving afatinib who have progressed despite prior platinum-based chemotherapy and who carry genomic *ErbB* family alterations.	
Methodology:	single-arm marker-selected continuation phase II study (previous phase of this study allowed all patients (no marker selection) and has been completed)	
No. of patients:	72 marker-selected patients (interim analysis after first 29 evaluable patients for futility assessment); the previously-enrolled 23 patients from the first portion of this trial (all enrolled during the first non-marker selected phase of the trial) were previously analyzed separately as summarized above and will not be analyzed with the 72 patients from this marker-selected phase	
total entered:	95 total (72 patients in marker-selected cohort; 23 in initial cohort)	
each treatment:	afatinib	
Indication :	patients with platinum-refractory metastatic urothelial cancer with genomic *ErbB* molecular alterations	

Protocol date: 7/9/2018	**Protocol number:** IRB13-0540/1200.171	
Main criteria for inclusion:	• Adults with urothelial carcinoma of the bladder, upper tract, or urethra • Must have tumor evidence of somatic molecular alteration in *EGFR, HER2, ERBB3, or ERBB4* • Prior treatment with a platinum-based regimen administered in the perioperative or metastatic setting • Evidence of disease progression prior to enrollment • Adequate hepatic and marrow function • ECOG 0-1	
Main criteria for exclusion:	• Prior therapy with afatinib • Breastfeeding or pregnant women • Uncontrolled intercurrent illness • Concurrent receipt of other investigational agents • Patients with untreated known brain metastases, or treated brain metastases that are clinically unstable • Uncontrolled HIV or HIV currently being treated with antiretrovirals	
Criteria for efficac*y:*	Progression-free survival rate at 6 months in patients treated with afatinib	
Duration of treatment:	Until disease progression or intolerable toxicity	
Criteria for safety:	Reporting of serious adverse events	
Criteria for efficac*y:*	Progression-free survival rate at 6 months in patients treated with afatinib	
Statistical methods:	In a meta-analysis of second-line clinical trials in patients with advanced urothelial carcinoma (Pond et al., 2013), the estimated overall progression-free survival (PFS) rate at 6 months was 22.6% (95% CI: 18.8%-25.9%), although it varied from 34.6% in patients with no risk factors (liver metastases, ECOG 1+, Hb<10 g/dl, or time from previous chemotherapy <6 months) to 4.9% in patients with 3-4 risk factors. Thus over three-quarters of patients will have disease progression within 6 months, and we propose that PFS at 6 months would be an informative endpoint for assessing drug activity. A Simon, optimal two-stage design will be employed to assess the primary end point of 6-month PFS rate. The null hypothesis (H_0), a 6-month PFS of <25%, will be considered representative of lack of efficacy of the drug in this biomarker-specific patient population consisting of patients with *ErbB* alterations. The alternative hypothesis (H_A), a 6-month PFS rate of >40%, will be considered indicative of activity. If 23 or more of the 72 total patients (>32%) exhibit progression-free survival of 6 months or more the regimen will be considered promising and worthy of further study.	
Study duration	Until all treatment is concluded and data is collected on enrolled patients (total = 72 evaluable patients in marker-selected cohort)	

FLOW CHART

Study Period	**Screening***	**Cycle 1 ** [A]**		**Cycle 2 ** [A]**		**Subsequent Cycles (3, 4, etc.) ** [A]**	**End of Treatment and Post-Study treatment**		
Visit Days	**Day -21 through day 0**	**Day 1 ‡[C]**	**Days 15, 29, and 43 ‡**	**Day 57(C2D1) ‡**	**Days 15 and 29 ‡**	**Days 1 and 29 ‡**	**EOT ‡**	**FU ‡**	**Add. FU[ᵀᵀ] ‡**
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X		X		X	X		
Documentation of qualifying somatic genomic molecular alteration in *EGFR*, *HER2*, *ERBB3*, or *ERBB4*	X								
Physical exam	X	X[C]	X	X	X	X	X	X	
Vital signs including O_2 sat	X	X	X	X	X	X	X		
Height	X								
Weight	X						X		
Performance status	X						X		
CBC w/diff, plts	X	X[C]	X	X	X	X	X		
Serum chemistry#	X	X[C]	X	X	X	X	X		
Serum BHCG¥	X								
MUGA[£]	X				X[£]	X[£]			
Dispense study drug to subject		X¶		X¶		X¶			
Radiologic evaluation (CT or MRI)	X			X		X[B]	X[B§]		
Tumor measurements	X			X		X[B]	X		
Adverse event evaluation	X	X	X	X	X	X	X	X	
Archival research tumor tissues[%]	X --->	-->	--> X						
Pharmacogenomic blood sample	X --->	-->	--> X						
Survival status								X	X

*Baseline evaluations, including imaging studies, are to be conducted within 21 days prior to start of protocol therapy.
% Archival tissues to be used for exploratory biomarker research studies described in Section 6.4. These research tissue samples are not required for eligibility nor registration and may be submitted during screening or after registration but must be received by the end of cycle 1. See section 6.4 for details.
** Treatment courses continue until disease progression or unacceptable drug intolerance.
#Comprehensive metabolic panel (Na, K, Cl, HCO_3, BUN, Creatinine, Glc, Ca, Total Bilirubin, Total Protein, Albumin, AST, ALT, Alkaline Phosphatase), Mg, PO_4
¥ BHCG = beta human chorionic gonadotropin. Only required in women with intact uterus. If elevated, pt ineligible unless pregnancy otherwise proven to be excluded.
A: Each cycle is 56 days in length.
¶ Patient supplied with two bottles of study drug on day 1 of each 56-day cycle. Each bottle contains 30 tablets. See Section 4.3 for adherence reporting requirements (pill counting/pill diary).
‡ (+/-) 4 day visit window
C: It is encouraged that patients for whom a treating physician feels may be at higher than average risk for toxicity from afatinib should be seen at one extra in-person visit, 1 week after starting study therapy (on cycle 1 day 8). This visit should include physical exam and CBC with diff, plts and serum chemistry assessment.
£ MUGA (multi-gated acquisition scan) must also be performed every 12 weeks during therapy B: Radiographic assessment of responses to be performed every 8 weeks until disease progression is observed or until drug intolerability.
EOT = end of treatment
§ A scan performed for clinical reasons mid-cycle (e.g., for clinical symptoms of possible disease progression) which indeed confirms progressive disease and which results in the patient being taken off study, will count as the EOT radiologic evaluation.
FU = follow-up
Add FU = additional follow-up
ᵀᵀPatients should be followed for 3 years after end of treatment

TABLE OF CONTENTS

1. INTRODUCTION

1.2 DRUG PROFILE

Afatinib is a novel, oral, irreversible, ErbB family blocker (ErbB1/EGFR, ErbB2/HER2, and ErbB4/HER4) that offers the chance to control both recurrent as well as distant metastatic disease on an outpatient basis with continuous treatment. Afatinib final formulation is available in 20, 30, 40 and 50 mg film-coated tablets to be used for clinical studies up to Phase III.

Afatinib is a potent, irreversible, ErbB family blocker, both *in vitro* and *in vivo*. Receptor tyrosine kinases other than the EGFR (Class I) family and non-receptor type tyrosine kinases were not inhibited. Afatinib is bioavailable after oral administration in several species.

1.2.1 Preclinical pharmacology and toxicology

In mice, afatinib reaches efficacious plasma exposure with once-daily dosing throughout the treatment period. Afatinib displays antitumor activity, including tumor regression, against established subcutaneous xenografts in nude mice either as a single agent or in combination with a cytotoxic agent like docetaxel. The necessary maximum plasma concentrations were between 80 to 285 nM for single agent activity. The absolute bioavailability was medium-high in rats (45%). The median t_{max} after oral administration was 4 hours and the terminal half-life was 4.5 hours. The terminal half-life of the radiolabelled compound was considerably longer indicating persistence of metabolites in the system. The exposure was dose proportional without gender-related effects. Some accumulation in the 13-week and 26-week toxicology study appeared more pronounced in males. In minipigs there was a slight tendency towards supra-proportional increases in $AUC_{0\text{-}24h}$ with increasing doses, which was considered to be of minor relevance. A consistent effect on accumulation was not seen.

In the whole body autoradiography in rats, afatinib was distributed in all organs with the exception of the CNS after oral administration. The highest concentrations were found in the kidney, liver, lung, and spleen. In general, a slow elimination of radioactivity was seen. The major excretion pathway is via faeces (91%). Afatinib covalently binds to plasma proteins. Whether such protein haptens are immunogenic and capable of inducing allergic reactions is unknown.

Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions as based on this mechanism will occur. *In vivo*, afatinib was metabolized only to a minor extent and the metabolism was governed by adduct formation to proteins or nucleophilic small molecules. It was found that metabolism is of subordinate role for afatinib and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib *in vivo*. Only approximately 2 % of the dose were metabolized by FMO3 *in vivo*. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers. Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications) effects on the activity of FMO3 or

CYP3A4 *in vivo* are expected to be of little, if any, relevance for the pharmacokinetics of afatinib.

In vitro, afatinib was found to be a P-gp substrate (estimated K_m 10-30 µM) and a moderate to weak inhibitor of P-gp (estimated K_i of 3.4 µM). It cannot be excluded that concomitant treatment with other P-gp substrates or P-gp inhibitors may alter the plasma concentrations of afatinib. Since I/K_i of afatinib is resulting in values considerably below 0.1 which would be the defined "cut off" value for considerable drug-drug interactions based on P-gp (afatinib acting as a P-gp inhibitor) it is unlikely that afatinib may alter the plasma concentrations of other P-gp substrates.

Safety pharmacology studies (GLP) in rats indicate no adverse effects on behavior or respiratory function. In minipigs, minor effects on heart rate (tachycardia) and the ECG (QT-shortening) were observed. Cardiovascular systemic effects observed were non-significant, with the exception of reduced contractility at higher intravenous doses. An effect on renal and liver function was seen with a very high oral dose of 300 mg/kg in rats. Furthermore, a dose dependent effect on gastrointestinal function was seen, leading to a substantial inhibition at the highest dose.

