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Protocol PI	Mehrad Adibi
Department	Urology
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Tolerability and Activity of Neoadjuvant Infigratinib, an Inhibitor of FGFR, in Upper Tract Urothelial Carcinoma

Investigational Product: Infigratinib

Phase of Development Phase 1b

Investigator: Dr. Mehrad Adibi

LIST OF ABBREVIATIONS and definition of terms

Abbreviation	Term/Definition
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvic transaminase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AUA	American Urological Association
AUC_{ss}	area under the concentration-time curve over the dosing interval (24 hours) at steady-state
BCRP	breast cancer resistance protein
BGJ398	infigratinib
BICC1	bicaudal c homolog 1
BOR	best overall response
cfDNA	cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent (oral) clearance
C_{max}	maximum observed plasma concentration after drug administration
C_{min}	measured concentration at the end of a dosing interval
CR	complete response
CRO	contract research organization
C_{ss}	average plasma concentration at steady-state
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome p
CYP3A4	cytochrome P450 family 3 subfamily A member 4
CyTOF	cytometry by time-of-flight
DEB-TACE	drug eluting bead-TACE
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation	Term/Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ESMO	European Society of Medical Oncology
FAX	facsimile
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
FGFR	fibroblast growth factor receptor
FGFR1	fibroblast growth factor receptor 1
FGFR2	fibroblast growth factor receptor 2
FGFR3	fibroblast growth factor receptor 3
FGFR4	fibroblast growth factor receptor 4
FGR3	fibroblast growth factor receptor 3
FMS	Feline McDonough Sarcoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous

Abbreviation	Term/Definition
K-M	Kaplan-Meier
KMT2C	lysine methyltransferase 2C
KMT2D	lysine-specific methyltransferase 2D
KMT6A	lysine N-methyltransferase 6A
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen activated protein kinase kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NCCN	National Comprehensive Cancer Network
nM	nanomolar
NUx	Nephroureterectomy
N0	No cancer in nearby lymph nodes
OC	operating characteristics
ORR	overall response rate
OS	overall survival
OTC	over the counter
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PHI	protected health information
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	pharmacokinetics
PR	partial response
QD	once a day
QOL	quality of life
QTcF	QTc corrected by Fridericia's formula
R_{acc}	accumulation ratio calculated as C_{min} steady-state/C_{min}
RBC	red blood cell
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Term/Definition
RFS	recurrence-free survival
RNA	ribonucleic acid
RNAseq	Ribonucleic acid sequencing
RPTD	recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
TACE	transarterial chemoembolization
TCGA	The Cancer Genome Atlas
TdP	Torsades de Pointes
t_{max}	time at which the maximum observed concentration (C_{max}) occurs
TMP/SMX DS	trimethoprim and sulfamethoxazole
TP53	tumor protein p53
UCC	urothelial cell carcinoma
ULN	upper limit of normal
UNK	unknown
URS	Ureteroscopy
UTMDACC	University of Texas MD Anderson Cancer Center
UTUC	Upper tract urothelial carcinoma
Ux	Ureterectomy
WBC	white blood cell
WOCBP	woman of childbearing potential
ypT0	complete pathologic response after treatment
ypT1	pathologic superficial invasion after treatment

1. SCHEDULE OF ASSESSMENTS

	SCRE E NI N G PHAS E	TREATMENT PHASE				FOLLOW UP PHASE	
VISIT/CYCLE	**SCREENING[a]**	**CYCLE #1**	**CYCLE #2**	**PRE-OP/ SAFETY VISIT**	**SURGERY**	**POST-OP FOLLOW-UP**	**1-YEAR FOLLOW-UP**
Scheduling window (days)	**-28 to -1**	**1**	**29(±7)**	**57 (±14)**		**30 post-op (±14)**	**365 post-op (±30)**
Informed Consent	X						
Eligibility Criteria	X						
Medical History	X						X
Physica l Examination	X	X		X			X
Vita l Signs	X	X	X	X		X	X
URS/Tumor Mapping	X				X		X[b]
Nephroureterectomy					X		
Surgica l Specimen Assessment/Tumor Ma pping	X				X		
Ophthalmic Assessment	X		X			X[d]	
Sa fety Laboratories[c]	X	X	X	X		X	X
Urina lysis	X	X	X	X		X	
Pregna ncy Test	X	X	X	X		X	
12-lea d ECG	X			X			
Echocardiogram	X						
AE Assessment	X	X	X	X		X	
Concomitant Meds	X	X	X	X	X	X	
EORTC QLQ-C30 QOL Questionnaire	X			X		X	
Drug Dispensing		X	X				
Drug Accountability			X				
Blood for Correlatives	X			X		X	
Urine for Correla tives	X			X		X	
Tissue for Correlatives	X				X		

Abbreviations

a. Baseline/screening assessments that are conducted within 3 days prior to first treatment can be used to satisfy the Day 1 requirements. Every effort must be made to follow the schedule outlined.
b. CT scan and cystoscopy (+/-URS)
c. Blood draw (phosphate level testing only) on Day 14 (+/-7 days)
d. as per physician discretion

2. BACKGROUND

Upper tract urothelial carcinoma (UTUC) is typically considered similar as bladder urothelial cancer just occurring upstream in the ureter or renal pelvis, but there are unique molecular and clinical aspects that differentiate it from its more common counterpart. Unique aspects of UTUC include causation by exposure to aristolochic acid (found in many eastern herbal remedies and accounting for the high rates in the East), high rates of microsatellite instability, strong predisposition in those with Lynch syndrome, and high rates of FGFR3 mutations.

Generally, treatments are allocated based on biopsy showing low grade versus high grade disease. Treatments for those with low-grade disease include endoscopic management only, which allows preservation of kidney function but is associated with multiple procedures and high rates of recurrence. Endoscopic treatment of UTUC is often imperatively needed to avoid placing older patients on dialysis, or in those with low-grade, low-volume disease who wish to retain their kidney and avoid major surgery. Limitations of endoscopic management include the need to perform multiple procedures in staged fashion, an inability to manage large volume disease, and a 30-80% recurrence rate. No standard adjuvant therapy exists in this population although many, including us, have tried topical therapies with variable success rates of 40-70% RFS. The standard accepted treatment however is surgery with nephroureterectomy or ureterectomy (NUx/Ux), which creates or worsens existing renal insufficiency in many cases, and is associated with high complication rates given the typically elderly population. Ureteroscopic (URS) management is an option that can preserve the kidney but is associated with significant recurrence rates.

Patients with high-grade disease are preferentially treated with neoadjuvant chemotherapy followed by NUx/Ux with lymph node dissection, or initial NUx/Ux followed by adjuvant chemotherapy. Reductions in kidney function limit the effective delivery of adjuvant therapy. Based on our seminal work showing significant downstaging and improved survival, the first intergroup prospective trial for this disease showed that the majority of patients had downstaging to ypT1 or less with a 14% ypT0N0 rate (Censits-Hoffman J et al, AUA 2018). As one of the highest recruitment sites for this trial, however, we noted a 50 -70% screen failure rate for this population, rendering a significant portion of patients ineligible. Thus, for both low and high risk patients, there are still major unmet needs.

Recent genomic studies indicate a high rate of FGR3 mutations in patients with UTUC. We reported an integrated, comprehensive genomic study on UTUC, using whole exome sequencing, RNAseq, and protein expression. These data confirm that the most common mutation in UTUC occurs in FGFR3 (74.1% prevalence for the entire cohort of 31 patients). Low-grade UTUC tumors were associated with a 92% rate of FGFR3 mutations, and, more interestingly, high-grade with a 60% rate of FGFR3 mutations, much higher than is seen in bladder cancer (19% in TCGA bladder cohort, if all somatic mutations, fusions, and amplifications are counted), and largely consistent with another UTUC genomic study from Memorial Sloan Kettering. Other mutations in order of decreasing f requency were KMT2D, PIK3CA, TP53, KMT2C, and KMT6A. Mutations of other FGFR subtypes were identified at a much low rate. Expression profiling revealed 4 subtypes that do not exactly match the subtypes described for bladder cancer, with 2 of the 4 subtypes having 100% rate of FGFR3 mutations but with varying clinical correlates between these 2 subtypes.

The emerging data from infigratinib, an inhibitor of FGFR1-3, showed a well-tolerated drug with activity against tumors with FGFR alterations. This represents a unique opportunity to study the tolerability of this compound in those without metastatic disease but who have a great need for therapeutic options, and also provides an opportunity to study the inhibition of FGFR-related pathways in UTUC. In a recently published study (Pal S et al, Cancer Discovery 2018) in patients with incurable urothelial cancer, the most common adverse events were asymptomatic, reversible laboratory derangements: hyperphosphatemia (46%), elevated creatinine (42%), fatigue (37%), constipation (37%), anemia (36%) and decreased appetite (33%). The most common grade 3/4 AEs were hyperlipesemia (10%), and fatigue, hypophosphatemia, and palmar-plantar erythrodysesthesia each at 7%. The current proposal involves patients with localized and locally advanced disease, who may have a different tolerability profile as well as different motivations to pursue novel therapeutic options.

Given its relatively low serious adverse event profile, the high rates of FGFR3 mutations in UTUC, and the major unmet needs for this disease, sufficient rationale exists to further study its activity in UTUC. We propose a study in patients with localized/locally advanced UTUC in order to further understand tolerability and biologic consequences of FGFR inhibition with a biomarker-informed neoadjuvant study, which could help inform a future phase 2 e fficacy study in this population.

2.1. Overview of Disease Pathogenesis, Epidemiology and Current Treatment

2.2. Overview of Infigratinib

Infigratinib is an orally bioavailable, potent and selective inhibitor of FGFRs 1-3, which has demonstrated anti-tumor activity in preclinical *in vitro* and *in vivo* tumor models harboring FGFR genetic alterations (data on file). Infigratinib belongs to the pyrimidinyl aryl urea chemical class and its chemical name is 3-(2,6-Dichloro-3,5- dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1methylurea phosphate(1:1).

Please refer to the Investigator's Brochure for additional information on infigratinib.

2.3. Preclinical Experience with Infigratinib

At the cellular level, infigratinib selectively inhibits the kinase activity of FGFR1, FGFR2 and FGFR3, as measured by inhibition of receptor autophosphorylation, with half maximal inhibitory concentration (IC_{50}) values of 3 to 7 nM for FGFR1, FGFR2 and FGFR3. Infigratinib is less selective for FGFR4, with an IC_{50} of 168 nM. In cellular kinase selectivity assays, the most potently inhibited kinases, in addition to the FGFRs, were vascular endothelial growth factor receptor 2 and FMS-related tyrosine kinase 1, with IC_{50} values of 1510 nM and 1591 nM, respectively (data on file).

Consistent with inhibition of FGFR autophosphorylation, infigratinib inhibits FGFR downstream signaling and proliferation of human cancer cell lines harboring genetic alterations of the FGFRs. These include, among others, lung and breast cancer cell lines with FGFR1 gene amplification, gastric cancer with FGFR2 gene amplification, endometrial cancer with FGFR2 mutations and bladder cancer with FGFR3 mutations or FGFR3 translocations (Wesche et al., 2011; Guagnano et al., 2012; Konecny et al., 2013).

In vivo, infigratinib is widely distributed to tissues in the rat. A battery of *in vivo* safety pharmacology studies in rats and dogs did not reveal any effects on central nervous or respiratory systems and on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, infigratinib did lead to increases in serum fibroblast growth factor 23 and serum phosphorous associated with partially reversible ectopic mineralization (kidney, lung, vascular and digestive systems) along with largely reversible changes in renal function parameters and bone growth plate thickening / retention of the primary spongiosa in rats (≥ 10 mg/kg/day) and dogs (≥ 10 mg/kg/day). These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

The no observed adverse effect level in the dog and rat was 1 mg/kg.

2.4. Clinical Experience with Infigratinib

2.4.1. Clinical Pharmacokinetics and Phase 1 Data

The pharmacokinetics (PK) of infigratinib and its active metabolites have been evaluated following single and repeat daily doses in a phase 1 study (CBGJ398X2101).