In repeat-dose toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks) and minipigs (up to 52 weeks), the main target organs were the skin (mice and rats; inflammatory changes), the gastrointestinal tract (mice, rats and minipigs; diarrhea and epithelial changes) and the kidneys (rats; papillary necrosis). This spectrum is in line with findings reported for other ErbB targeting drugs. Changes were generally minimal to moderate and often fully reversible or ameliorated after drug withdrawal (skin, kidneys); they are most likely related to the EGFR-inhibiting effect of afatinib.

In the gastrointestinal tract, increasing systemic exposure was associated with dose dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomachs of rats and minipigs. Clinically, this was characterized by diarrhea in both species and faecal occult blood in a single minipig. Other organs affected by the epithelial atrophy in the rat were the skin, prostate, uterus, and vagina. In minipigs, the upper respiratory tract, seminal vesicles, and the corneal epithelium were affected by epithelial atrophy. In the gastrointestinal and respiratory tract, atrophy of the mucinous glands, e.g. salivary glands, was also found. These atrophic changes were minimal to slight and fully reversible during the recovery periods and are most likely related to the pharmacodynamic mechanism of afatinib.

Afatinib is not irritating to intact skin but may have a phototoxic potential. Afatinib is slightly mutagenic in a single bacteria strain, but it did not show genotoxic potential *in vivo* when tested up to overt toxic/lethal doses. The reproductive and developmental toxicity studies showed no marked adverse effects on fertility and early embryonic development, and only a small effect on birth weight and bodyweight gains of offspring in rats. No indication of teratogenicity was identified in rats and rabbits. Because systemic drug exposure in the studies generally was only slightly above clinical exposure (rat embryo-fetal development, male rat fertility) or below, in the absence of safety margins, a final conclusion on the potential of afatinib for adverse reproductive and developmental effects in humans is not possible.

Based on these toxicological findings and the experience with other EGFR- and HER2-inhibitors, the risks of anti-EGFR and anti-HER2 therapy with afatinib might primarily consist of gastrointestinal effects (including diarrhea) and skin rash.

1.2.2 Clinical pharmacokinetic and safety

PK data available from clinical trials until now indicate that afatinib was moderately fast absorbed after oral administration, with median t_{max} values mainly between 1 and 6 hours. For afatinib there was no deviation from dose-proportionality detectable. However, moderate to high inter- and intra-individual differences in plasma concentrations were seen. Afatinib was highly distributed out of the blood and had a moderate to high clearance. The mean terminal half-life was mainly in the range of 13-57 h. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via the faeces. After food intake, a decreased systemic exposure was observed compared to administration of afatinib under fasted conditions. Therefore, afatinib should be taken without food (i.e. afatinib should be taken at least 1 hour before or at least 2 hours after a meal). Typically, an accumulation ratio based on AUC values between 1.8 and 4.0 has been observed. At doses of 40 mg and above individual $C_{max,ss}$ and $AUC_{\tau,ss}$ values were mainly in the same range as those found to demonstrate anti-tumor activity in nude mouse tumor xenograft models.

Adverse events observed with afatinib are consistent with those reported for other EGFR inhibitors and include predominantly gastrointestinal (GI) and dermatological AEs which are dose-dependent. Diarrhea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhea most frequently occurred within the first 6 weeks of treatment. Patients of low body weight, females, and patients with low baseline renal function appear to be at increased risk for developing Grade 3 diarrhea. A small number of patients experienced dehydration and prerenal insufficiency, most likely secondary to GI AEs, particularly diarrhea.

Rash/acne occurs at a high frequency; with half of the cases beginning within 4 weeks of exposure to afatinib. Those at higher risk for Grade 3 rash/acne appear to be the patients of low body weight/body surface area and patients with low baseline renal function.

Early, proactive, and effective management of these adverse events is mandated in ongoing and forthcoming clinical trials with early intervention to manage diarrhea and skin toxicities.

Interstitial lung disease (ILD) is a rare and serious (potentially fatal) AE reported with other EGFR tyrosine kinase inhibitors. Considering reports of suspected cases of ILD on afatinib, ongoing trials have been amended to exclude patients with known or pre-existing ILD from treatment with afatinib. Careful assessment of all patients with acute onset and/or unexplained worsening of pulmonary symptoms (including dyspnea, cough, and fever) are emphasized. Interventions including interruptions of study drug pending investigations and permanent discontinuation if ILD has been diagnosed must be considered.

Besides diarrhea, other GI AEs include nausea, vomiting, stomatitis, mouth ulceration, dry mouth, and oral pain. Besides acne/rash, other dermatological AEs include dermatitis acneiform, dry skin, pruritus, and skin reaction. Other AEs seen in clinical trials of afatinib

include general disorders such as fatigue/asthenia; mucosal inflammation; infections and infestations such as paronychia and folliculitis; respiratory disorders such as epistaxis and rhinorrhea; eye disorders such as conjunctivitis and keratitis; and metabolism and nutritional disorders, such as anorexia and dehydration. Other AEs were in the expected range for patients with advanced malignancies.

1.2.3 Clinical efficacy

Efficacy of afatinib has been demonstrated in multiple studies of NSCLC patients and has FDA approval in this disease for patients with specific EGFR mutations.

Objective responses have been observed in phase II studies in selected breast cancer patients and patients with squamous cell cancer of the head and neck.

Objective responses and durable stable disease in patients with advanced solid tumors have been observed in phase I monotherapy studies as well as in phase I combination studies.

Afatinib demonstrated activity in platinum-refractory urothelial cancer patients in the first stage of this study, with all responders bearing *ErbB* family molecular alterations.

2. Rationale, objectives, and Benefit - Risk Assessment

2.2 STUDY OBJECTIVES

Therapy for Urothelial Cancer as an Unmet Need
Despite the fact that urothelial carcinoma of the bladder is often a curable disease with surgical intervention alone, a significant number of patients will relapse and die of their disease. In fact, urothelial cancer of the bladder is the 6th most common cancer and the 8th-leading cause of cancer death in the United States[1]. Each year, approximately 80,000 individuals are diagnosed with urothelial cancer in the U.S. alone, and over 17,000 die[1]. Cisplatin-based therapy and immunotherapy remain the only accepted standards of care for treatment of metastatic disease[2,3]. Despite these therapies, the median overall survival remains short[4,5]. Therefore, novel agents are desperately needed.

We hypothesize that a targeted, tolerable novel agent like afatinib could delay disease progression (and thereby potentially increase overall survival rates) for patients with this difficult disease.

EGFR Targeting as a Rational Therapeutic Strategy
The concept of targeting the epidermal growth factor receptor (EGFR/ErbB1/HER1) pathway in urothelial cancer has been the subject of intense study over the past two decades[6]. Recent successes when targeting this pathway in other tumors (head and neck, colon, and lung cancers) also encourage its continued exploration in other relevant tumor types.

First, it is known that EGFR overexpression is increased in urothelial cancer compared to the normal urothelium[7], and the majority of invasive urothelial cancers (in contrast to non-invasive tumors) overexpress EGFR[8]. In a comparison of primary bladder urothelial tumors

versus sites of metastasis in the same patients from one study, EGFR expression levels in the primary tumors were generally found to correlate with expression levels in the metastatic sites[9]. Importantly, EGFR was found to be significantly expressed in 65% of the metastatic sites[9]. EGFR expression has also been shown to correlate with higher tumor grade[8], muscle invasiveness[8], tumor recurrence[10,11], and overall survival[11,12] in patients with urothelial cancer. These composite pre-clinical and clinical data support the putative significance of the EGFR pathway in urothelial cancer and led to the development and initial clinical testing of EGFR-targeted therapies in this disease over the past 5-10 years.

Clinical data on EGFR inhibition have been mixed. Two prior trials have demonstrated lack of activity for the anti-EGFR drug gefitinib in patients with metastatic disease[13,14]. These negative studies could simply be due to the fact that gefitinib may be an inferior agent within the anti-EGFR family (as perhaps also suggested by its ultimate failure in lung cancer). This possibility may be suggested by the recent promising data reported by Pruthi et al[15] in their phase II trial of the EGFR inhibitor erlotinib as neoadjuvant monotherapy in patients with cT2 urothelial cancer. Demonstrating a pathologic downstaging rate of 35% and a pT0 rate of 25%, Pruthi et al. concluded that erlotinib "may have activity" in the neoadjuvant setting for urothelial cancer[15]. As theirs was a single-arm study, we are forced to rely on historical comparisons to interpret the results. However, the authors' claim of possible activity for erlotinib is supported by the fact that the pT0 rate in their study (25%) appears to be higher than in other studies where no neoadjuvant therapy was used—studies which consistently show pT0 at 15% or lower[16,17].

We believe the combination of these promising clinical data and considerable pre-clinical evidence strongly support further strategies aimed at EGFR inhibition in urothelial cancer in a randomized fashion. We believe afatinib is an ideal choice to test not only because of its potent activity and role as an EGFR inhibitor, but because of its dual mechanism of HER2 inhibition as well.

HER2 Targeting as a Rational Therapeutic Strategy

Overexpression of HER2 (ErbB2) in urothelial carcinomas has been repeatedly shown. Estimates of the prevalence vary, partly because of utilization of different cutoffs for measuring overexpression by immunohistochemistry (IHC) and partly because gene amplification is instead sometimes tested. In the most prominent clinical study in which HER2 testing was conducted on urothelial cancer patients, 52% were designated as HER2 "positive", with 49% demonstrating overexpression (at least 2+) by IHC[18].

Another recent series by a well-respected pathology center found that among urothelial patients with high-grade invasive disease (a population which would mirror the proposed study population here), HER2 overexpression (2+ or higher by IHC) was present in 36% of primary tumors and 30% of metastases[19]. These composite data suggesting a significant prevalence of HER2 positivity has led many to advocate that HER2 is one of the most attractive molecules for therapeutic targeting in urothelial cancer[20].

Further pre-clinical evidence supports this idea. In a series of 90 patients undergoing cystectomy and adjuvant cisplatin-based chemotherapy, HER2 status (IHC 2+ or 3+) was

significantly related to tumor stage (P = 0.001) and lymph node involvement (77% in N+ versus 23% in N0; P = 0.001). Worse disease-related survival (log rank P = 0.011) was found for patients with HER2 overexpressing tumors than for those without overexpression, and HER2 status (relative risk = 2.22) was identified as an independent predictor for disease-related survival in a multivariate analysis (P = 0.02)[21].

Similarly, Fleischmann et al.[22] suggested a possible concordance between HER2 amplification and metastasis, demonstrating that HER2 amplification was significantly more frequent in lymph node metastases (15.3%) of patients with urothelial cancer than in matched primary bladder tumors (8.7%; p=0.003). Interestingly, HER2 amplification also significantly predicted poor outcome (p=0.044).

Clinical evaluation of HER2 targeting in urothelial cancer has previously been reported by a study which used trastuzumab combined with carboplatin, gemcitabine, and paclitaxel in patients with previously untreated advanced disease[18]. The regimen demonstrated significant activity (70% response rate). However, the design was non-randomized, making conclusions difficult, and furthermore there was an unexpectedly high rate of cardiac toxicity seen with the use of trastuzumab.

Another study examined maintenance lapatinib (versus placebo) after first-line chemotherapy in patients with EGFR or HER-2 "positive" metastatic urothelial cancer[23]. Positivity was defined as 2+ or 3+ immunohistochemical staining. The trial failed to show any improvement in progression free or overall survival for lapatinib.

Finally, analysis of the first 23 patients enrolled in the first phase of this study showed evidence for activity in urothelial cancer patients. Specifically, in the overall (molecularly unselected) population, five of 23 patients (21.7%) had progression-free survival at three months (PFS3; two partial response, three stable disease). Most importantly, five of six patients (83.3%) with *HER2* and/or *ERBB3* alterations achieved PFS3 (PFS = 10.3, 7.0, 6.9, 6.3, and 5.0 months, respectively) versus none of 15 patients without alterations (P < .001). Three of four patients with *HER2* amplification and three of three patients with *ERBB3* somatic mutations (G284R, V104M, and R103G) met PFS3. One patient with both *HER2* amplification and *ERBB3* mutation never progressed on therapy, but treatment was discontinued after 10.3 months as a result of depressed ejection fraction. The median time to progression/discontinuation was 6.6 months in patients with *HER2/ERBB3* alterations versus 1.4 months in patients without *HER2/ERBB3* alterations (P < .001)[24].

The primary purpose of the expansion study is to identify which *ErbB* family alterations confer sensitivity.

In the earlier phase of the study, no somatic nonsynonymous mutations in *EGFR* were detected in any patients, and no alterations in *ERBB4* were identified in any patients, consistent with previously reported findings that *EGFR* somatic mutations and *ERBB4* alterations are rare in urothelial cancer. Response data for patients with *EGFR* amplification and/or high EGFR expression were unclear. Given this, the sensitivity of such patients to afatinib is unknown. However, given the mechanisms of *EGFR* and *ERBB4*, the known activity of afatinib in patients with select *EGFR* mutations and true amplifications (in lung

cancer), and the clear sensitivity seen in *ERBB2*- and *ERBB3*-altered patients in the earlier study, it is rational to include *EGFR* mutated and amplified and *ERBB4* altered patients in the eligible group for this larger (expansion) study.

Given the compelling scientific rationale for pursuing the ErbB family and the significant clinical opportunity provided by a paucity of other therapeutic options in urothelial cancer, we believe afatinib is therefore an attractive agent for testing in this disease.

2.3 BENEFIT-RISK ASSESSMENT

This drug is inviting for testing in this setting due to its tolerability profile[25] and its route of oral administration. This study addresses an important unmet need in urothelial cancer. In a disease which has seen the successful introduction of no new agents in the past ~20 years and for which outcomes remain dismal especially for high risk patients, development of novel, rational agents like afatinib is desperately warranted.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.2 OVERALL STUDY DESIGN AND PLAN

This continuation phase II study is designed to evaluate whether afatinib has activity in patients with unresectable urothelial cancer who are refractory to prior platinum-based chemotherapy and carry somatic molecular alterations of *ErbB* family genes. Patients must have received prior treatment with a platinum-based regimen administered in the perioperative or metastatic setting and must have evidence of disease progression prior to enrollment.

In this single-arm continuation phase II study, all patients will receive afatinib at a starting dose of 40 mg/day given continuously. Radiographic assessment of responses will be performed via CT or MRI every 8 weeks until disease progression is observed or until drug intolerability. The first portion of this study (non-marker selected; already completed- Figure 1) permitted enrollment of patients without consideration of somatic genomic ErbB status. The continuation portion of this trial (the 'marker-selected' phase) will only enroll patients whose tumors harbor *ErbB* family genomic alterations. The trial design for the new cohort of the study is shown in Figure 2.

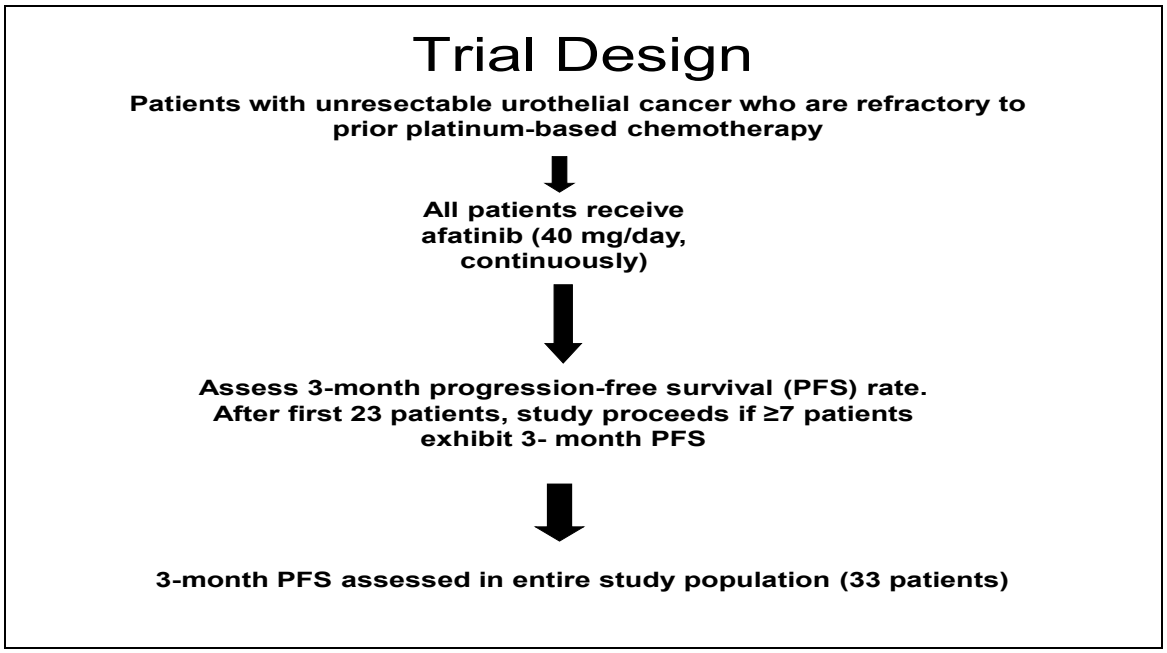

Figure 1: Trial Design for the first portion (non-marker selected phase) of the study

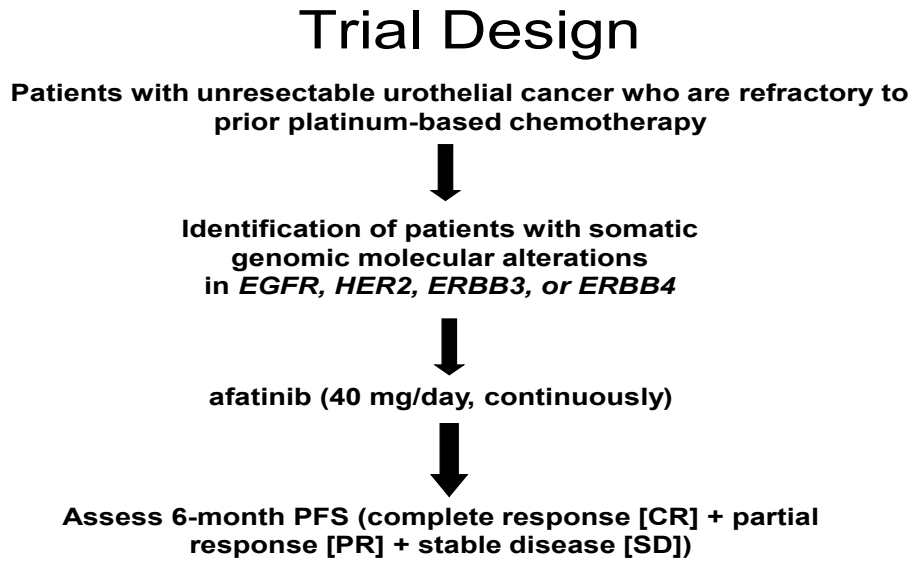

Figure 2: Trial design for the new cohort (marker selected phase) of the study

3.3 SELECTION OF STUDY POPULATION

3.3.1 Main diagnosis for study entry

3.3.1.1 Patients must have locally advanced or metastatic urothelial cancer that

is not amenable to surgical treatment

3.3.1.2 Patients must have histologically or cytologically confirmed urothelial tract carcinoma. Patients with urothelial carcinoma of the bladder, upper tract, or urethra are eligible.

3.3.2 Inclusion criteria

3.3.2.1 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. See Section 10.2 (Appendix 2) for the evaluation of measurable disease (RECIST v1.1). Lesions that have been irradiated as the most recent line of treatment are not eligible as RECIST target lesions.

3.3.2.2 Patients must have evidence of disease progression prior to enrollment.

3.3.2.3 All patients must have received a prior platinum-based chemotherapy regimen for treatment of urothelial cancer and must now be considered refractory to platinum-based chemotherapy. Patients may have received the platinum-containing regimen either in the peri-operative or metastatic setting. Patients may have received any number of additional prior therapies, and may have received prior immune therapies.