Following a single dose, median T_{max} was approximately 2-3 hours. Infigratinib had a relatively short median elimination half-life ranging from 2.69 to 5.71 hours on Day 1. Despite the relatively short half -life on Day 1, accumulation was observed with daily dosing at doses ≥ 60 mg, likely due to auto-inhibition of CYP3A4 mediated clearance pathways (data on file). Mean accumulation ratio (R_{acc}) ranged from 3 to 8 on Days 15 and 28. The interpatient variability was high for infigratinib.

In the single agent, first-in-human phase 1 study (CBGJ398X2101), infigratinib was evaluated at 9 different dose levels and 3 different dose schedules, ranging from 5 mg/day to 150 mg/day. Eight dose levels were administered on the once daily continuous 28-day cycle schedule, and one dose level was administered on a twice a day continuous 28-day cycle schedule. One subject at 100 mg experienced Grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation, 1 subject at 125 mg daily experienced hyperphosphatemia, and 2 subjects at 150 mg experienced Grade 1 corneal toxicity (1 subject) and Grade 3 ALT and AST elevation (1 subject). The dose of infigratinib 125 mg once daily continuously was declared as the maximum tolerated dose (MTD).

While dose levels of 100 mg QD and higher were tolerated by subjects, the majority of subjects experienced reversible hyperphosphatemia, which led to study drug interruptions (data on file). An evaluation of the drug administration records for subjects prior to receiving prophylactic phosphate-lowering therapy indicated that the median time until first dose interruption was approximately 22 days and the median duration of interruption was 7 days. This observation led to the introduction of an expansion arm to evaluate the administration of 125 mg QD on a 3 week on (21 days) / 1 week off (7 days) schedule in 28-day cycles. Subjects treated with this alternative dosing schedule required less dose interruption (n=24, 49.0%) compared with subjects treated with 125 mg continuously (n=40, 70.2%). Thus, infigratinib 125 mg once daily on a 3 weeks on/1 week off schedule was declared as the recommended phase 2 dose (RPTD).

In the dose escalation cohort of 92 subjects, no complete response (CR) was observed, and 4 subjects had partial response (PR) (1 subject at 100 mg; 3 subjects at 125 mg continuous dose).

Of the 173 subjects treated at the 125 mg continuous or intermittent schedule, CR was observed in 2 subjects (1.2%), and 22 subjects (12.7%) had PR. The ORR (95% confidence interval [CI]) and disease control rate (95% CI) were 13.9% (9.10, 19.94) and 49.1% (41.47, 56.83), respectively.

The median PFS for all subjects treated at the MTD/RPTD was 3.12 months (95% CI: 2.10, 3.65 months).

Please refer to Investigator's Brochure for more details regarding phase 1 studies and pharmacokinetics.

2.4.2. Clinical Safety

The majority of Study BGJ398X2101 patients (99.0%) evaluable f or safety experienced at least one AE, with a Grade 3/4 AE reported in 58.7%, regardless of study treatment relationship. The incidence of Grade 3/4 AEs was similar at the MTD (52.6%). The majority of these patients (95.7%) experienced at least 1 AE suspected to be study treatment related, with Grade 3/4 AEs suspected to be study treatment related reported in 38.0%. The incidence of Grade 3/4 AEs suspected to be study treatment related (38.0%) was similar at the MTD (31.6%).

The most common AEs (occurring in ≥ 30% of all patients, all grades), regardless of study treatment relationship were: hyperphosphataemia (65.4%), constipation (39.9%), decreased appetite (37.5%), fatigue (36.1%), stomatitis (34.1%), and nausea (32.2%). Th e most common AEs suspected to be study treatment related (occurring in ≥ 30% of all patients, all grades) were: hyperphosphatemia (63.5%) and stomatitis (33.7%).

The most commonly reported Grade 3/4 AEs (in ≥4% of all patients), regardless of study treatment relationship were: hyperlipasaemia (6.7%), hypophosphatemia (6.3%), ALT elevation (5.3%), hyperphosphatemia (4.8%), and fatigue (4.8%). The most frequently occurring Grade 3/4 AEs suspected to be study treatment related (in ≥4% of all patients) were: hyperlipasaemia (5.8%), hyperphosphatemia (4.8%), and ALT increased (4.8%).

A total of 57 deaths (27.4%) occurred during the study, and most of these deaths were due to disease progression (24.0%). Of the total deaths, 11.1% were on-treatment deaths; of these, 8.6% patients died due to disease progression, 2 patients died due to sepsis, and 1 patient each died due to respiratory failure, cardiac arrest, and unknown reason.

At least one SAE (occurring in ≥5% patients) of any grade, regardless of study treatme nt relationship, was reported in a total of 37.5%, with a similar incidence reported at the MTD (40.4%). SAEs suspected to be drug-related were reported in 8.6% of patients. The most commonly reported SAEs, by preferred term (occurring in ≥5% patients) were: general physical health deterioration (2.9%); pneumonia (2.9%); vomiting (2.9%); dyspnoea (2.4%); and, hypercalcaemia (2.4%).

Adverse events leading to study drug discontinuation were reported in a total of 14.4%. Most commonly reported AEs leading to discontinuation of study drug, in all patients, by preferred term were: visual impairment, hypercalcemia, hypercreatininaemia, hyperlipesaemia, and palmar-plantar erythrodysaethesia syndrome in 1.0% each. Twenty-one patients (10.1%) discontinued treatment due to AEs that were suspected to be related to study treatment. The common suspected AEs leading to study treatment discontinuation were: visual impairment, hypercalcemia, hypercreatininaemia, hyperlipasaemia, and palmar-plantar erythrodysaethesia syndrome in 1.0% each.

AEs requiring dose interruption or reduction occurred in 68.3% of patients. The most common AEs (incidence ≥ 10%) requiring dose adjustment or temporary in terruptions regardless of study drug relationship were hyperphosphatemia (28.8%) and hypercreatininaemia (15.9%).

Overall, Grade 3 hematology abnormalities were reported in 13.9%, of which, two SAEs of anemia were reported in 2 patients (one patient had Grade 2 anemia and the other had Grade 3 anemia). New or worsened Grade 4 hematology abnormality of lymphocytes decrease was reported in 1.5% of patients.

Eye-related AEs were reported in a total of 44.7% of patients. Of these, AEs suspected to be study treatment related were reported in 33.7%. There was one Grade 2 SAE of keratitis reported which was suspected to be treatment related and led to study drug discontinuation (BGJ398X2101 Clinical Study Report; Pal et al 2018).

Please refer to the Infigratinib Investigator Brochure for additional safety information.

2.4.3. Clinical Efficacy

Efficacy data for all patients in the dose escalation and dose expansion parts of Study BGJ398X2101 are available in the Investigators Brochure. The following efficacy data presented are for study expansion part patients with UCC.

Arm 4 of the expansion part of Study BGJ398X2101 included 67 patients with advanced/metastatic UCC with FGFR3 mutations or FGFR gene fusions who had either progressed on or were intolerant of platinum-based chemotherapy, or had contraindications to platinum-based chemotherapy. Permitted FGFR3 mutations included mutations in exon 7 (R248C, S249C), exon 10 (G372C, A393E, Y375C), or exon 15 (K652M/T, K652E/Q). Permitted FGFR3 gene fusions included, but were not limited to the FGFR3-TACC3 fusion. Patients were treated with oral BGJ398 125 mg/day for 21 days followed by 7 days without treatment as 28-day cycles.

All 67 patients were evaluable for response. Seventeen patients (25.4%) had responses (1 CR and 16 PR). Forty-three patients (64.2%) had disease control (CR + PR + SD). Sixteen patients (23.9%) had progressive disease and eight patients (11.9%) had an indeterminate response. One patient with an indeterminate response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria actually had a pathologic complete response; however, due to changing imaging modalities between assessments, the response was reported as unknown. The patient had primary bladder cancer and a histologically confirmed metastasis in the humerus. During BGJ398 treatment, the patient had surgical resection of a suspected

pathologic fracture of the humerus. Histologic assessment revealed no evidence of residual disease (BGJ398X2101 Clinical Study Report; Pal et al 2018).

Please refer to the Infigratinib Investigator Brochure for additional efficacy information.

2.5. Rationale

2.5.1. Study Rationale and Purpose

Given the relatively low serious adverse event profile of Infigratinib, the high rates of FGFR3 mutations in UTUC, and the major unmet needs for this disease, sufficient rationale exists to further study its activity in UTUC. We propose a study in patients with localized/locally advanced UTUC in order to further understand the tolerability and biologic consequences of FGFR inhibition with a biomarker-informed neoadjuvant study, which will help inform a future phase 2 efficacy study, as well as a phase 3 adjuvant study in this population.

2.5.2. Rationale for the Study Design

This neoadjuvant, window of opportunity trial will allow the evaluation of tolerability by a drug previously exposed only to metastatic patients. In the process, we also have an opportunity to study response rates of UTUC and immunologic consequences of FGFR3 inhibition. Arguments supporting this trial are: 1) A strong scientific rationale with an obligation to study this drug given the very high rates of FGFR3 alterations in this population, 2) an unmet clinical need, and 3) supportive Phase 1 data.

2.5.3. Rationale for Dose and Regimen Selection

In this study, subjects will receive 125 mg QD of infigratinib on a 3 week on (21 day) /1 week off (7 day) schedule in 28-day cycles, for a total of 2 cycles. This dose level and regimen is based on experiences from previous phase 1 and 2 trials.

OBJECTIVES AND ENDPOINTS

2.6. Objectives

The **primary objective** is to evaluate the tolerability of infigratinib in patients with low-grade and high-grade platinum ineligible UTUC.

The **secondary objectives** are to:

- Assess tolerability in those with GFR 30-49
- Evaluate the objective response rate (CR+PR) of infigratinib after 2 cycles in UTUC with and without FGFR3 alterations
- Correlate tumor tissue FGFR3 alteration (presence/absence, alteration type, and clonal status) with response and occurrence/severity of AEs such as hyperphosphatemia

- Evaluate, bladder and local/distant recurrence within 12 months in those undergoing NUx/Ux and upper tract, bladder, and local/distant recurrence within 12 months in those undergoing endoscopic management.
- Evaluate renal function pre-treatment and after two treatments.
- Evaluate patient-reported quality of life (QOL) outcomes during treatment.

The **exploratory objectives** are to:

- Explore intra-tumor heterogeneity, gene expression profiles, and changes in tumor microenvironment using single cell RNA sequencing (scRNA-seq) and CyTOF pre and post treatment to identify potential mechanisms of response and/or resistance, and correlation with the occurrence/severity of AEs.
- Explore urinary/upper tract washing FGFR3 alterations as potential biomarker for detection and response
- Explore cfDNA for detection of FGFR3 alterations and as a predictor of response

2.7. Endpoints

The primary endpoint is the proportion of patients who are not able to complete treatment due to excessive toxicity. Toxicity will be tabulated by type, frequency, and severity of AEs and serious AEs (SAEs), laboratory abnormalities, and other safety findings.

The secondary endpoints are:

- Percentage of patients achieving a point in time objective response (either complete or partial response [CR or PR]) after 2 cycles of infigratinib. Tumor mapping will be performed from the endoscopic evaluation (after any biopsies) and this will be used to compare to pathologic (NUx/Ux cohort) or ureteroscopic (endoscopy cohort) findings in order to determine responses.
- Tumor mapping will be performed based on endoscopic findings, noting location, number of tumors, tumor architecture, and location of biopsies; and will again be performed during pathologic evaluation again noting size, location, number of tumors, architecture, and absence of tumor at any previously identified tumor. A difference of 3mm will be considered within error of measurement.
- Mutational analysis will be performed on FFPE tumor tissue using a comprehensive mutation panel (T200.2) which we have used in prior studies and includes all previously identified UTUC mutations, including all relevant FGFR3 alterations including hot spots, copy number variations and fusions. Blood collected at baseline will be used as germline source.
- All analyses will be performed on patients stratified as having or not having FGFR3 alterations. Descriptive statistics will be used to summarize various clinical parameters.
- The same methods will also be used to explore the association of AEs such as hyperphosphatemia with response.
- Percentage of patients with no evidence of disease 12 months after surgery

- Changes in patient reported QOL outcomes will be measured using a validated questionnaire (EORTC QLQ-C30 v3), administered at 3 time points: 1. enrollment (after enrollment and before first dose), 2. after completion of 2 cycles and prior to surgery, and 3. at 1 month postoperative check.