3.3.2.4 Patients must have tumor evidence of somatic genomic molecular alteration in *EGFR, HER2, ERBB3, or ERBB4*, from a test result generated in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. The tumor tissue sample used to generate the qualifying report must be from a muscle-invasive or higher stage urinary tract cancer specimen (metastatic tissue is also acceptable). Final determination about whether a specific tissue source or molecular genomic finding meets criteria as a qualifying result rests with the central study PI. Germline genomic findings will not be returned to patients.

3.3.2.5 Patients must be 18 years of age or older.

3.3.2.6 ECOG performance status 0-1.

3.3.2.7 Patients must have adequate organ function as defined below:

- absolute neutrophil count ≥1,000/mcL
- platelets ≥100,000/mcL
- hemoglobin ≥ 8.5g/dL
- total bilirubin ≤ 1.5 institutional upper limit of normal (IULN)
- AST(SGOT)/ALT(SGPT) ≤ 2.5 X IULN
- calculated creatinine clearance ≥ 30 mL/min by the modified Cockcroft and

Gault Formula OR glomerular filtration rate $\geq$ 30 mL/min/BSA by Modification of Diet in Renal Disease or CKD-EPI formula

3.3.2.8 Women and men of child-bearing potential 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 treating physician immediately.

3.3.2.9 Patients must have the ability to understand and the willingness to sign a written informed consent document.

3.3.3 Exclusion criteria

3.3.3.1 Patients may not receive any other anti-cancer treatments while on study. Patients cannot have received another anti-cancer chemotherapy or immunotherapy or radiotherapy or investigational agent within 2 weeks prior to the first dose of study treatment.

3.3.3.2 Patients with untreated known brain metastases, or treated brain metastases that are clinically unstable.

3.3.3.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3.3.4 Women known to be pregnant.

3.3.3.5 Women who are breastfeeding and who are unwilling to stop breastfeeding prior to study entry.

3.3.3.6 Patients with known prior HIV-positive status on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions. Known prior HIV-positive patients with $CD4^{+} \leq 500/mm^{3}$ are ineligible because of the potential increased risk of infection. (HIV testing is not required as part of this study).

3.3.3.7 Pre-existing interstitial lung disease

3.3.3.8 Inability to take oral medications

3.3.3.9 Prior therapy with afatinib

3.3.4 Removal of patients from therapy or assessments

In the absence of treatment delays due to adverse event(s), treatment may continue until

one of the following criteria applies:

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

3.3.5 Specifics regarding tumor testing for study enrollment

Analysis of results of tumor somatic testing from a CLIA-certified laboratory is required for study eligibility determination. Such testing may have been performed historically (previously), or testing may be conducted specifically for the purposes of study eligibility screening. If the latter, it is encouraged that patients consider signing the consent in advance of desired study entry so as to allow time for tumor results to become available (tissue pre-screening). It is permissible to consent patients even while they are receiving other anti-cancer therapy as long as such patients have unresectable metastatic urothelial carcinoma. Patients without measurable metastatic disease are not eligible for genomic pre-screening under the auspices of this study. A central (sponsor-provided) CLIA-certified laboratory is available to conduct tumor sample pre-screening for this study. If testing is sought through this dedicated (sponsor-provided) central laboratory, a turn-around time of at least 14 days from the time of receipt of the sample should be expected. If a result from a local CLIA-certified laboratory is proposed for eligibility screening, the local laboratory must be first approved by the central study PI. No new (fresh) tumor biopsies should be sought under the auspices of this study, however such biopsies may of course be performed for standard of care reasons or if felt to be clinically appropriate as part of routine care in the view of the treating physician.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will receive afatinib.

4.1.1 Identity of investigational product

Substance (INN): afatinib

4.1.2 Selection of doses in the study

All patients will receive afatinib at a starting dose of 40 mg/day given continuously.

4.1.3 Drug assignment and administration of doses for each patient

4.1.3.1 Afatinib

For administrative purposes treatment will be divided into treatment courses, which are each 8 weeks (56 days) in duration. Patients will take a single oral dose of 40 mg afatinib each day (56 days/cycle). All patients will start with 40 mg tablets and in the event that dose reduction is necessary, the patient will return to the clinic and new medication will be dispensed.

Dose reductions should be performed according to Table 4.1.3.2:1.

The medication should be taken at approximately the same time each day (± 2 hours) and should be taken without food (i.e. afatinib should be taken at least 1 hour before or at least 2 hours after a meal).

Missed doses of afatinib can be made up if taken within 6 hours of the regularly scheduled time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis should not take a replacement dose.

4.1.3.2. Dose reduction/drug discontinuation scheme for afatinib

In the event of treatment-related toxicities, the treatment with afatinib should be handled according to the schedule in Table 4.1.3.2:1.

Table 4.1.3.2:1 Dose reduction/dose discontinuation scheme

AE Type and grade	Action	Dose reduction/ discontinuation scheme
Grade 4 rash	Permanently discontinue afatinib	Permanently discontinue afatinib
Grade ≥3 interstitial lung disease	Permanently discontinue afatinib	Permanently discontinue afatinib
Grade 4 hepatic impairment	Permanently discontinue afatinib	Permanently discontinue afatinib
Grade ≥3 keratitis	Permanently discontinue afatinib	Permanently discontinue afatinib
Grade 2 left ventricular dysfunction (i.e., new resting ejection fraction of 40-50%; OR a 10-19% drop from baseline)[4]	Pause treatment with afatinib for 14 days and then repeat MUGA scan. If the ejection fraction has resolved to grade 1 or better at the time of the repeat MUGA, study drug will be resumed. If the toxicity has not resolved, afatinib should be permanently discontinued.	If patient was receiving 40 mg, resume treatment at 30 mg[3]. If patient was receiving 30 mg, resume treatment at 20 mg[3]. If patient was receiving 20 mg, discontinue afatinib.
Any symptomatic (grade ≥3) left ventricular dysfunction[5]	Permanently discontinue afatinib	Permanently discontinue afatinib
CTCAE grade ≥2 diarrhea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrheal medication/hydration	Pause treatment with afatinib until toxicity has recovered to CTCAE grade ≤1 or baseline[1]. If patient has not recovered to CTCAE grade ≤1 within 14 days, study treatment should be permanently discontinued[2]	If patient was receiving 40 mg, resume treatment at 30 mg[3]. If patient was receiving 30 mg, resume treatment at 20 mg[3]. If patient was receiving 20 mg, discontinue afatinib.
CTCAE grade ≥2 nausea and/or vomiting persisting for 3 or more consecutive days despite anti-emetic treatment/hydration		
CTCAE grade 2 or grade 3 worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50% from baseline		
CTCAE grade 4 worsening of renal function	Permanently discontinue afatinib	Permanently discontinue afatinib
Any other drug related AE CTCAE grade ≥3	Pause treatment with afatinib until toxicity has recovered to CTCAE grade ≤1 or baseline[1]. If patient has not recovered to CTCAE grade ≤1 within 14 days, study treatment should be permanently discontinued[2]	If patient was receiving 40 mg, resume treatment at 30 mg[3]. If patient was receiving 30 mg, resume treatment at 20 mg[3]. If patient was receiving 20 mg, discontinue afatinib.

[1] Baseline is defined as the CTCAE grade until start of treatment

[2] In the event that the patient is deriving obvious clinical benefit in the opinion of the investigator, but has not recovered within 14 days, the further treatment of the patient will be decided by the lead PI who may consult with the appropriate individuals at BI.

[3] Once a dose reduction is applied, the reduced dose is maintained unless further dose reduction is needed.

[4] Defined according to CTCAE version 4.0, page 109, adverse event denoted as "ejection fraction decreased"

[5] Defined according to CTCAE version 4.0, page 9, adverse event denoted as "left ventricular systolic dysfunction"

Dose reduction should always follow a treatment pause. In the event of a treatment pause, subsequent visits/courses should not be delayed.

In the event of a prolonged (≥7 consecutive days) Grade 2 drug-related event not listed in Table 4.1.3.2:1, which is poorly tolerated by the patient, the treating investigator may choose to pause the medication for up to 14 days to allow the patient to recover followed by a dose reduction according to the schedule in Table 4.1.3.2:1.

In the event of any unrelated adverse events or unrelated serious adverse events, the treating investigator may choose to pause the medication for up to 7 days to allow the patient to recover, but no dose reduction should occur. If the treating investigator chooses to pause the medication for more than 7 days and believes that the patient would derive clinical benefit from continuing medication, the decision to continue medication will be made by the lead investigator who may consult with BI's medical monitor.

4.1.4 Packaging, labelling, and storage

Medication numbers will be unique to each bottle and will be used for tracking purposes only.

4.1.4.1 Afatinib dispensing

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 40, 30, and 20 mg. Tablets will be supplied in HDPE, child-resistant, tamper-evident bottles.

Bottles/boxes will be labelled according to local regulations and will include the following as a minimum;

- Study number (13-0540/ 1200.171)
- Product name: afatinib
- Contents of the bottle (30 tablets)
- Tablet strength (mg)
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical study use only
- A caution statement

Since pill bottles contain #30 tablets, patients will be given two pill bottles on day 1 of the first cycle (to have adequate supply to complete the entire cycle), and two bottles on day 1 of each subsequent cycle. All patients will start with 40 mg tablets and in the event that dose reduction is necessary, the patient will return to the clinic and new medication will be dispensed.

4.1.4.2 Storage conditions

Afatinib must be stored in the original packaging. Film-coated tablets are humidity and light sensitive and therefore bottles must be kept tightly closed. Tablets will be stored at the study site in a limited access area and must be stored in accordance with the instructions on the label.