The exploratory endpoints are:

Tumor Studies:

- Single cell (sc)RNAseq will be performed on fresh frozen tumors using 10x Genomics platform. Tumor cell heterogeneity, FGFR3 gene expression, and tumor microenvironment will be profiled. All bioinformatics data analysis will be performed in the MD Anderson Genomics core as part of the Rare Tumor Initiative Program (2014-0938)
- Multiplex immunohistochemistry will be performed using FFPE tissue (biopsy and final pathologic specimen) and undergo interrogation for immunologic studies by the MD Anderson Rare Tumor Initiative Program. For patients with a complete response without residual tumor, the bed of the largest pretreatment tumor (based on tumor map) will be used for immune studies.
- Tissue prioritization: Given the potentially limited biopsy samples, use of biopsy and pathologic tumor tissue will be prioritized in the following order and sources: 1. Mutational analysis (FFPE), 2. RNAseq (fresh fozen), 3. TMA (FFPE).

Biomarkers:

Voided urine will be collected preferentially but will be substituted with selective upper tract washings when voided urine is not available or insufficient. Urine and blood will be collected at 3 time points (pretreatment/enrollment, after completion of infigratinib treatment/preoperatively, and 30 days postoperatively). Urine processing follows established standard operating procedures. Samples are stored at -80^{o}C and then sent to Fox Chase Cancer Center for further analyses (Dr. Phil Abbosh laboratory, with whom we have an existent collaboration and MTA). DNA is isolated from the urine sample and DNA is checked for quality, typically yielding several micrograms of high molecular weight DNA. DNA is also isolated from PBMC prior to initiation of therapy to use as a germline reference sample. DNA from germline and pre/post-treatment/post-op time points are subjected next generation sequencing using the HaloPlexHS platform with a targeted depth of 1000X covering 54 well characterized cancer genes. These genes are enriched in patients with urothelial carcinoma (including FGFR3). HaloPlexHS uses pre-amplification single molecule tags to filter taq errors occurring during PCR, thus greatly enhancing the power to detect rare alleles. In preliminary experiments, our approach was validated to be highly sensitive and accurate, detecting >60% of tumor tissue mutations in the urine and identifying additional mutations in the urine that a

re not seen in tissue. Urine will be characterized for FGFR3 hotspots or other missense variants and we will track their variant allele frequency in longitudinal samples. Presence of point mutations in the pre-treatment urine will be correlated with pathological response as an a priori predictive biomarker. Separately, we will also correlate clearance of all pre-treatment

mutations after treatment with infigratinib and after surgery with pathologic response as a post hoc biomarker. Correlation will be determined using Fishers exact test for both analyses.

Cell-free DNA (cfDNA):

To explore the association of cfDNA with response, we will collect blood at pretreatment/enrollment, post-treatment/preoperatively, and 30 days postoperatively (30mL each time point). These samples will be processed and stored until tumor studies are completed and results available. Of all patients identified as having tumor FGFR3 alterations, 5 will be randomly selected to have their baseline cfDNA assayed; if 3 or more are found to have detectable FGFR3 alterations, then up to 5 more patient baseline samples will be run. Those found to have detectable baseline FGFR3 alterations in their cfDNA will have their second time point assayed. These results will be correlated to disease burden, pathologic findings, disease grade, stage, objective response, and immune correlates. For cfDNA we will leverage the availability of a 70-Gene Liquid Biopsy Panel (LBP-70). The validated next generation sequencing (NGS)-based panel will be run in the MD Anderson Department of Pathology and Laboratory Medicine. Peripheral blood is collected into Streck tubes designed to reduce admixture of circulating cfDNA with cellular DNA from blood cells during transport. The NGS-based panel is designed to detect single nucleotide variants (SNVs) and small insertion-deletions (Indels) in all 70 genes included in the panel. In addition, amplifications (copy number variants; CNVs) and fusions (translocations) involving selected genes can also be detected. Specifically in regard to this study, the panel is able to detect mutations/indels, amplifications, and fusions of FGFR3. The comprehensive liquid biopsy test utilizes molecular barcode technology and sophisticated error detection algorithms to allow a sensitive and accurate detection of low level mutations.

3. INVESTIGATIONAL PLAN

3.1. Overall Study and Correlative Design

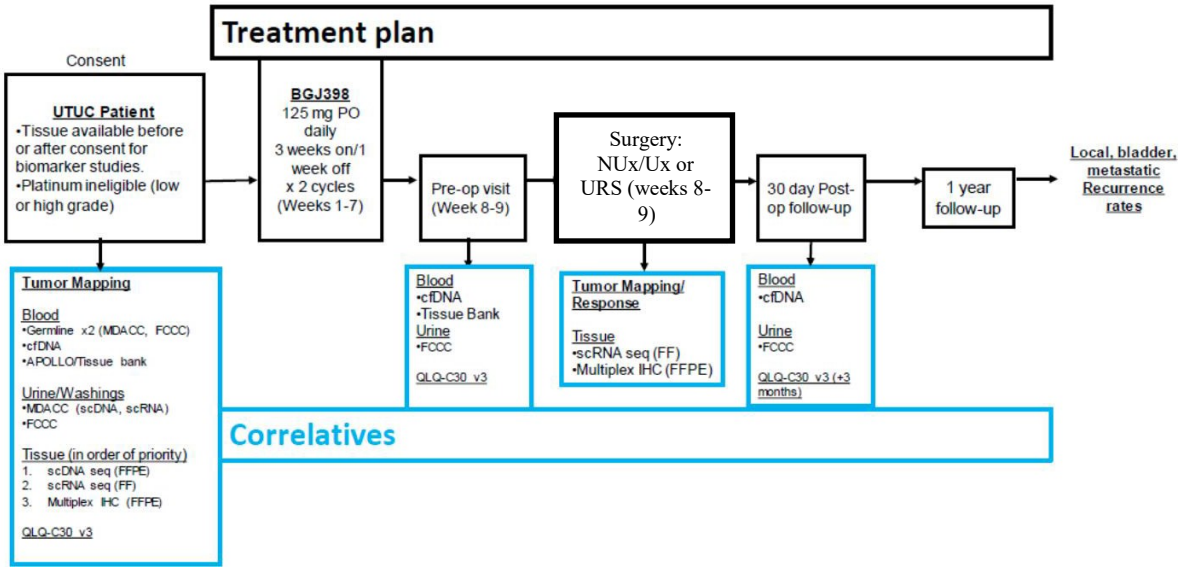


Figure 1: Study Design. Top row shows the clinical design, bottom row the correlative data and tissue collected.

4. STUDY POPULATION

4.1. Inclusion Criteria

1. Low grade UTUC, or high grade UTUC and not eligible for cis-platin neoadjuvant chemotherapy either due to medical comorbidities (eg, cardiac dysfunction, hearing loss, GFR<50), or based on <49% risk prediction of non-organ confined disease by clinical nomogram (PetrosF et al Urol Oncol 2019 Apr;37(4):292).
2. Undergoing: A) Nephroureterectomy or ureterectomy, or B) ureteroscopic management
3. Have adequate pre-treatment biopsy tissue available for mutational analysis, as determined by the study pathologist, prior to enrollment. Any biopsy of index UTUC tissue available within 8 weeks of enrollment may be used. Patients with recurrent low grade UTUC can have tissue used within 12 weeks of enrollment at the PIs discretion.
4. Calculated or measured creatinineclearance ≥30 mL/min.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
6. Are able to read and/or understand the details of the study and provide written evidence of informed consent as approved by IRB/IEC.
7. Have recovered from AEs of previous systemic anti-cancer therapies to baseline or Grade 1, except for alopecia.
8. Are able to swallow and retain oral medication.
9. Are willing and able to comply with scheduled visits, treatment plan and laboratory tests.
10. f a woman of childbearing potential (WOCBP), must have a negative pregnancy test within 7 days of the first dose of study drug. A woman is not of childbearing potential if she has undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she is post-menopausal and has had no menstrual bleeding of any kin d including menstrual period, irregular bleeding, spotting, etc., for at least 12 months, with an appropriate clinical profile, and there is no other cause of amenorrhea (e.g., hormonal therapy, prior chemotherapy).

    WOCBP and males whose sexual partners are WOCBP must agree to use barrier contraception and a second form of highly effective contraception (Clinical Trials Facilitation Group, 2014) while receiving study drug and for 3 months following their last dose of study drug. Alternatively, total abstinence is also considered a highly effective contraception method when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Sexually active males must use a condom during intercourse while taking drug and for 3 months after the last dose of the study drug and should not father a child during this period. A condom is required to be used also by vasectomized men as well as

during intercourse with a male partner to prevent delivery of the drug via seminal fluid.

4.2. Exclusion Criteria

1. Have a history of another primary malignancy within 3 years except: a. adequately treated in situ carcinoma of the cervix, non-melanoma carcinoma of the skin, b. any other untreated cancer deemed by treating physician to be at low risk for progression during the study period (such as low or intermediate risk prostate cancer), c. curatively treated malignancy that is not expected to have recurrence or require treatment during the course of the study.
2. Have uncontrolled bladder cancer. Patients with bladder cancer must have bladder cleared of disease by transurethral resection prior to initiating treatment and must not be at need for systemic therapy.
3. Have any other medical condition that would, in the investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
4. Have current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis, confirmed by ophthalmologic examination. Subjects with asymptomatic ophthalmologic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
5. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vasculature and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.
6. Have impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
7. Have current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc.
8. Are currently receiving treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.
9. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits within 7 days prior to first dose of study drug.
10. Have used medications known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes (TdP) 7 days prior to first dose of study drug.
11. Have used amiodarone within 90 days prior to first dose of study drug.

12. Are currently using therapeutic doses of warfarin sodium or any other coumadin - derivative anticoagulants or using direct thrombin inhibitors (e.g., argatroban) or Factor Xa inhibitors (e.g., rivaroxaban) that are primarily metabolized by CYP3A4. Heparin and/or low molecular weight heparins or direct thrombin inhibitors and/or Factor Xa inhibitors that are not metabolized by CYP3A4 (e.g., dabigatran, edoxaban) are allowed.
13. Have insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) < 1,000/mm^3 (1.0×10^9/L)
    b. Platelets < 100,000/mm^3 (75×10^9/L)
    c. Hemoglobin < 9.0 g/dL
14. Have insufficient hepatic and renal function:
    a. Total bilirubin > 1.5 × upper limit of normal (ULN) (unless documented Gilbert's syndrome)
    b. AST/ serum glutamic-oxaloacetic transaminase (SGOT) and ALT/ serum glutamic-pyruvic transaminase (SGPT) > 2.5 × ULN (AST and ALT > 5 × ULN in the presence of liver involvement of cholangiocarcinoma)
    c. Calculated or measured creatinine clearance of < 30 mL/min
15. Have amylase or lipase > 2.0 × ULN
16. Have abnormal calcium-phosphate homeostasis:
    a. Inorganic phosphorus >ULN
    b. Total corrected serum calcium >ULN
17. Have clinically significant cardiac disease including any of the following:
    a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2), LVEF < 50% or local lower limit of normal as determined by echocardiogram (ECHO), or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [Williams et al., 2018])
    b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 or later Grade ≥ 2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality
    c. Unstable angina pectoris or acute myocardial infarction ≤ 3 months prior to first dose of study drug
    d. QTcF > 470 msec (males and females). Note: If the QTcF is >470 msec in the first ECG, a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤ 470 msec, the subject meets eligibility in this regard
    e. Known history of congenital long QT syndrome
18. Have had a recent (≤ 3 months) transient ischemic attack or stroke

5. TREATMENTS

5.1. Treatments Administered

Patients will receive infigratinib 125 mg orally every day for a total of 2 cycles. Each cycle will consist in 28 days, with a schedule of 3 weeks on, 1 week off. Surgery will be performed during weeks 8-9 (week 8 being the off-week of 2nd cycle), and patients will have taken last dose of Infigratinib at least 48 hours prior to surgery.