4.1.5 Drug accountability

Drug supplies, which will be provided to the study sites by Boehringer Ingelheim, will be kept in a secure, limited access storage area under the storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The responsible person must maintain records of the product's delivery to the study site, the inventory at the site, the use by each patient, and the return to the Boehringer Ingelheim or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and study patients. The responsible person will maintain records that document adequately that the patients were provided the doses specified and reconcile all investigational product(s) received from Boehringer Ingelheim. The responsible person must verify that all unused or partially used drug supplies have been returned by the clinical study patient.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, PRECAUTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medications to reverse the actions of afatinib are not available. Side effects of these treatments should be treated symptomatically. Growth factor support will be used following ASCO Guidelines.

The current version of the investigator brochure lists the AEs expected with afatinib. Suggested treatments for diarrhea, nausea, vomiting and rash/acne are described in Section 4.2.3.

During study participation symptomatic treatment of tumor associated symptoms is allowed. Treatment with corticosteroids is allowed. Concomitant medications or therapy to provide adequate care may be given as clinically necessary. All concomitant (non-oncological) medications which are taken between study informed consent and the first follow-up visit should be recorded in the case report form (CRF) with the start and end of treatment dates, the total daily dose, the respective unit and the reason for use.

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD. Study drug should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug should be permanently discontinued and appropriate treatment instituted as necessary.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients may not receive any other anti-cancer treatments while on study (bone-directed supportive therapies such as bisphosphonates or RANKL inhibitors are permitted). Patients cannot have received another anti-cancer chemotherapy or immunotherapy or investigational agent within 2 weeks prior to the first dose of study treatment, and cannot have received radiotherapy within 4 weeks prior to the first dose of study treatment.

4.2.2.2 Restrictions on diet and life style

<u>For afatinib</u>:

Afatinib should be taken without food (i.e. afatinib should be taken at least 1 hour before or at least 2 hours after a meal).

In the event of diarrhea, patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhea.

To prevent skin related adverse events it is currently proactively recommended to avoid intense irradiation with UV light, e.g. sunbathing or visiting a solarium, and to use strict sun

protection during the treatment period of the study. In case of sun exposure a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide, should be used, preferably a thick, alcohol-free emollient cream. Harsh detergents should be avoided.

4.2.2.3 Precautions

Keratitis is a known adverse event associated with afatinib, and it should be used with caution in patients with a known history of keratitis, ulcerative keratitis, or severe dry eye. Although contact lens use is a risk factor for keratitis and ulceration, the use of contact lenses will not preclude patient enrollment to this study.

4.2.3 Concomitant therapy

4.2.3.1 Management of diarrhea following treatment with afatinib

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with afatinib. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide controls diarrhea caused by afatinib. Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating treatment with afatinib.

The recommendations for management are as follows (see also Section 4.2.2.2):

- If any diarrhea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg).

- Oral hydration is essential regardless of severity; appropriate rehydration (1.5 L/m^2/day plus equivalent of actual fluid loss) and electrolyte replacement has to be ensured in the event of CTCAE Grade 2 and Grade 3 adverse events.

- For CTCAE Grade ≥2 diarrhea lasting ≥ 2 days (48 hours) despite adequate antidiarrheal treatment, afatinib must be paused until recovery to CTCAE ≤ Grade 1. Upon recovery, afatinib should be resumed at a reduced dose according to the dose reduction scheme outlined in Section 4.1.3.2.

The occurrence of diarrhea and the outcome of treatment will be recorded in the AE section of the CRF.

If despite optimal supportive care and a treatment pause diarrhea does not resolve to CTC Grade ≤ 1 within 14 days, the patient must not receive any further afatinib treatment.

4.2.3.2 Management of nausea and vomiting following treatment with afatinib

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should be treated according to the recommendation given in Table 4.2.3.2:1.

Table 4.2.3.2: 1 Management of nausea and vomiting

CTCAE Grade	**Antiemetic treatment**
Nausea = grade 0 and Vomiting = grade 0	No antiemetic prophylactic treatment
Nausea = grade 1 and Vomiting = grade 0	Antiemetic treatment if deemed necessary by the investigator
Nausea = grade 2 and Vomiting = grade 0 Nausea = grade 0, 1 or 2 and Vomiting = grade 1 or 2	Antiemetic treatment[1] Pause afatinib treatment if grade 2 vomiting or grade 2 nausea persists for 3 or more consecutive days despite optimal supportive care. Resume treatment when CTCAE grade ≤ 1.
Vomiting ≥ grade 3 or Nausea ≥ grade 3	Antiemetic treatment[1] Pause afatinib treatment until return to CTCAE grade ≤ 1 or baseline[2].

1 Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic
Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference (R06-0986).

2 Baseline is defined as the CTCAE grade at the start of treatment.

After a treatment pause the dose of afatinib should be reduced according to the dose reduction scheme in Table 4.1.3.2:1.

The occurrence of nausea and/or vomiting and the outcome of treatment will be recorded in the AE section of the CRF.

In case of nausea and/or vomiting ≥ CTCAE grade 2, appropriate hydration (1.5 L/m²/day plus hydration deficit) must be ensured.

4.2.3.3 Management of rash following treatment with afatinib

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and to reduce the rash.

The recommendations for management are as follows:

- General/Prevention: see Section 4.2.2.2

- CTCAE Grade 1 rash: mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.

- CTCAE Grade 2 rash: relief from major symptoms caused by CTCAE Grade 2 skin-related adverse events should be achieved by a combination of local and systemic therapies including:

    - Systemic antibiotics (e.g. doxycycline or minocycline, etc.).

    - Topical treatment (e.g. hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream)

    and / or

    - Antihistamines (e.g. diphenhydramine, etc.)

- Oral corticosteroid (low dose and short term, i.e. < 10 days treatment) may be added at the investigator's discretion.

    - Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continued until improvement or resolution to CTCAE Grade ≤ 1. If grade 2 rash persists for ≥ 7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment for up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 4.1.3.2: 1.

- CTCAE Grade 3 rash: may be treated in a manner similar to CTCAE Grade 2 rash. In the event of CTCAE Grade 3 rash, treatment with afatinib should be paused until recovery to CTCAE Grade ≤ 1. Treatment should be resumed at a reduced dose (see Section 4.1.3.2). If CTCAE Grade 3 rash does not resolve to CTCAE Grade ≤ 1 within 14 days of stopping afatinib treatment and despite optimal supportive care, the patient should not receive any further treatment with afatinib.

- CTCAE grade 4 rash: permanently discontinue afatinib. Treatment should be in a manner similar to CTCAE Grade 2/3 rash

4.3 TREATMENT COMPLIANCE

Assessment for compliance will be conducted using pill counting at the end of each cycle. Remaining pills at the end of the cycle will be noted in the patient's research chart and discarded prior to provision of study drug for the subsequent cycle. A pill diary will be used and completed by the study nurse after each cycle.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 End point(s) of efficacy

The first portion of this trial which aimed to determine PFS3 in an unselected population of urothelial cancer patients has been fully accrued, analyzed, and published[24]. Based on those data, the below end points reflect those of the new amendment for this study.

Primary endpoint:

To determine the 6-month PFS rate of molecularly-selected metastatic urothelial cancer patients treated with afatinib who have progressed despite prior platinum-based chemotherapy.

Radiographic assessment of responses will be performed via CT or MRI every 8 weeks until disease progression is observed or until drug intolerability.

Secondary endpoints:

To determine the overall response rate (CR + PR), median progression free survival, and overall survival for the same treated population.

To examine the role of different *ErbB* alterations in determining afatinib activity in urothelial cancer.

Exploratory Endpoints:

To determine the PFS6 rate, overall response rate, and OS among the predefined subset of patients with qualifying alterations exclusive of *EGFR* alterations.

To determine whether tumor EGFR and/or HER2 expression, or, alternatively, whether certain microRNAs, influence 6-month PFS in patients treated with afatinib.

This exploratory endpoint is based on the hypothesis that the level of EGFR and/or HER2 expression may influence drug activity. One study which required expression of either EGFR or HER2 prior to enrollment examined the variability of these markers in patients with refractory advanced/metastatic urothelial cancer[26]. For EGFR, the respective percentages of patients with each expression quartile were 12% (0), 35% (1), 33% (2), and 19% (3). For HER2, the quartile percentages were 23% (0), 32% (1), 37% (2), and 7% (3). Notably, 71%

of patients had high overexpression (defined as 2+ or 3+) of at least one of the targets. Additionally, 22% of patients had high co-overexpression (2+ or 3+ for both EGFR and HER2). The method used for quantifying expression will follow standard commercially developed assays.

Alternatively, studies have suggested that epithelial-to-mesenchymal transition, a cellular development process that is associated with cellular invasion and migration, may confer resistance to EGFR-directed therapy[27,28]. Specifically, in cell line models, expression of the microRNA miR-200 has been shown to induce mesenchymal-phenotype bladder cancer cells to adopt a phenotype resembling their epithelial counterparts, and to simultaneously increase sensitivity to EGFR inhibition[29]. We will therefore consider evaluation of tumor tissue for determination of whether tumor microRNAs like miR-200 have bearing on the 6-month PFS in this study.

Finally, RNA profiling of available tissue may be performed if technically feasible. On a DNA level, specific genomic alterations may be confirmed/investigated post-hoc for scientific purposes (not for eligibility purposes), and overall mutational profiling may be assessed.

5.1.2 Assessment of efficacy

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Safety of afatinib will be evaluated as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 4.0. Safety endpoints include:

- events leading to dose reduction
- events leading to permanent treatment discontinuation
- the overall incidence and CTC criteria grade of adverse events, as well as relatedness of adverse events to treatment
- causes of death

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical

judgement which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction (SAR) if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon in the study population, or an aggregate analysis of specific events occurring at greater frequency than expected.

Unexpected events are those not listed at the observed specificity or severity in the listed adverse event section of the investigator brochure for the product.

ALL SUSARS occurring on this clinical trial must be reported to the FDA by the University of Chicago/IND Holder. Participating institutions that are not the University of Chicago will report SUSARS to the University of Chicago who will then report to the FDA. Refer to Sections 5.2.2.2 - 5.2.2.3 for full reporting guidelines.

Intensity of adverse event

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 in the University of Chicago CRF (eVelos system).