If patients are not able to tolerate the study drug, every effort will be made to schedule the surgery as soon as possible after the patient has recovered and/or the investigator determines it is the best course of action for the patient.

5.2. Information on Infigratinib

5.2.1. Subject Instructions for Infigratinib Dosing

Subjects should be instructed to take the daily dose of infigratinib in the morning, at approximately the same time each day (24 ± 2 hour interval).

Infigratinib should be taken in the fasted state at least 1 hour before or 2 hours after a meal. It should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Subjects should be instructed to swallow the capsules whole and not chew them.

If the subject forgets to take the scheduled dose of infigratinib in the morning, he/she should not take the dose more than 2 hours after the usual time and should continue treatme nt the next day. Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.

If vomiting occurs following dosing with infigratinib, re-dosing is not permitted the same day. Dosing should resume the next day.

Infigratinib is characterized by pH-dependent solubility; therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (e.g., omeprazole), H_2-antagonists (e.g., ranitidine) and antacids. If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H_2-antagonists or antacids. Infigratinib should be taken at least 2 hours before or 10 hours after dosing with a gastric protection agent.

Subjects must avoid the consumption of grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period. This is due to a potential CYP3A4 interaction with study drug. Normal oranges and orange juice are allowed.

Last dose of Infigratinib should be at least 48 hours prior to surgery.

5.2.2. Description and Dispensing of Infigratinib

Infigratinib will be supplied as hard gelatin capsules for oral use at dose strengths of 25 and 100 mg. Excipients will include microcrystalline cellulose, lactose monohydrate, HPMC2910, crospovidone, colloidal silicon dioxide, magnesium stearate, and hard gelatin

capsule. Infigratinib will be manufactured under Good Manufacturing Practice for investigational use.

5.2.3. Packaging and Labeling

Infigratinib capsules will be packaged in high density polyethylene bottles with child resistant closures. Study drug labels will be in the local language and comply with the legal requirements of each country. Labels will include storage conditions for the drug.

5.2.4. Study Drug Accountability, Handling, and Disposal

Infigratinib capsules will be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, infigratinib should be stored according to the instructions specified on the drug label and in the Investigator's Brochure . Refer to the Pharmacy Manual for further details.

The investigator or designee must maintain an accurate record of the shipment and dispensing of infigratinib in a drug accountability log. Subjects will be asked to return all used and unused bottles of infigratinib and packaging on a regular basis, at the end of the study, or at the time of study drug discontinuation. Drug accountability will be assessed by the investigator's delegated study personnel, and captured in a subject drug accountability log. This information must be captured in the source document at each subject visit.

At study close-out, infigratinib will be destroyed per UTMDACC Institutional Policy # ADM0166.

5.2.5. Dose Modifications for Infigratinib

Each subject will be allowed a maximum of 2 dose reductions as noted in Table 2. Subjects should discontinue infigratinib if toxicity persists as per criteria in Table 3. Subject management will be based upon investigator evaluations.

5.2.5.1. Dose Modifications and Delays

The following guidelines should be applied:

Following resolution of toxicity to baseline or ≤ Grade 1, treatment is resumed at either the same or lower dose of study drug as per the criteria in Table 2. If treatment is resumed at the same dose of study drug, and the same toxicity recurs with the same or worse severity regardless of duration, dose must be reduced to the next lower dose level. If treatment is resumed at the lower dose of study drug, and the same toxicity recurs with the same or worse severity, the subject should have a second dose reduction.

Subjects who are withdrawn from the study for a study related AE or an abnormal laboratory value must be followed as described in Section 5.2.5.2.

Table 1: Dose Reduction Scheme for Infigratinib

Dose Reduction			
	Starting dose level 0	Dose level -1	Dose level -2

Infigratinib	125 mg	100 mg	75 mg

Table 2: Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	Recommended Dose Modifications any Time During a Cycle of Therapy
CARDIAC DISORDERS	
Cardiac - Prolonged QTcF Interval	
Grade 1 and 2: QTcF ≥ 481 msec and ≤ 500 msec (asymptomatic)	Maintain dose level of infigratinib. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, single ECG assessments should be performed for 2 additional cycles at the same frequency as in Cycle 1, or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.
Grade 3: QTcF > 500 msec as identified on the ECG by the investigator	Hold infigratinib. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, monitor subject with hourly ECGs until the QTcF has returned to baseline and perform further monitoring as clinically indicated. • Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia and decreased blood oxygenation. • Subjects should receive appropriate electrolyte replacement and should not receive further infigratinib until electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved, subjects may be re-treated at one lower dose level at the investigator's discretion. Single ECG assessments should be performed for 2 additional cycles at the same frequency as in Cycle 1 or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. o If ECG assessments show no QTcF ≥ 481 msec, ECG monitoring will be performed as per visit schedule for subsequent cycles. o If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles. • Subjects who experience recurrent QTcF ≥ 500 msec after one dose reduction will be withdrawn from study.
Grade 4: QTcF > 500 or > 60 msec change from baseline and Torsade de pointes or	Discontinue infigratinib.

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	If QTcF > 500 msec or > 60 msec change from the baseline is observed, a plasma sample for determination of infigratinib concentration should be obtained with the time of sample collection noted.
Cardiac Disorders – Others	
Gra de ≥ 3, or congestive heart failure Gra de ≥ 2	Discontinue subject from study drug.
INVESTIGATIONS-HEMATOLOGY	
ANC Decreased (Neutropenia)	
Gra de 3 (ANC < 1.0 - 0.5 × 10^9/L)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then • If resolved within ≤ 7 days, maintain dose level of infigratinib • If resolved between > 7 days and 14 days, ↓ 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue subject from study drug
Gra de 4 (ANC < 0.5 × 10^9/L)	Hold dose of infigratinib until resolved to CTCAE ≤ Gra de 1, ↓ 1 dose level of infigra tinib • If not resolved within ≤ 14 days, discontinue subject from study drug
Febrile Neutropenia	
Gra de 3 (ANC < 1.0 × 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, then • If resolved within ≤ 7 days, ↓ 1 dose level of infigratinib. • If not resolved within 7 days, discontinue subject from study drug
Gra de 4	Discontinue subject from study drug
Anemia	
Gra de 3 (hemoglobin <8.0 g/dL)	Hold dose of infigratinib until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then maintain dose level
Gra de 4	Hold dose of infigratinib until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Platelet Count Decreased (Thrombocytopenia)	
Grade 3 (platelet < 50 - 25 × 10^9/L) without ≥ Gra de 2 bleeding	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days, maintain dose level of infigratinib • If resolved between > 7 days and 14 days, ↓ 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue subject from study drug
Grade 3 (platelet < 50 - 25 × 10^9/L) with bleeding or Grade 4 (platelet < 25 × 10^9/L)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level • If not resolved within ≤ 14 days, discontinue subject from study drug

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
INVESTIGATIONS – RENAL	
Serum Creatinine	
Grade ≥ 2	If serum creatinine CTCAE Grade ≥ 2 has been demonstrated in conjunction with hyperphosphatemia, serum creatinine levels must be repeated at least weekly until resolution. 24-hour urine collection should be obtained as clinically indicated for total phosphate, calcium, protein, and creatinine clearance. Ultrasound examination of the kidneys should be performed as indicated to evaluate de-novo calcifications until resolution or stabilization of creatinine.
Grade 2 (≥ 2.00- 3.0 × ULN or 2.0-3.0 × baseline)	Hold dose of infigratinib until resolved to Grade ≤1 or baseline • If resolved within ≤ 7 days, maintain dose level of infigratinib • If resolved between > 7 days and 14 days, ↓ 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue subject from study drug
Grade ≥ 3 (> 3.0 × ULN or >3 × baseline)	Discontinue subject from study drug
INVESTIGATIONS – HEPATIC	
AST or ALT	
Grade 3 (> 5.0 - 20.0 × ULN) without bilirubin elevation > 2.0 × ULN	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days ↓ 1 dose level of infigratinib • If not resolved within ≤ 7 days, discontinue subject from study drug
Grade 4 (> 20.0 × ULN) without bilirubin elevation > 2.0 × ULN	Discontinue subject from study drug
AST or ALT and Bilirubin	
AST or ALT > 3.0 – 5.0 × ULN and total bilirubin > 2.0 × ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of infigratinib until both transaminases and bilirubin resolved to CTCAE Grade ≤ 1 or baseline. • If resolved within ≤ 7 days, ↓ 1 dose level of infigratinib. • If not resolved within ≤ 7 days, discontinue subject from study drug
AST or ALT > 5.0 × ULN and total bilirubin > 2.0 × ULN	Discontinue subject from study drug
LABORATORY / METABOLIC DISORDERS	
Asymptomatic Amylase and/or Lipase Elevation	
General Comment:	A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be performed as clinically indicated within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase
Grade 3 (> 2.0 - 5.0 × ULN)	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2 • ↓ 1 dose level of infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
	• If not resolved within ≤ 14 days, discontinue subject from study drug For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2.
Grade 4 (> 5.0 × ULN)	For any Grade 4 asymptomatic lipase or amylase elevation, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2.
Hyperphosphatemia	
Serum phosphorus > 5.5 – 7.0 mg/dL	Maintain dose level of infigratinib and optimize phosphate lowering therapy as clinically indicated
Serum phosphorus > 7.0 mg/dL for more than 7 days despite maximal phosphate-lowering therapy Or, single serum phosphorus > 9.0 mg/dL regardless of duration or dose of phosphate lowering therapy (Optimize/maximize dose and schedule of phosphate lowering therapy in accordance with package insert, country or institutional guidelines)	• Hold infigratinib dose until resolved to serum phosphorus ≤ 5.5 mg/dL. • Restart infigratinib at the same dose level with maximal phosphate binder dosing if the subject did not receive maximal phosphate binder dosing for serum phosphorus > 7.0 mg/dL for > 7 days. • Reduce one dose level of infigratinib if the subject had received maximal phosphate lowering therapy for serum phosphorus > 7.0 mg/dL for > 7 days or if subject had a one-time serum phosphorus of > 9.0 mg/dL. Restart infigratinib with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during infigratinib dose interruptions for hyperphosphatemia and that serum phosphorus values be monitored frequently, e.g., every 2-3 days. Phosphate binder dosing should be held during the week off infigratinib therapy each cycle (Days 22-28) unless serum phosphorus is not normalized and during infigratinib dose interruptions for non-hyperphosphatemia AEs.
Hypercalcemia	
Serum calcium Grade 2	Hold infigratinib dose until resolved to Grade 1 or baseline: • If resolved within ≤ 7 days after suspending infigratinib, maintain dose level • If resolved between > 7 days and 14 days after suspending infigratinib, ↓ 1 dose level • If not resolved within ≤ 14 days, discontinue subject from study drug
Serum calcium ≥ Grade 3	Discontinue subject from study drug
NERVOUS SYSTEM DISORDERS	
Any Grade 2 neurotoxicity	Omit dose of infigratinib until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue subject from study drug
Any Grade ≥ 3 neurotoxicity	Discontinue subject from study drug