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, MUGA, physical examination, and laboratory test results

Changes in vital signs, MUGA, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

5.2.2.2 Adverse event and serious adverse event reporting

Upon inclusion into the study, the patient's condition is assessed (e.g. documentation of history / concomitant diagnoses and diseases), and relevant changes from baseline are noted subsequently.

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the 28 days follow-up period) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRFs / SAE reporting forms (BI SAE report form or alternatively the CIOMS form/MEDWATCH form).

Serious Adverse Event reporting will be done according to the specific definitions and instructions detailed in Section 5.2.2.3 below.

For each adverse event, the treating investigator will provide the onset date, end date, CTC AE grade, treatment required, outcome, seriousness, and action taken with the investigational drug. The treating investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

Adverse events with onset within first administration of afatinib therapy and 28 days after last administration of afatinib will be considered as on treatment. All AEs, including those persisting after end of study treatment must be followed up until they have resolved or have been sufficiently characterized or the principal investigator decides to not further pursue them.

Serious and non-serious adverse events occurring later than 28 days after last administration of trial drugs will only be reported in case they are considered drug-related or trial (procedure) related.

Deaths (unless they are considered drug-related or trial related) will not be reported as SAE when they occur later than 28 days after last administration of the trial.

5.2.2.3 Responsibilities for SAE reporting

All SAEs occurring on this trial must be reported to the Study Chair/IND Holder, University of Chicago Comprehensive Cancer Center (UCCCC), and Boehringer Ingelheim Pharmaceuticals. Events meeting the additional reporting criteria noted below will be reported to the Institutional Review Board and/or the FDA as applicable.

5.2.2.3.1 Reporting Events to the UCCCC

All serious adverse events and protocol violations/deviations must be reported to the UCCCC Cancer Clinical Trials Office (CCTO) in accordance with the UCCCC Data Safety Monitoring Plan.

All serious adverse events occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UCCCC) Clinical Trials Office (CCTO). The responsible Research Nurse or other designated individual at the treating site

should report the SAE to the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form. Please scan and send via email (preferred) or FAX to:

University of Chicago Phase II CRA General
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-1746
FAX: 773-702-4889

UC CCC Cancer Clinical Trials Office of Quality Assurance
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to both the IND holder and FDA. The responsible Research Nurse or other designated individual at the treating site should also provide a more complete written report using the FDA MedWatch 3500A form/CIOMS form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu, within the timelines specified below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

Participating sites should not forward any adverse event reports directly to the FDA. The UCCCC CCTO will report all events to the FDA as per the current FDA guidelines.

5.2.2.3.2 Reporting Events to the Institutional Review Board

Events meeting current UChicago IRB reporting criteria must be submitted by the principal investigator via the IRB's electronic submission system within **the IRB's designated reporting timeframes**. Details of the IRB's current reporting policy and timelines can be found on their website at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html .

The responsible UChicago research nurse and/or clinical research associate/data manager are responsible for entering the appropriate information into the IRB's electronic submission system and forwarding the submission to the principal investigator for reporting to the IRB.

Events occurring at a participating site should be reported to the local IRB of record according to their policies and procedures.

5.2.2.3.3 Reporting Events to Boehringer Ingelheim Pharmaceuticals

Each site shall report all SAEs and non-serious AEs occurring at the same time and/or which are medically related to the SAE and Adverse Events of Special Interest by fax:

FAX #: 203-837-4329

using the BI SAE report form or alternatively CIOMS/MEDWATCH form with BI cover letter form to the BI Unique Entry Point in accordance with the following timelines:

within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

5.2.2.3.5 Reporting Events to Participating Investigators

It is the responsibility of the assigned CCTO Regulatory Manager on behalf of the IND Holder to notify all participating sites of all unexpected and serious suspected adverse reactions that occur on this clinical trial and which are reported to the FDA as an IND Safety Report (21 CFR 312.32). A copy of the completed Form 3500A (MedWatch) and/or IND Safety Report Narrative will be provided to the responsible Regulatory Manager by the IND Coordinator for distribution to all participating sites.

5.2.2.4 Adverse Events of Special Interest

Although rare, drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators and is considered a protocol-specified significant adverse event. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes are important for patient safety. The following are considered as Protocol-specified significant events:

Hepatic injury defined by the following alterations of liver parameters:

- For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline, an elevation of AST and/or ALT >3 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to this clinical trial protocol.

- For patients with abnormal liver function at baseline, an elevation of AST and/or ALT >5 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to this clinical trial protocol.

Protocol-specified significant events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria - for details please see section 5.2.2.2.

If the investigator determines any protocol-specific significant event is related to study drug, the administration of the study drug must be managed according to section 4.1.3 of the protocol.

5.2.3 Assessment of safety laboratory parameters

Blood samples will be collected at the time points specified in the Flow Chart and analyzed in a laboratory facility at (or close to) the investigational site. Safety laboratory examinations include hematology and biochemistry. In case of neutropenia, blood will be examined as clinically indicated at the discretion of the treating investigator until recovery.

Safety laboratory assessment may be performed according to local practice but must include at least the following parameters:

Hematology	Red blood cell count (RBC), neutrophils, hemoglobin, white blood cell count (WBC) and differential, platelets.
Biochemistry	Sodium, potassium, calcium, magnesium, creatinine, aspartate amino-transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, urea (BUN), PO4. Glomerular Filtration Rate (GFR) will be estimated by the modified Cockroft Gault, MDRD, or CKD-EPI Formula utilizing serum creatinine values

5.2.4 Assessment of other safety parameters

5.2.4.1 Physical examination, performance score

A physical examination will be performed at screening and at the time points specified in the Flow Chart.

A full physical exam serves as a clinical tumor assessment and should include a cardiopulmonary examination and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. Wherever possible the same investigator should perform this examination.

Measurement of height (in cm), body weight (in kg) and body temperature and the evaluation of the ECOG performance score will be performed at the time points specified in the Flow Chart.

5.2.4.2 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by Multi-Gated Acquisition Scan (MUGA) will be assessed at time points specified in the Flow Chart.

5.2.4.3 Vital signs

Vital signs (blood pressure and pulse after 2 minutes supine rest) and temperature will be recorded at the screening visit and at the time points specified in the Flow Chart.

5.3 OTHER

5.3.1 Demographics and history

Demographics (sex, birth date), information on smoking and alcohol history, and baseline conditions will be collected during the screening visit.

The date of first histological diagnosis (month and year may be sufficient) and type of tumor histology will be reported in the CRF. The number and locations of metastatic sites (liver, lung, peritoneum, brain, other) as well as the stage according to the tumor, (lymph) node, metastasis (TNM) classification will be provided as obtained at diagnosis and at the inclusion into the trial. Previous surgery and radiotherapy will be reported.

Previously administered chemo- or radiotherapy will be reported including start and end dates (month and year may be sufficient), the therapy protocol with the number of courses (chemotherapy), total radiation dose and radiation field (radiotherapy) and the best response obtained (complete response, partial response, stable disease, progressive disease, unknown).

5.4 APPROPRIATENESS OF MEASUREMENTS

The RECIST criteria 1.1 to be used for evaluation of tumor response are well established and scientifically accepted. The US NCI CTCAE criteria Version 4.0 are used in the assessment of adverse events in cancer patients. Lesions that have been irradiated as the most recent line of treatment are not eligible as RECIST target lesions.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must be seen to complete the informed consent process in person and to undergo a baseline assessment according to the Flow Chart. After screening and registration, the patient will be seen on Day 1 of treatment initiation, and every 2 weeks during study treatment for the first 12 weeks. After 12 weeks, patients remaining on treatment will be seen in person monthly. *It is permissible and encouraged that patients who a treating physician feels may be at higher than average risk for toxicity from afatinib should be seen at one extra in-person visit, 1 week after starting study therapy (on cycle 1 day 8).*

Radiographic assessment of responses will be performed via CT scans of the chest/abdomen/pelvis every 8 weeks until disease progression is observed or until drug intolerability.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Baseline evaluations are to be conducted within 21 days prior to start of protocol therapy. See the Flow Chart for details of required screening procedures.

6.3. REGISTRATION PROCEDURES

6.3.1 General Guidelines

All eligible patients will be registered centrally by the University of Chicago Clinical Research Associate assigned to the study. All sites should call the CRA to verify availability of a slot. Following registration, patients should begin protocol treatment within the window specified in 6.2.1. Issues that would cause treatment delays should be discussed with the Lead Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The CRA should be notified of cancellations as soon as possible.

6.3.2 Registration Process

Pre-registration for Screening

- All patients must be pre-registered with the UC Phase II coordinator to obtain a screening ID number. This ID number will be used for the screening mutation testing involved on this trial. Please email the UC Phase II coordinator at PhaseIICRA@medicine.bsd.uchicago.edu to obtain this screening number.

Treatment Registration

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the University of Chicago a patient will be registered on study.

When a potential patient has been identified, notify the CRA via phone or email to ensure a reservation on the study. Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

To register a patient, the research nurse or data manager must complete the eligibility/registration form and contact the central study office at the University of Chicago (Phone 773-834-1746) or fax a copy of the completed eligibility checklist, signed Informed Consent, medical history documents, and results from the baseline evaluations (FAX Number 773-702-4889) or email (email preferred) to:

PhaseIICRA@medicine.bsd.uchicago.edu

When registering a subject, the following must occur:

- Confirm that the institution has current IRB approval of the correct version of protocol/consent and has an annual update on file.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the above CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.
- The date the patient is randomized if randomization is involved or receives treatment for the first time will be considered the patient's "OnStudy Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

Data Reporting

Data reporting will be performed utilizing the eVelos electronic data capture system. Prior to study initiation, all participating sites must have eVelos users registered and trained on use of the system. The University of Chicago CRA will provide each site with the applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, you may be required to provide supporting source documentation. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

6.4 After Registration

Biomarker Studies

As exploratory endpoints of this trial, we propose retrospective tumor testing of (1) EGFR and/or HER2 expression status; (2) epithelial to mesenchymal transition states[30]; (3) novel microRNAs[29] since they may relate to response rates in this study; (4) post hoc investigational/confirmatory testing of specific somatic genomic alterations to understand the role of specific alterations in drug sensitivity; and (5) investigation of germline pharmacogenomic determinants that may be associated with drug activity and/or toxicity. These analyses (and the requested research tissues) are separate from those required for study eligibility.