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
GASTROINTESTINAL SYSTEM DISORDERS	
Pancreatitis	
Grade ≥ 2	Discontinue subject from study drug
Diarrhea	
General Comment:	Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
Grade 1	Maintain dose level of infigratinib, initiate anti-diarrheal treatment
Grade 2	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, ↓ infigratinib by 1 dose level
Grade 3	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • ↓ infigratinib by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal antidiarrheal treatment, discontinue subject from study drug
Grade 4	Discontinue subject from study drug
Vomiting	
Grade 2 not controlled by optimal anti-emetic therapy	Hold infigratinib doses until ≤ Grade 1, ↓ 1 dose level • If not resolved within ≤ 14 days, discontinue subject from study drug
Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Discontinue subject from study drug
EYE DISORDERS (CONFIRMED BY OPHTHALMOLOGIC EXAMINATION)	
Retinal Disorders	
Grade 2 central serous retinopathy and central serous retinopathy-like events	Hold infigratinib until resolved to ≤ Grade 1 and continue ophthalmologic evaluation • If resolved within ≤ 14 days, ↓ infigratinib by 1 dose level • If resolved after > 14 days, discontinue infigratinib
Grade 3 central serous retinopathy and central serous retinopathy-like events and any other Grade 3 eye disorders	Hold infigratinib until resolved to Grade ≤ 1 • If resolved within ≤ 14 days, ↓ infigratinib by 1 dose level • If resolved after > 14 days, discontinue infigratinib
Grade ≥ 1 retinal vein occlusion, Grade 4 central serous retinopathy and central serous retinopathy-like events, and Grade 4 other eye disorders	Discontinue subject from study drug
Other Ocular/Visual Toxicity	

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
Gra de ≥ 3	Hold infigra tinib until resolution to ≤ Gra de 1 • If resolution within ≤ 14 days, ↓ 1 dose level • If resolved after > 14 da ys, discontinue infigratinib
GENERAL DISORDERS	
Fatigue	
Gra de ≥ 3	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 da ys, maintain dose level of infigratinib. • If resolved after > 7 da ys, discontinue subject from study drug
SKIN ANDSUBCUTANEOUS TISSUE DISORDERS	
Alopecia	
Gra de 1	Continue infigratinib • Minoxidil 5% (OTC) solution or foam once daily to scalp
Gra de 2	Continue infigratinib • Minoxidil 5% (OTC) solution or foam twice daily to scalp • Fluocinonide 0.05% solution daily to scalp
Palmar-plantar erythrodysesthesia syndrome	
Gra de 0/1	Continue infigratinib • Urea 20% or a mmonium lactate 12% lotions bid to hands and feet
Gra de 2	Continue infigratinib • Urea 20% or a mmonium lactate 12% bid to hands and feet • Fluocinonide 0.05% cream bid to hands and feet
Gra de 3	Hold infigra tinib until resolved to Gra de ≤1 • Urea 20% or a mmonium lactate 12% bid to hands and feet • Fluocinonide 0.05% cream bid to hands and feet
Paronychia	
Gra de 1	Continue infigratinib • Clinda mycin 1% solution around and under nails tid • Soa k for 15 minutes daily in white vinegar in tap water 1:1
Gra de 2	Continue infigratinib • Cefa droxil 500mg bid or TMP/SMX DS bid for 14 days • Soa k for 15 minutes daily in white vinegar in tap water 1:1 • Obta in bacterial cultures to confirm sensitivity to a ntimicrobial • Dermatology consultation

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
Gra de 3	Hold infigra tinib until resolved to Gra de ≤1 • Cefa droxil 500mg bid or TMP/SMX DS bid for 14 days • Obta in bacterial cultures to confirm sensitivity to a ntimicrobial • Derma tology consultation
Stomatitis	
Gra de 1 Gra de 2 Gra de 3	Continue infigratinib • Dexa methasone elixir 0.5mg/mL swish a nd spit 1 teaspoon (5mL) tid. Continue infigratinib • Dexa methasone elixir 0.5mg/mL swish a nd spit 1 teaspoon (5mL) tid. Hold infigra tinib until resolved to Gra de ≤1 • Dexa methasone elixir 0.5 mg/mL swish a nd spit 1 teaspoon (5 mL0 tid • Clotrimazole 10 mg lozenges qid
OTHER CLINICALLY SIGNIFICANT AEs	
Gra de 3 Gra de 4	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of infigra tinib • If not resolved within ≤ 14 days, discontinue subject from study drug Discontinue subject from study drug

Abbrevia tions: AE, a dverse event; ALT, a lanine aminotransferase; ANC, a bsolute neutrophil count; AST, a spartate aminotransferase; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; QTcF, QTc corrected by Fridericia's formula; ULN, upper limit of normal.

5.2.5.2. Follow-up for Toxicities

Subjects whose study drug is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at the discretion of the investigator until resolution or stabilization of the event, whichever comes first. Clinical experts or specialists, such as, but not limited to, an ophthalmologist, endocrinologist, or dermatologist, should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific infigratinib-induced toxicities (hyperphosphatemia, diarrhea) are provided in Table 2. All subjects must be followed up for AEs and SAEs for 30 days following last dose of infigratinib or until surgery, whichever occurs last.

5.3. Compliance

The investigator or responsible site personnel should instruct the subject to take infigratinib exactly as prescribed to promote compliance. All dosages prescribed and dispensed to the subject and all dose changes or missed doses during the study must be recorded

5.4. Supportive Care Guidelines

5.4.1. Infigratinib Group

Any palliative and supportive care for disease related symptoms, including any medic ation or therapy for a concurrent medical condition are permitted, except if specifically prohibited below.

Hematopoietic Growth Factors

Hematopoietic growth factors (e.g., erythropoietin [EPO], granulocyte colony -stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor [GM-CSF]), and blood transfusions <2 weeks prior to enrollment are not to be administered prophylactically or to be used to meet eligibility criteria. However, these drugs may be administered as per the label of these agents or as dictated by local practice or guidelines established by the American Society of Clinical Oncology (ASCO), ESMO, or other appropriate regional societies.

Management of Hyperphosphatemia

Hyperphosphatemia is a recognized on-target effect of potent and selective inhibitors of the FGFR pathway. While on infigratinib, subjects should avoid foods that are especially high in phosphate and, if possible, should restrict dietary phosphate to 600 – 800 mg/day. High-phosphate foods include dairy products; meats, nuts, and other high-protein foods; processed foods; and dark colas. Prophylactic phosphate binders, started in the evening of first dose of study drug, should be considered (e.g., sevelamer 800 mg three times a day with meals). Subjects who have experienced hyperphosphatemia should take a phosphate binder such as sevelamer, sacroferric oxyhydroxide, lanthanum carbonate, ferric citrate, etc. within 30 minutes of a meal on the day while taking infigratinib. Once the subject has had hyperphosphatemia, the subject should remain on a low phosphate diet, if possible, and take phosphate binder on the days infigratinib is taken, even if the serum phosphorus is normalized. The dose and schedule for phosphate lowering therapy should be in accordance with the package insert, country, or

institutional practice. For patient with GFR 30-49, phosphate binders will be started with first dosing and phosphate levels will be followed every 3 -4 days for the first week of treatment and then phosphate-binder dosage and serum phosphate level monitoring modified depending on serum phosphate levels. An example of a phosphate lowering regimen to manage hyperphosphatemia is provided for consideration below:

- Start sevelamer 800 mg three times a day with meals
- For serum phosphorus >5.5 – 7.0 mg/dL
    - Increase the dose of sevelamer up to 1200 mg every 8 hours
- For serum phosphorus >7.0 – 9.0 mg/dL
    - Increase the dose of sevelamer up to 1600 mg (2 tablets per meal) every 8 hours
    - Consider adding acetazolamide two to three 250 mg tablets per day.

During the infigratinib cycle, subjects do not need to be on a low phosphate diet or take a phosphate binder during their 1-week off period unless serum phosphorus is not normalized.

Management of Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/anti-motility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control th e diarrhea to tolerable levels, study drug should be temporarily interrupted or dose reduced per Table 2.

5.5. Prior and Concomitant Medications

At Screening, subjects are to be asked about their history of prior therapies (including p rior anticancer therapy); investigators are to check for use of any disallowed prior medications, as outlined in the exclusion criteria for the study (Section 4.2).

All prescription and non-prescription medications administered from the time of first dose of study drug through 30 days after last dose are to be recorded for each subject on the appropriate page of the eCRF. Dates for the start and stop of each concomitant medication are to be recorded, as well as the reason for administration (particularly if administered for an AE). Any changes in dose of concomitant medications are to also be recorded.

Hormone replacement therapies such as thyroid and growth hormones are allowed, as well as estrogen replacement hormone treatment.

5.5.1.1. Permitted Concomitant Therapy Requiring Caution and/or Action

Details for specific medications which require action and/or caution while on study in subjects taking infigratinib are provided in Appendix 1. The rationale for these medications is provided below.

Infigratinib is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib, and limit bioavailability.

Infigratinib was shown to inhibit the CYP3A4 in *in vitro* assays, thus suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A4. Infigratinib is a substrate of CYP3A4. Therefore, moderate inhibitors and inducers should be used with caution if an alternative is not available.

Infigratinib was shown *in vitro* to inhibit the drug transporter breast cancer resistance protein (BCRP), with an IC_{50} of 210 nM. While the clinical relevance of this inhibition is unknown, drugs transported by BCRP should be used with caution.

Anti-emetics are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines.

It is recommended to avoid using drugs that are known to cause QT prolongation. Note that some anti-emetics have a known risk for Torsade de Pointes, and therefore need to be used with caution. See Appendix 1 for list of drugs that need to be used with caution. Aprepitant (brand name: Emend) is both a sensitive substrate and a moderate CYP3A4 inhibitor and should be used with caution if an alternative is not available.

Preliminary clinical data have shown that infigratinib has no effect on cardiac conduction or ECG intervals (see current version of the infigratinib Investigator's Brochure). However, medications that have the potential to prolong the QT/QTc interval or induce Torsade de Pointes (possible and conditional risk of TdP/QT prolongation) are allowed with caution. Investigators at their discretion may co-administer such medications, but subjects should be carefully monitored . See Appendix 1 for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

5.5.1.2. Prohibited Concomitant Therapy

A concomitant medication is considered prohibited if it appears on any of the prohibited medication lists for any clinical pharmacology property of the drug (e.g., CYP, BCRP).

Details for specific medications prohibited while on study are provided in Appendix 2. The rationale for the restricted medications is provided below.

Other investigational therapies must not be used while the subject is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study drug must not be given to subjects while the subject is on study drug. If such agents are required, then the subject must be discontinued from study drug.

Strong inhibitors of CYP3A4 such as the ones listed in Appendix 2 are prohibited because infigratinib is a likely substrate of this isoenzyme.

Strong inducers of CYP3A4 are prohibited because their usage may decrease the exposure of infigratinib. Therefore, agents such as those listed in Appendix 2 are prohibited. Please note that the list may not be exhaustive.

Subjects must also avoid the consumption of grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period due to a potential CYP3A4 interaction with study drug.

Medications that increase the serum levels of phosphorus and/or calcium are prohibited.

Preliminary clinical data have shown that infigratinib has no effect on cardiac conduction or ECG intervals (See current version of the infigratinib Investigator's Brochure). However, medications that are known to prolong the QT/QTc interval or induce TdP (risk of TdP/QT prolongation) are prohibited. List of these medications is given in Appendix 2. Please note that the list might not be comprehensive.

5.6. Non-drug Therapies

Any significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered from the time of first dose of study drug through 30 days after last dose are to be recorded for each subject on the appropriate page of the eCRF. Dates for the start and stop of each therapy are to be recorded, as well as the reason for administration (particularly if administered for an AE).

Non-drug therapies are prohibited if they appear on any of the prohibited medication lists for any clinical pharmacology or PK property of the drug (e.g., CYP, BCRP) (see Appendix 2.

6. SUBJECT WITHDRAWAL AND STUDY TERMINATION

6.1. Subject Withdrawal

6.1.1. Discontinuation of Study Drug

Subjects must be discontinued from study drug for:

- Pregnancy

In addition, subjects may be discontinued from study drug for any of the following reasons:

- AE
- Protocol deviation, including non-compliance with dosing regimen
- Lost to follow-up (defined as no contact after 3 documented attempts by phone followed by 1 attempt via certified letter)
- Subject request
- Investigator request
- Death

6.1.2. Withdrawal from Study

Subjects have the right to withdraw from the study at any time without prejudice. Study drug must be discontinued and no further assessments conducted. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up. Patients withdrawing after enrollment but prior to receipt of study drug will be considered screen failures.

Subjects may also be discontinued from the study for the following reasons:

- Subject request
- Investigator request
- Lost to follow-up (defined as no contact after 3 documented attempts by phone followed by 1 attempt via certified letter)
- Discontinuation of the study by the IND Office, or the supporting drug company
- Study complete
- Death

6.2. Study Termination

End of Trial is defined as the time at which all patients enrolled in the study have completed the last study visit and data from those visits have been reviewed by the Investigator or designee.

Premature termination of this study may occur at any time because of a regulatory authority decision, change in opinion of the IRB, drug safety concerns, or at the discretion of the IND Office, or the supporting drug company. In addition, the IND Office, or the supporting drug company retains the right to discontinue development of infigratinib at any time. If termination becomes necessary, the IND Office, or the supporting drug company will inform the appropriate regulatory authorities of the termination and the reason. The Principal Investigator will inform the IRB of the same. In terminating the study, the IND Office, or the supporting drug company and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

7. STUDY VISITS AND PROCEDURES

7.1. **Main** Informed Consent

The subject will sign the study's informed consent form (ICF) prior to conducting any study-specific procedures. The study team will be allowed to use standard of care assessments/procedures that were done prior to obtaining consent if these fall within the allowed time window.

7.2. Screening (Day −28 to −1)

After the main ICF is signed, screening activities will include the following:

- Collection of blood, tissue and urine for correlative studies
- Demography
- ECOG performance status
- Relevant medical history/current medical conditions
- Diagnosis and extent of cancer
- Prior anticancer therapy
- Height and weight
- AEs
- Prior medication use
- Physical examination
- Vital signs
- Ophthalmic assessment
- Blood draw for hematology, chemistry, and coagulation assessment
- Urinalysis (macro, micro only if necessary)
- Pregnancy test (blood or urine) for WOCBP (within 7 days before first dose of study drug)
- 12-lead ECG
- Cardiac imaging (ECHO)
- URS/Tumor Mapping
- EORTC QLQ-C30 QOL Questionnaire

7.3. Treatment Period: Day 1

Before the start of dosing on Day 1, the following assessments are to be performed. Baseline/screening assessments that are conducted within **7** days prior to first treatment can be used to satisfy the Day 1 requirement.

- Weight
- Prior and concomitant medication use
- Symptom-directed physical examination (if needed)
- Vital signs
- Blood draw for hematology, chemistry; blood draw for coagulation, if clinically indicated
- Urinalysis (micro- or macroscopic), if clinically indicated
- Pregnancy test (blood or urine) for WOCBP
- AEs

7.4. Rest of Treatment Period

Throughout the treatment period, subjects will be monitored for AEs and concomitant medication use. Other safety assessments, including symptom-directed physical examinations; vital signs; ophthalmic assessment, laboratory measures (hematology, blood chemistry, coagulation, pregnancy) and urinalysis; and 12-lead ECG and cardiac imaging will be conducted at the times indicated in the schedule of assessments in Section 1. (Note: Blood draws for laboratory measures may be drawn and measured at a local diagnostic lab)

7.5. Pre-op Visit

All patients will be required to return to clinic for pre-operative assessment within 14 days prior to the surgical procedure. Assessments will include the following:

- Weight
- Concomitant medication use
- Physical examination
- Vital signs
- Blood draw for hematology, chemistry
- Collection of blood and urine for correlative studies
- Pregnancy test (blood or urine) for WOCBP
- 12-lead ECG
- AEs
- EORTC QLQ-C30 QOL Questionnaire

NOTE: Collection of tissue for correlative studies **at surgery**

7.6. 30-day Safety Follow-up Visit

All subjects must complete safety follow-up assessments 30 days (+/- 14 days) after the last dose of the study drug or surgery, whichever occurs last. Information relating to anticancer therapies taken since discontinuation of study drug and AEs (including concomitant medication taken for ongoing AEs) will be collected for 30 days after the last dose of the study drug. Assessments will include the following:

- Vital signs
- Ophthalmic assessment (per treating physician's discretion)
- Blood draw for hematology, chemistry
- Urinalysis (macro, micro only if necessary)
- Collection of blood and urine for correlative studies
- Pregnancy test (blood or urine) for WOCBP
- EORTC QLQ-C30 QOL Questionnaire

7.7. End of Study

All subjects must complete one last visit approximately one year (+/- 30 days) after discontinuation or study treatment or surgery, whichever occurred last. Assessments will include the following:

- Relevant medical history/current medical conditions
- Physical examination
- Vital signs
- Blood draw for hematology, chemistry
- CT scan and cystoscopy(+/- URS)

8. STUDY ASSESSMENTS

8.1. Efficacy Assessments

Efficacy will be assessed by tumor response to study drug. To assess each subject's response, the surgical specimen will be assessed/compared against the pre-treatment tumor mapping (Section 12.3, Appendix 3)

Table 3: Response Criteria for UTUC Lesions

Response criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions as documented in Tumor Mapping.
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all mapped lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of mapped lesions, taking as reference 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 at least 5 mm.[a] Or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Abbrevia tions: CR, complete response; PD, progressive disease; PR, pa rtial response; SD, sta ble disease.
[a] The a ppearance of one or more new lesions is a lso considered progression.
Source: Eisenhauer et a l2009

Table 4 (NOT APPLICABLE TO THIS STUDY, KEPT FOR TABLE REFERENCING): Response Criteria for Non-target Lesions

Response criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Abbreviations: CR, complete response; PD, progressive disease.
Source: Eisenhauer et a l2009
Note: Unequivocal progression in non-target lesions must be substantial a nd generally sufficient to require change in

therapy. The increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion).

Table 5: Overall Lesion Response at each Assessment

Target lesions	Non-target lesions	New lesions	Overall lesion 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

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Source: Eisenhauer et al 2009

8.2. Safety Assessments

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

The safety evaluation will be based on AE reporting, laboratory parameters, vital signs, physical examinations, 12-lead ECGs, cardiac imaging, and ophthalmic assessments. Tolerability will be assessed by the incidence of AEs leading to study drug discontinuation.

8.2.1. Adverse Events

8.2.1.1. Definitions

An Adverse Event is defined as any untoward medical occurrence in a p atient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study therapy.An SAE is defined as oneof the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the subject's general condition

8.2.1.2. Clarifications for AE Definitions

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic ab normality that requires transfusion or hematological stem cell support), or require changes in study drug(s).

Progression of underlying malignancy is not considered as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria v1.1, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE.

Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some subjects. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being due to progression of the disease under study, it should be reported as an AE or SAE.

8.2.1.3. Recording Adverse Events

AEs will only be captured if they are ≥ Grade 3 and are reported to be causally related with the investigational study drug.

Conditions already present at the time of informed consent should be recorded in the Medical History eCRF. These baseline conditions will be graded at study entry and monitored throughout the study. If at any point there is a worsening of the baseline condition to ≥ Grade 3 this will also be captured in the eCRF and reported accordingly.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

AEs exclusively related to surgery will not be collected in the databa se.

The following information is to be captured in the eCRF for each AE: severity grade (CTCAE v5.0 Grade 1-5); duration (start and end dates); relationship to study drug (reasonable possibility that AE is related: No, Yes); action taken with respect to study drug (none, dose reduction, temporarily interrupted, permanently discontinued, unknown, not applicable); whether medication or therapy was given (no concomitant medication/non-drug therapy given, concomitant medication/non-drug therapy given); outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown); and whether the event is serious and seriousness criteria.

AE monitoring should be done from the time of informed consent and continue through 30 days after the last dose of study drug.

8.2.1.4. Reporting Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as

it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communications with Supporting Drug Company

SAEs causally related with study procedures will be captured on a SAE Report Form and must be reported to Helsinn Healthcare SA (email: drug-safety@helsinn.com) within 24 hours of learning of its occurrence.

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has taken the first dose of study drug through 30 days after the subject has taken his/her last dose of study drug must be reported to Helsinn Healthcare SA on the SAE eCRF within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 -day period should only be reported to Helsinn Healthcare SA if the investigator suspects a causal relationship to the study drug.

Any additional information for the SAE including recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, a Helsinn Healthcare SA Associate may urgently require further information from the investigator for Health Authority reporting. Helsinn Healthcare SA may need to issue an investigator notification, to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

SAEs in association with surgery will be reported if the investigator discerns association with the study drug. If the SAE is related to surgery alone, it will not be reported.

8.2.1.5. Follow up of Adverse Events

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded in the electronic medical record.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

All SAEs should be followed per standard of care until resolution or stability.

8.2.2. Pregnancies

All females of child bearing potential are to undergo pregnancy testing (blood or urine) at the times specified under the schedule of assessments table.

Female subjects must be discontinued from study drug in the event of pregnancy.

To ensure subject safety, each pregnancy of a subject or partner of a male subject occurring while the subject is on study drug must be reported to Helsinn Healthcare SA within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Consent to report information regarding pregnancy and pregnancy outcomes should be obtained from the partner of the male subject.

Pregnancy of a subject or partner of a male subject should be recorded on a Pregnancy Notification Form and entered on the Pregnancy eCRF. Pregnancy follow-up should be recorded and include an assessment of the possible relationship to the study drug of any pregnancy outcome. Pregnancy and pregnancy follow-up should be reported to Helsinn Healthcare SA (email: drug-safety@helsinn.com).

Any SAE experienced by a subject during pregnancy must be reported on the applicable SAE Report Form.

8.2.3. Laboratory Parameters

Laboratory tests will be collected and analyzed on the scheduled day, even if study drug is being withheld. More frequent assessments may be performed at the discretion of the investigator and if medically indicated, and should be recorded on the Unscheduled Visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the CTCAE v5.0.

Table 6: Safety Laboratory Parameters

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, RBC counts, WBC counts with differentials, pla telets
Biochemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), calcium (can be corrected), chloride, crea tinine, blood urea nitrogen, potassium, sodium, magnesium, phosphate Direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase
Urina lysis	Macroscopic panel (dipstick) (blood, glucose, ketones, pH, protein, specific gravity). Microscopic panel (RBC, WBC)
Coa gulation	Prothrombin time or international normalized ra tio, partial thromboplastin time

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBC, red blood cell; SGOT, serum glutamic-pyruvic transaminase; SGPT, serum glutamic-oxaloacetic transaminase; WBC, white blood cell

8.2.4. Vital Signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed in the same position, either sitting or supine, before dosing at the times specified in . Vital signs should be assessed on the scheduled day, even if study drug is being withheld. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.

8.2.5. Physical Examinations

A complete physical examination (including height and weight) must be performed at the Screening and at all other times indicated in Section 1, targeted, symptom-based physical examinations are to be performed, as needed.

8.2.6. Electrocardiograms and Cardiac Imaging

For each subject, 12-lead ECGs and ECHO are to be performed at the Screening Visit. A 12-lead ECG will be performed at the Pre-Op visit. Additional assessments should be obtained as dictated by symptoms.

8.2.7. Ophthalmic Assessments

Ophthalmologic examination will be performed by an ophthalmologist, or optometrist who is supervised by an ophthalmologist, at the times indicated in Section 1. These assessments will include visual acuity testing, slit lamp examination of the anterior eye segment, intraocular pressure, and fundoscopy. Additional examinations such as specular microscopy (that enables a magnified, direct view of the corneal epithelium), corneal pachymetry, retinal optical coherence tomography (OCT), and dilated fundoscopy will be performed as clinically indicated.