For each registered patient, the enrolling institution will pursue and obtain archival tumor tissue from the patient's primary urothelial cancer surgery. Patients will be asked to consent to release of this tissue during enrollment. For these exploratory biomarker studies, if a patient's tumor is not able to be located, this does not make the patient ineligible for the study, however, full attempts at procurement of this tissue for all enrolled patients is mandatory. The following archival tissue types are needed (one from each below category is needed):

1. 10 unstained slides cut at 5 microns for IHC purposes.

AND

2. Paraffin blocks containing a tumor specimen measuring at least 0.5 cm x 0.5 cm x 100 microns; OR 15-20 additional unstained slides cut at 10 microns; OR 8-10 core needle tissue punches of the tumor region deposited in a microcentrifuge tube.

Tissue samples may be from original diagnosis or biopsy any time prior to first drug treatment, and as long as from a muscle-invasive or higher-stage urothelial cancer specimen (metastatic is permitted). Securely label the specimens with the patient's initials, registration number, and study number (University of Chicago IRB#). Submitted tissues should be sent in a dry container at room temperature, boxed and labeled appropriately.

Additionally, a single peripheral venous blood sample will be collected from each registered patient for the purposes of germline DNA extraction and potential future exploratory pharmacogenomic testing. Whole blood (totaling 10 mL) should be drawn at one timepoint into ONE, 10 mL plastic lavender top tube (i.e. BD catalog # 366643). Whenever possible, this blood draw should occur in conjunction with other standard of care phlebotomy. The tube should be labeled with the patient's ID#, initials, assigned study ID, date and clock time of sample acquisition. The Pharmacogenomic Sample Sheet (APPENDIX 5) should be completed and provided with the samples.

The above samples described in this Section, Section 6.4, should be sent by overnight delivery to:

Attn: Briana Rhodes
Lab: Peter H. O'Donnell (PI)

5841 S. Maryland Ave.
MC 2115
The University of Chicago
Chicago, IL 60637

Please notify Briana Rhodes by e-mail on the day of mailing at:

brhodes@medicine.bsd.uchicago.edu

6.5 Treatment period(s)

A cycle will be defined as 56 days (8 weeks) of continuous daily therapy. Treatment may continue indefinitely in the absence of disease progression or unacceptable toxicity.

6.6 End of study treatment and follow-up period

All patients must be seen for an end of study visit to occur 28 days following their date of treatment discontinuation. Patients will thereafter be followed at a minimum of every 3 months until the patient dies or refuses further follow up, or until three years of follow up are reached.

7. STATISTICAL METHODS

7.1 PLANNED ANALYSES

7.1.1 Primary analyses

This is a continuation of a single-arm phase II study. The previous phase of this study allowed enrollment of patients without respect to genomic marker status ('non-marker selected population'). That prior phase has been fully accrued (total n=23 patients), completed, and has been analyzed separately per the original statistical plan[24].

The present continuation portion of this phase II trial will enroll only patients whose tumors harbor genomic alterations in one or more of the *ErbB* family genes. This will comprise the 'marker-selected population' of this continuation trial.

In a meta-analysis of second-line clinical trials in patients with advanced urothelial carcinoma[31], the overall estimated progression-free survival (PFS) rate at 6 months was 22.6% (95% CI: 18.8%-25.9%), although it varied from 34.6% in patients with no risk factors (liver metastases, ECOG 1+, Hb<10 g/dl, or time from previous chemotherapy <6 months) to 4.9% in patients with 3-4 risk factors. Thus over three-quarters of patients will have disease progression within 6 months, and we propose that PFS at 6 months would be an informative endpoint for assessing drug activity.

For this continuation (marker-selected population) phase, a Simon[31], optimal two-stage design will be employed to assess the primary end point of 6-month PFS rate. The null hypothesis (H_0), a 6-month PFS of <25%, will be considered representative of lack of efficacy of the drug in this biomarker-specific patient population consisting of patients with *ErbB* alterations. The alternative hypothesis (H_A), a 6-month PFS rate of >40%, will be

considered indicative of activity. PFS will be defined as the time from enrollment until disease progression or death from any cause, and will be estimated using the Kaplan-Meier method, although we will follow the last patient entered for a minimum of 6 months to ensure that there is no censoring prior to 6 months. For determination of the PFS curve, patients who are alive and progression-free will be censored as of the date of the last negative evaluation.

For 90% power at one-sided alpha = 0.10, n=72 patients will be needed. Assuming the frequency of having an alteration in any of the four genes is 20%, this will require screening approximately 360 patients. In the first stage, 29 patients will be enrolled and if 7 or fewer are alive and progression-free at 6 months the trial will be terminated for futility. Otherwise an additional 43 patients will be enrolled. At the end of the second stage, if 22 or fewer are alive and progression-free at 6 months the null hypothesis will be accepted and the treatment considered to be of insufficient efficacy, whereas if 23 or more (> 32%) exhibit progression-free survival of 6 months or more the regiment will be considered promising and worthy of further study.

Vinflunine is approved for use in urothelial cancer patients in the second-line setting in Europe[32]. Separately, atezolizumab[3], nivolumab[33], durvalumab[34], and pembrolizumab[5] have recently been FDA approved and/or studied in this setting as well and have shown significant activity despite not showing demonstrable changes in PFS. We therefore contend that our chosen 6-month observed PFS rate of 32% or higher required to consider afatinib promising would compare afatinib very favorably in this disease. This level of activity would warrant consideration of further testing of afatinib in this disease and biomarker subgroup.

We also considered in this statistical plan whether there are any relevant data about progression free survival in the subset of patients with *ERBB* alterations? Our prior data (from the first 23 patients of this trial)[24] is the largest cohort we are aware of reporting PFS data in patients with different types of *ERBB*-altered tumours. However, two other prior studies may be additionally indirectly informative. Powles et al.[23] recently examined 232 patients with metastatic urothelial cancer who had undergone primary platinum-based chemotherapy and were then randomly assigned to lapatinib vs placebo. To be randomized, patients had to have "high expression" of HER1/2 (defined as immunohistochemistry 2+/3+ staining). While genomic alteration status was not reported in this study—making these data only tangentially pertinent to the present question—it is reasonable based on known correlation data between IHC and genomic amplification to assume that the trial would have included a higher portion of patients with true amplification than an entirely unselected metastatic urothelial cancer population. The authors found no difference in PFS between patients randomized to lapatinib (4.5 months) vs placebo (5.1 months). These PFS estimates correlate extremely well with the meta-analysis data that we have cited above (see also Sonpavde et al.[37]—data which showed 4.3-4.5 months as the estimated "PFS" for the immediate post-platinum setting in the absence of treatment). While not directly answering the question of a truly *ERBB*-altered population, the Powles et al. data therefore suggest that PFS is not significantly different in HER1/2-overexpressing patients compared to historical controls.

More relevant are the data from Fleischmann et al.[22] which reported on 150 patients who had undergone cystectomy and were followed for survival. The primary tumours of these patients were assessed for *HER2* amplification. Twelve (12) patients were found to be *HER2* amplified. While PFS data are not reported, it was interestingly noted that overall survival was significantly *poorer* in patients with *HER2* amplified tumours (with an absolute shortening of overall survival by approximately 1 year; p=0.04). It would follow that PFS is also likely to be shorter (tracking with OS) in this genomic population. This would mean that the historical PFS estimate used in our study (which included all urothelial cancer patients notwithstanding genomic status) is, if anything, likely an over-estimate of the actual PFS of patients with *ERBB* alterations. We thus feel that our historical comparator assumptions in this statistical plan in fact thus set a very high bar (perhaps even higher than may be truly present for this genomic population, although the above data are very limited). This means that the success endpoint for detecting an effect of afatinib on PFS is likely very stringent, or, said another way, the above data do not suggest that the study design has an inherent bias in favor of detecting the effect (if anything, the bias is in the other direction).

We would also argue that one of the potential values of our proposed selected cohort-expansion study will be to better define the PFS in this only-recently appreciated population of patients.

Secondly, afatinib treatment in the context of this trial will most likely be used as a "third line" therapy given the advent and FDA approval of immunotherapies in the traditional "second line" setting. We therefore examined recent data on immune therapy-treated patients to ensure that the above PFS estimates remained reasonable.

First, none of the studies which have reported on the impressive activity of immunotherapies in the platinum-refractory setting for urothelial cancer have shown an impact on PFS compared to historical controls[3,38,39]. In fact, even in the landmark phase III pembrolizumab vs cytotoxic chemotherapy study for platinum-refractory patients[5]—which is the only study to show in a prospective, randomized fashion an overall survival benefit for immunotherapy in urothelial cancer—the PFS was not different between the two arms (median 2.1 months in the pembrolizumab arm and 3.3 months in the cytotoxic arm, HR 0.98 [0.81-1.19]; P=0.42). The PFS6 rate in both arms was approximately 26%. These PFS times compare very favorably to the estimates used to define our historical comparator estimate in the above statistical plan. Additionally, in the *NEJM* phase III trial[5], 115 of the 542 (21%) randomized patients were indeed actually receiving the pembrolizumab or comparator cytotoxic chemotherapy in the "3rd line", so the PFS estimates reported above in this paragraph from that trial do reflect the best available data from both "2nd" and "3rd" line populations.

Secondly, Sonpavde et al. recently published cancer progression and survival data for patients in the post-PD-1/PD-L1 setting[40]. Reporting data from 62 patients across 4 institutions, the median time from last PD-1/PD-L1 inhibitor therapy to subsequent therapy (a mark which approximates the "PFS", or the progression-free interval in the absence of ongoing treatment after immune therapy) was 58 (range 14-242) days. Additionally, of the 22/62 patients who received post-PD-1/PD-L1 inhibitor therapy, the median time to progression (on subsequent therapy) was 124 days. Both of these "3rd line" estimates overlap with the confidence

interval for the PFS data from the "second line" meta-analysis that was used for the above statistical assumptions.