9. STATISTICAL PLAN:

The primary objective is to evaluate the safety and tolerability of infigratinib as neoadjuvant therapy. Up to 20 patients will be enrolled in the study. The study will estimate proportion of patients who are not able to complete treatment (discontinuation) due to excessive toxicity along with the 90% exact confidence interval (NOTE: excessive toxicity is defined as treatment related adverse events that cause patients not to complete 2-cycles of planned treatment schedule). Toxicities will be tabulated using frequency and percentage by grade and their relations to treatment. Assuming a 30% of discontinuation due to excessive toxicity, the 90% confidence interval would be (13.1%, 46.9%) with a sample size of 20. Toxicity data will be summarized for the whole group of patients and for patients with eGFR≥50 and eGFR 30-49 separately. The safety analysis included all patients who received at least one dose of infigratinib.

Toxicity monitoring:
The study will monitor the incidence of not completing treatment or delay >14 days of surgery due to excessive toxicity using this monitoring rule. That is stop the trial early if Prob (Ptox > 0.3 | data) > 0.85. Where Ptox denotes the proportion of patients not being able to complete treatment or delay >14 days of surgery. The corresponding stopping boundaries are that the trial will be stopped early if at any time it is observed that (n of patients not completing treatment or delay >14 days of surgery due to excessive toxicity / N of patients treated) >= 3/5, 4/(6-8), 5/(9-10), 6/(11-13), 7/(14-16), and 8/(17-19). This stopping rule will be applied for each cohort of eGFR≥50 and eGFR 30-49 separately. If one cohort stops early due to excessive toxicity, the other will continue accruing as per protocol criteria and toxicity monitoring rule.

The following table displays the operating characteristics for safety monitoring, assuming prior distribution for Ptox is beta(0.3, 0.7) and for a maximum sample size of 20. Since we do not have information for proportions of eGFR≥50 and eGFR 30-49, it would not be feasible to assess OCs for each cohort.
OCs for toxicity monitoring using a maximum sample size of 20

Rate of discontinued treatment due to toxicity/intolerance	Probability of early stop	Avg. N of patients treated
0.1	0.012	19.8
0.2	0.10	18.7
0.3	0.341	16.0
0.4	0.655	12.4
0.5	0.886	9.0

The secondary efficacy endpoint is objective response after 2 cycle treatment of infigratinib. We will estimate the objective response rate along with the 90% confidence interval. Fisher's exact test will be used to explore the difference in response between the two cohorts of patients.

Descriptive statistics will be used to summarize quantifications as continuous variables and frequency and percentage along with 90% CI will be used to summarize categorical variables. Wilcoxon rank sum test and Fisher's exact test will be used to explore the association between objective response and secondary outcomes, e.g. cfDNA, expression of markers, FGFR3 alteration type. The same methods will also be used to explore the association of AEs such as hyperphosphatemia with response. Recurrence at 12 months will be summarized using proportion and 90% confidence interval as a binary outcome, and also be estimated using the Kaplan-Meier method as a time to event variable. The association between time to event variables and markers will be explored using log rank test and univariable Cox model. With the small sample size, the analysis will probably only descriptive. The analysis will be performed in all patients and by FGFR3 alteration status if applicable. For data collected using the EORTC QLQ-C30 questionnaire, we calculate raw score (RS) and linear transformed score (Score) for each of the five functional scales, three symptom scales, a global health status / QOoL scale, and six single items at each time point [Reference: Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001]. For each of these scales, paired t test or Wilcoxon signed rank test will be used to evaluate the changes of the Scores between two time points. Linear mixed models will also be fitted to evaluate the changes in Scores over time.

9.1.1.1. Adverse Events: Safety analyses will be performed for all subjects who receive at least one dose of study drug according to the treatmentthey receive.

AEs will be considered to be treatment emergent if the event occurs on or after the first administration of protocol specified treatment and within last dose date + 30 days. The subject incidence rates of AEs will be tabulated by system organ class, preferred term and severity grade for all treatment emergent, serious, treatment related, and serious treatment related AEs. Each of these outputs will include tabulation by maximum severity f or each system organ class and preferred term as reported by the investigator based on CTCAE, version 5.0. Summary tables will be provided separately for AEs leading to study drug discontinuation. All "on study drug" deaths, ie, deaths that occur within 30 days after last dose of study drug, will be summarized. Listings and/or narratives of "on study drug" deaths, serious and significant AEs, including study drug discontinuation due to AEs, will also be provided.

The summaries of the subject incidence rates of treatment emergent AEs by system organ class and preferred term reported AEs will also be provided for subgroups defined by age, sex, and race (if feasible).

9.1.1.2. Other Safety Findings

Laboratory parameters for hematology and serum blood chemistry will be summarized at baseline, by visit, and at the last observed value. Additionally, the maximum and minimum observed post baseline values will be summarized along with the change from baseline to the maximum observed value, minimum observed value and last observed value. Tables of shifts in severity (by CTCAE version 5.0) from baseline for selected laboratory parameters and selected

time points may also be provided. Graphical representations of aggregate data may also be presented for parameters of interest.

Vital signs, physical examination results, ophthalmic assessment and ECG and cardiac imaging results will be summarized by treatment group using descriptive statistics (including changes from baseline).

9.1.1.3 Safety and Efficacy Monitoring

The Investigator is responsible for completing a toxicity/efficacy summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 5 evaluable patients per cohort, complete 2 cycles of study treatment, and every 2-3 evaluable patients per cohort, thereafter, as illustrated by the stopping boundaries in section 10.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

10. DATA COLLECTION AND MANAGEMENT

10.1. Data Confidentiality

Information about study subjects will be kept confidential and managed under applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g., has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

10.2. Data Collection

Source documents include hospital or clinical patient charts, pertinent historical medical records, laboratory test reports, ECG tracings, pathology reports, radiographs, etc. All source documents must be legible. Data reported in RedCap and evidence of patient's informed consent must be documented in source documents. All study data will be maintained in a confidential, password-protected, encrypted institutional database.

10.3. Study Documentation, Record Keeping and Retention of Documents

A CRF must be completed for each patient for whom informed consent for the study is obtained. The CRFs must be maintained by properly trained and delegated site representatives. The Principal Investigator has responsibility for ensuring the authenticity, accuracy, completeness and timeliness of all data collected in the CRF.

The study site will maintain a Site Trial Master File in accordance with GCPs.

The Investigator shall retain all records indefinitely.

11. REGULATORY AND ETHICAL CONSIDERATIONS

11.1. Regulatory and Ethical Compliance

11.2. Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start

The investigator will be responsible for informing IRBs and/or IECs in the event of early termination of the trial.

11.3. Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents. The date when a subject's informed consent is actually obtained must be captured in the eCRF and the medical records for the subject.

A copy of the ICF must be given to the subject or to the person signing the form.

Women of child bearing potential should be informed that takin g the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

11.4. Confidentiality of Study Documents and Subject Records

The investigator must ensure anonymity of the subjects; subjects must not be identified by names in any documents submitted to QED Therapeutics. Signed ICFs and subject enrollment log kept at the site to enable subject identification must be kept strictly confidential.

12. Appendices

12.1. Appendix 1: List of Concomitant Medications

In general, the use of any concomitant medication deemed necessary for the care of the subject is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or infigratinib.

The following lists are based on the Indiana University School of Medicine's "Clinically Relevant" Table (Flockhart Table™) and supplemented with the FDA draft guidance.

Table 7: Drugs to be used with Caution While on Study

Category	Drug Names
Sensitive CYP3A substrates	afentanyl, alpha-dihydroergocryptine, alprazolam, amlodipine, aplaviroc, aprepitant, aripiprazole, atorvastatin, boceprevir, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, cerivastatin, chlorpheniramine, darifenacin, darunavir, dasatinib, diazepam, diltiazem, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, imatinib, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nevirapine, nifedipine, nisoldipine, nitrendipine, perospirone, pimozide, quetiapine, quinine, ridaforolimus, saquinavir, sildenafil, simvastatin, tadalafil, tamoxifen, telaprevir, telithromycin, ticagrelor, tipranavir, tolvaptan, trazodone, triazolam, vardenafil, verapamil, vicriviroc, vincristine
Moderate inhibitors of CYP3A4	amprenavir, aprepitant, atazanavir, cannabinoids, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, dronedarone, erythromycin, fosamprenavir, imatinib, metronidazole, Schisandra sphenanthera, sertraline, suboxone, tofisopam, verapamil, zafirlukast
Moderate inducers of CYP3A4	bosentan, cotrimoxazole, efavirenz, etravirine, ethosuximide, genistein, metyrapone, mexiletine, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Medications which alter the pH of the GI tract [a,b]	antacids, H_2antagonists (e.g., ranitidine), proton-pump inhibitors (e.g., omeprazole)
Medications that have possible risk of TdP/QT prolongation	alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, dronedarone, eribulin, escitalopram, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, levofloxacin, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tacrolimus, tamoxifen, telithromycin, tizanidine, vardenafil, venlafaxine, voriconazole, ziprasidone

Category	Drug Names
Medications that have conditional risk of TdP/QT prolongation	amiptriptyline, amisulpride, ciprofloxacin, clomipramine, desipramine, diphenhydramine, doxepin, fluconazole, fluoxetine, galantamine, imipramine, itrazonazole, ketoconazole, nortriptyline, paroxetine, protriptyline, ritonavir, sertraline, solifenacin, trazodone, trimethoprim-sulfa, trimipramine
BCRP substrates	atorvastatin, irinotecan, methotrexate, rosuvatstatin, simvastatin, sulfasalazine, topotecan

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome p; FDA, Food and Drug Administration; GI, gastrointestinal; TdP, Torsades de Pointes
[a] Infigratinib should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
[b] If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H_2 antagonists or antacids.
Sources: FDA Guidance for Industry, 2017; Indiana University School of Medicine, 2016.

12.2. Appendix 2: List of Prohibited Medications and Substances

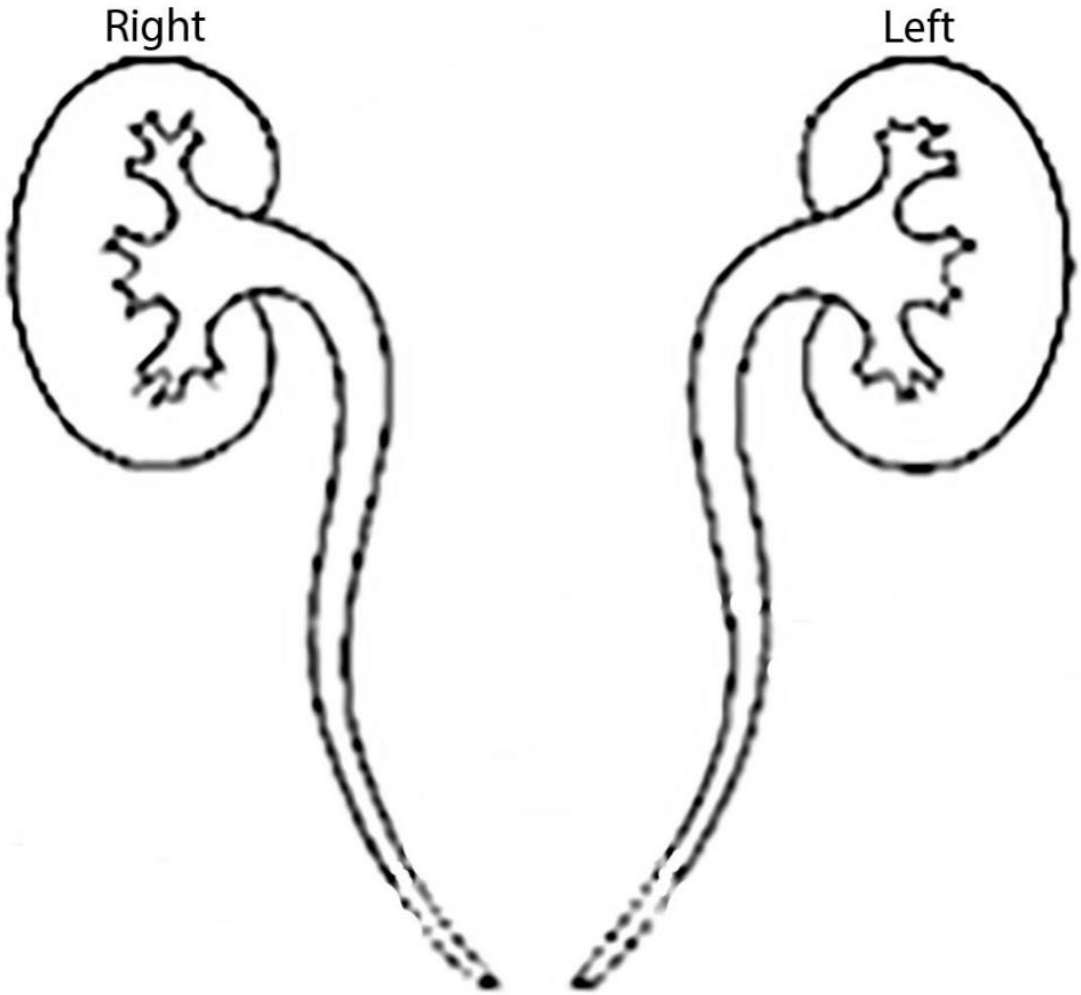
Table 8: List of Prohibited Medications and Substances While on Study

Category	Drug Names
Strong inhibitors of CYP3A4	clarithromycin, conivaptan, fluconazole, fluvoxamine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, micronazole, nefazodone, nelfinavir, norfloxacin, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits
Strong inducers of CYP3A4	avasimibe, carbamazepine, nevirapine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, St. John's wort, troglitazone
Medications which increase serum phosphorus and/or calcium	calcium, parathyroid hormone, phosphate, vitamin D
Narrow therapeutic index substrates of CYP3A4	alfentanil, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl thioridazine, pimozide, quinidine, sirolimus, tacrolimus, terfanadine warfarin sodium or any other coumadin-derivative anticoagulants, direct thrombin inhibitors (e.g., argatroban), and Factor Xa inhibitors (e.g., rivaroxaban)

Category	Drug Names
Medications with established potential for QT prolongation or TdP	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), dronedarone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US market), mesoridazine (off US market), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US market), procainamide (oral off US market), quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, vandetanib

Abbreviations: CYP, cytochrome p; TdP, Torsades de Pointes; US, United States

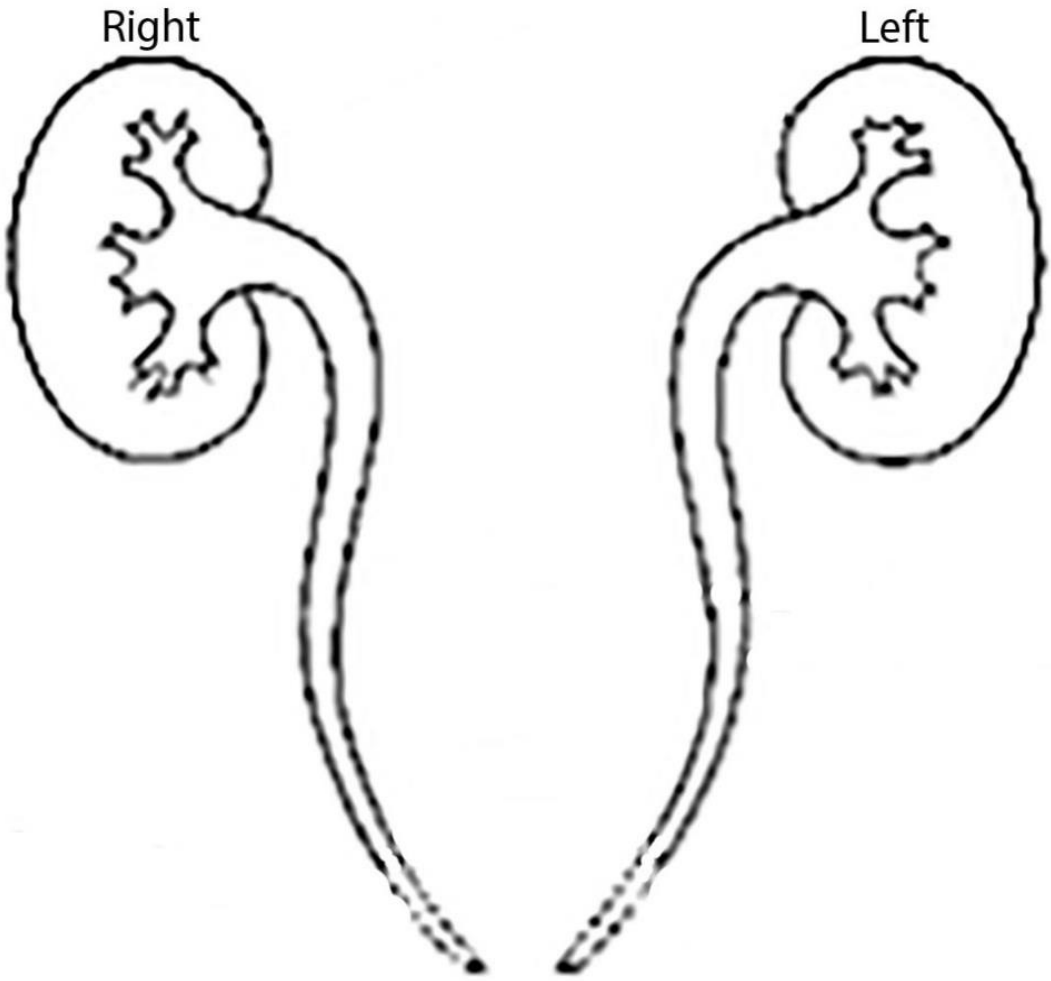
12.3. Appendix 3a: Tumor Mapping FormUreteroscopy



Lesion no.	Size (mm x mm)	Location (*see legend below)	Architecture (villous, papillary, sessile)	Other
1				
2				
3				
4				
5				

1. Renal pelvis (anterior, posterior, medial, lateral)
2. Upper calyx (or infundibulum)
3. Middle calyx (or infundibulum)
4. Lower calyx (or infundibulum)
5. UPJ
6. Proximal ureter
7. Mid ureter
8. Distal ureter

Appendix 3b: Tumor Mapping Form Pathology



Lesion no.	Size (mm x mm)	Location (*see legend below)	Architecture (carpeting, papillary, sessile)	Other
1				
2				
3				
4				
5				

1. Renal pelvis (anterior, posterior, medial, lateral)
2. Upper calyx (or infundibulum)
3. Middle calyx (or infundibulum)
4. Lower calyx (or infundibulum)
5. UPJ
6. Proximal ureter
7. Mid ureter
8. Distal ureter

12.4 Appendix 4: Correlative and Laboratory Studies

Tumor studies:

- **Tumor mapping** will be performed based on endoscopic findings, noting location, number of tumors, tumor architecture, and location of biopsies; and will again be performed after Infigratinib during pathologic evaluation (NUx/Ux cohort) or URS evaluation (endoscopic cohort, with reasonable attempt to biopsy any residual tumor) again noting size, location, number of tumors, architecture, and absence of tumor at any previously identified tumor. A difference of 3mm will be considered within error ofmeasurement.
- **Mutational analysis** will be performed on FFPE tumor tissue using a comprehensive mutation panel (T200.2) which we have used in prior studies and includes all previously identified UTUC mutations, including all relevant FGFR3 alterations including hot spots, copy number variations and fusions. Blood collected at baseline will be used as germline source
- **Single cell (sc)RNAseq** will be performed on fresh frozen tumors using 10x Genomics platform. Tumor cell heterogeneity, FGFR3 gene expression, and tumor microenvironment will be profiled. All bioinformatics data analysis will be performed in the MD Anderson Rare Tumor Initiative Program.
- **Multiplex IHC** will be performed from FFPE tissue (biopsy and final pathologic specimen or repeat biopsies in the endoscopic cohort) and undergo interrogation for immunologic studies, including lymphocyte subtypes and expression of relevant markers such as PD1, PD-L1, ICOS, among others. These data will be compared between FGFR3 mutant and wild-type tumors to evaluate the differences of the immunological environment between these two groups of tumors.
- **Tissue prioritization:** Given the potentially limited biopsy samples, use of biopsy and pathologic tumor tissue will be prioritized in the following order and sources: 1. Mutational analysis (FFPE), 2. RNAseq (fresh fozen), 3. TMA (FFPE).

Urinary biomarkers:

Voided urine will be collected preferentially but will be substituted with selective upper tract washings when voided urine is not available or insufficient. Preliminary data shows that urinary mutation clearance after neoadjuvant chemotherapy is strongly associated with pathologic complete response in radical nephroureterectomy and radical cystectomy specimens. Mutation clearance may therefore serve as a more general biomarker of response to other therapies such as FGFR3 inhibition, but this has yet to be rigorously tested. **In order to further investigate this phenomenon in the current trial, urine and blood will be collected at 3 time points (pretreatment/enrollment, after completion of infigratinib treatment/preoperatively, and 30 days postoperatively).** Urine processing follows established standard operating procedures. Samples are stored at -80^{o}C and then sent to Fox Chase Cancer Center for further analyses (Dr. Phil Abbosh laboratory, with whom we have an existent collaboration and MTA). DNA is isolated from the urine sample and DNA is checked for quality, typically yielding several micrograms of high molecular weight DNA. DNA is also isolated from PBMC prior to initiation

of therapy to use as a germline reference sample. DNA from germline and pre/post-treatment/post-op time points are subjected next generation sequencing using the HaloPlexHS platform with a targeted depth of 1000X covering 54 well characterized cancer genes. These genes are enriched in patients with urothelial carcinoma (including FGFR3). HaloPlexHS uses pre-amplification single molecule tags to filter taq errors occurring during PCR, thus greatly enhancing the power to detect rare alleles. In preliminary experiments, our approach was validated to be highly sensitive and accurate, detecting >60% of tumor tissue mutations in the urine and identifying additional mutations in the urine that are not seen in tissue. **Urine will be characterized for FGFR3 hotspots or other missense variants and we will track their variant allele frequency in longitudinal samples. Presence of point mutations in the pre-treatment urine will be correlated with pathological response as an *a priori* predictive biomarker. Separately, we will also correlate clearance of all pre -treatment mutations after treatment with infagratinib and after surgery with pathologic response as a *post hoc* biomarker. Correlation will be determined using Fishers exact test for both analyses.**

Cell-free DNA (cfDNA) assessment:

To explore the association of cfDNA with response, we will collect blood at pretreatment/enrollment, post-treatment/preoperatively, and 30 days postoperatively (30mL each time point). These samples will be processed and stored until tumor studies are completed and results available. **Of all patients identified as having tumor FGFR3 alterations, 5 will be randomly selected to have their baseline cfDNA assayed; if 3 or more are found to have detectable FGFR3 alterations, then up to 5 more patient baseline samples will be run. Those found to have detectable baseline FGFR3 alterations in their cfDNA will have their second time point assayed. These results will be correlated to disease burden, pathologic findings, disease grade, stage, objective response, and immune correlates** . For cfDNA we will leverage the availability of a 70-Gene Liquid Biopsy Panel (LBP-70). The validated next generation sequencing (NGS)-based panel will be run in the MD Anderson Department of Pathology and Laboratory Medicine. Peripheral blood is collected into Streck tubes designed to reduce admixture of circulating cfDNA with cellular DNA from blood cells during transport. The NGS-based panel is designed to detect single nucleotide variants (SNVs) and small insertion - deletions (Indels) in all 70 genes included in the panel. In addition, amplifications (copy number variants; CNVs) and fusions (translocations) involving selected genes can also be d etected. Specifically in regard to this study, the panel is able to detect mutations/indels, amplifications, and fusions of FGFR3. The comprehensive liquid biopsy test utilizes molecular barcode technology and sophisticated error detection algorithms to allow a sensitive and accurate detection of low level mutations.