These aggregate external data suggest therefore that the statistical assumptions around PFS and PFS6 remain very reasonable and robustly reproducible estimates to use in the above afatinib statistical plan.

Interim Analysis
The interim analysis will be performed when 29 patients have either (a) completed study treatment or (b) have reached the 6 month time point without being removed from study treatment, or when the combination of (a) and (b) reaches 29.

Patients remaining in the study at the time of the interim analysis will continue on treatment and will remain in the study, per the protocol.

Enrollment of new patients will be temporarily suspended after the first 29 evaluable patients (satisfying the above (a) and (b) criteria) are identified, in order to perform the primary interim analysis needed to determine whether to proceed to stage two, unless the data are such that reaching (or not reaching) the first-stage boundary is determinate.

7.1.2 Secondary and exploratory analyses

The overall response rate (CR + PR) will be calculated and reported, in addition to the median progression free survival and overall survival (OS) times for the study population. Median PFS and OS will be estimated along with 90% confidence intervals using the method of Brookmeyer and Crowley[35]. Patients will be followed via phone calls and or medical records review even after coming off treatment for completion of the data for the PFS and OS endpoints. The PFS6, overall response rate, and OS will also be calculated among the predefined subset of patients with qualifying alterations exclusive of *EGFR* alterations.

Exploratory analysis of tumor tissue in all patients will be conducted for determination of whether specific alterations (including investigation/confirmation of any alterations by alternative methods), tumor EGFR and/or HER2 expression status (IHC), epithelial to mesenchymal transition states, novel microRNAs, and/or RNA or DNA profiling have bearing on PFS. This will also include consideration of tumor genomic alterations found during screening via CLIA laboratory testing. We will also examine the rate of liver metastases (at enrollment) in patients reaching the PFS6 endpoint, versus those who do not. Cox regression models will be fit to test for associations with PFS. Additional analyses based on logistic regression modelling will examine associations between variables and partial or complete response.

For the IHC testing secondary analysis, patients with EGFR IHC scores of 2+ and 3+ will be compared against patients with 0 or 1+ EGFR IHC scores for the primary endpoint (PFS). Similarly, patients with HER2 IHC scores of 2+ or 3+ will be compared to those with 0 or 1+ for the primary endpoint. Finally, patients with overexpression of *either* marker (defined as 2+ or 3+ IHC score for either EGFR or HER2) will be compared against those lacking

overexpression for both markers (EGFR and HER2 0 or 1+) for the primary endpoint. Prior exploratory studies have demonstrated this to be a potentially informative stratification[26].

Somatic alteration results generated from the CLIA laboratory reports used for screening in this study will also be compiled and stored indefinitely in a research study database at The University of Chicago for the purposes of future cancer research by the study investigators. This will include all patients who screen for the study regardless of whether they ultimately receive treatment with study drug.

7.1.3 Safety analyses

Safety analyses can occur at any time deemed necessary by the lead investigator or the drug sponsor and must occur at the first interim analysis (29 patients) and at the end of the study. Adverse event rates will be summarized by type, grade, and attribution and descriptive statistics (frequency distributions) generated.

7.2 HANDLING OF MISSING DATA

A modified intention to treat (ITT) analysis will be performed which will include all patients who begin treatment with the drug (i.e., at least 1 dose administered). Thus patients who withdraw from therapy due to adverse events or for any other reason prior to 6 months will be counted as failures with respect to the primary endpoint (PFS). Additional secondary analyses may be conducted excluding patients who discontinued treatment for reasons other than drug toxicity.

8. Informed Consent, Data Protection, Study records

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the responsible Institutional Review Board IRB at each participating institution and the FDA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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

Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records.

A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative. The patient must be informed that his/her personal study-related data will be used by the Principal Investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CRA) or Clinical Quality Assurance auditors appointed by the Principal Investigator, by appropriate IRB members, and by inspectors from regulatory authorities.

Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (a copy of the completed form may be sent to the CCTO and the original should be retained in the site regulatory files)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

Data and Safety Monitoring

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with University of Chicago, Section of Hematology/Oncology standard operating procedures.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo site initiation teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the

conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

8.2 DATA QUALITY ASSURANCE

In addition to the clinical monitoring procedures, the University of Chicago Cancer Clinical Trials Office (CCTO) will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UCCCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements by performing annual quality assurance audits. The CCTO will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UCCCC Data and Safety Monitoring plan.

For institutions who are formal members of the PCCC, the University of Chicago Comprehensive Cancer Center (UCCCC) will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UCCCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory

authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.
- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment must be IRB approved by the institution within 3 months from the date that it was received.
- The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter. The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.
- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

Annual IRB Renewals, Continuing Review, and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

Obligations of the Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all

FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

8.3 DATA REPORTING AND RECORDS

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

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For CRFs all data must be derived from source documents.

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For afatinib, this is the current version of the Investigator's Brochure.

8.4.2 Expedited reporting to health authorities and IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), to the responsible participating site IRB will be done according to local

regulatory requirements. This study will be conducted under an IND held by Peter H. O'Donnell at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder.

9. REFERENCES

9.1 UNPUBLISHED REFERENCES

U03-3218-13 BI Investigators Brochure, Version 19, 12/6/2017

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10. APPENDICES

10.1 APPENDIX 1 ECOG SCALE

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	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
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead.	0	Dead.

10.2 APPENDIX 2 TUMOUR RESPONSE ASSESSMENT ACCORDING TO RECIST 1.1

Response criteria for target lesions

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of a least 5 mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

Overall response

Target lesions	**Non-Target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.3 APPENDIX 3 STUDY REPORT AND PUBLICATION POLICY

10.3.1 Study Report

After completion of the study, i.e. when the study has been concluded in accordance with this protocol and the last patient completed his/her last follow-up visit (last patient out), an integrated clinical and statistical study report containing a complete and detailed analysis and summary of all observations, results and conclusions related to or resulting from the study shall be written by the sponsor-investigator in consultation with the other investigators within twelve (12) months after completion of the study.

The study report shall be compiled in accordance with the ICH-E3 Guideline.

10.3.2 Publication Rules

The primary publication shall be a full publication of the study. If such a full publication is not submitted within twelve (12) months after conclusion of the study, investigator(s) may publish individually in accordance with this Section 10.3.2.

The Principal Investigator will have the unrestricted right to publish on data resulting from the study and will be given the choice to be the first author, or the last author.

The selection and order of the subsequent authors (i.e. author(s) 2.-x.) will be based on (a) the numbers of recruitment, i.e. the number of subjects randomized/enrolled in the study, (b) data quality and (c) significant scientific input to the study, unless otherwise agreed.

For any interim publication(s,) the order of the authors will be determined in accordance with (a) the numbers of recruitment and (b) data quality, after consultation with the Coordinating Investigator.

Any written, oral or audio-visual publication resulting from the study, either in part or in total (abstracts in journals or newspapers, oral presentations, posters, etc.) by investigators and/or their representatives, including publications of experimental substudies, will require pre-submission review by BIPI. BIPI is entitled to delay any publication in order to protect patentable inventions and/or to avoid disclosure of proprietary matters which require protection, including but not limited to, trade secrets and know-how (for details, see contract). Moreover, BIPI has the right to edit or remove confidential information, prior to submission for publication. In general, BIPI will not veto any publication.

For publication(s) of experimental substudies only, co-authorship will be offered to all authors according to their individual contributions, unless otherwise agreed. The Principal Investigator will be given the choice to be the first, or the last author.

The sponsor-investigator shall have the right to publish results of the study in whole or in part for regulatory purposes, unless otherwise agreed.

All publications of the results of the study shall be compiled in adherence to the rules of Good Scientific Practice and the guidelines for publications of clinical Study data as outlined e. g. by editors of the major medical journals.

10.3.3 Registration with clinical registry database

In accordance with the applicable statutory requirements, information about this study will be published with the Clinical Studies Registry of the US National Institutes of Health (ref. to Website clinicaltrials.gov) upon initiation of the clinical study.

10.4 APPENDIX 4

PATIENT REGISTRATION FORM

Afatinib in Advanced Refractory Urothelial Cancer

(UNIVERSITY OF CHICAGO PROTOCOL #: 13-0540/1200.171)

Today's Date: ___/___/____

I.1 Patient Name: _____

I.2 Enrolling institution: _____

I.3 Institutional Medical Record Number _____

I.4 Race (PATIENT must self-record this answer on this form):

- ☐1 American Indian/Alaska Native
- ☐1 Asian
- ☐1 Native Hawaiian or Other Pacific Islander
- ☐1 Black or African American
- ☐1 White
- ☐1 More Than One Race/Other

I.5 Ethnicity (PATIENT must self-record this answer on this form):

- ☐1 Hispanic or Latino
- ☐1 Not Hispanic or Latino

BELOW TO BE COMPLETED BY CENTRAL DATA MANAGEMENT:

I.6 Assigned Study ID Number: _____

10.5 APPENDIX 5

Pharmacogenomic Blood Sample Collection Form

Afatinib in advanced refractory urothelial cancer

(University of Chicago Protocol #: 13-0540/ 1200.171)

Labeling of Samples: Ensure that each tube is labeled with the patient's ID#, initials, study number, date, and time of sample acquisition.

Patient Information (Name, medical record #)	**Receivers Information** Attn: Briana Rhodes Lab: Peter H. O'Donnell (PI) 5841 S. Maryland Ave. MC 2115 The University of Chicago Chicago, IL 60637

LABORATORY REQUISITION FORM for EDTA blood samples

Patient Study ID# _____

Collection date _____ Collection time _____

Completed by _____ email _____ Date _____

Samples collected

To be completed by person collecting		**To be completed by receiving lab**		
expected specimen	# of specimens included	# of specimens received	Comments	Receiver's initials/date
ONE 10mL lavender top EDTA tube				

DNA isolation (to be completed by receiving lab upon DNA isolation)

Date	mL blood	barcode	location	ng/uL	A260/A280

Comments