Clinical Development

Protocol QBGJ398-302

Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations (PROOF 302)

Investigational Product:	Infigratinib (BGJ398)
Phase of Development	3
Medical Monitor:	PPD MD Executive Director, Clinical Development QED Therapeutics, Inc. PPD PPD
Sponsor:	QED Therapeutics, Inc. 8000 Marina Boulevard, Suite 400 Brisbane, CA 94005
US IND Number:	144,007
EudraCT Number:	2019-003248-63
Protocol Version / Date:	0.0 (original protocol) 03 September 2019 1.0 (Amendment 1) 19 May 2021

INVESTIGATOR'S AGREEMENT

I have read Protocol QBGJ398-302 titled "Phase 3, multicenter, double-blind, randomized, placebo-controlled trial of infigratinib for the adjuvant treatment of subjects with invasive urothelial carcinoma with susceptible FGFR3 genetic alterations (PROOF 302)" and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

_____

Study Center Number

_____

Study Center Name

Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Additionally, investigator agrees to give access to all relevant data and records to QED Therapeutics monitors, auditors, QED Therapeutics Clinical Quality Assurance representatives, designated agents of QED Therapeutics, IRBs/IECs/REBs, and regulatory authorities as required.

TRIAL CONTACTS

Table 1: Trial Contact Information

Role in Study	Name	Contact Information
Medical Monitor	PPD MD	email: PPD Telephone: PPD
Pharmacovigilance/ Safety Management	Covance Safety	email: SAEintake@covance.com

PROTOCOL VERSION HISTORY

Protocol Version Number	Amendment Number	Date
0.0 (original protocol)	NA	03 September 2019
1.0 (Amendment 1)	1.0	19 May 2021

Abbreviations: NA=not applicable.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term/Definition
ADL	activities of daily living
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
AUC	area under the curve
BCG	Bacillus Calmette-Guerin
BCRP	breast cancer resistance protein
BGJ398	Infigratinib
BICR	blinded independent central review
BMI	body mass index
BUN	blood urea nitrogen
cfDNA	cell-free DNA
CI	confidence interval
C_{max}	maximum observed plasma concentration after drug administration
C-G	Cockcroft-Gault
C_{trough}	trough observed plasma concentration (before drug administration)
COVID-19	Coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXD1	first day of Cycle number
CYP	cytochrome P450
DFS	disease-free survival
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
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
EQ-5D-5L	EuroQOL 5 dimensions, 5 levels questionnaire
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor

Abbreviation	Term/Definition
FGFR1	fibroblast growth factor receptor 1
FGFR2	fibroblast growth factor receptor 2
FGFR3	fibroblast growth factor receptor 3
FGFR3 alterations	FGFR3 genetic alterations (mutations, and gene fusions or translocations [ie, rearrangements])
FGFR4	fibroblast growth factor receptor 4
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
GMP	Good Manufacturing Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
GSM	global study manager
HDPE	High-density polyethylene
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	intent-to-treat
IV	intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLN	lower limit of normal
LLOQ	lower limit of quantification
LND	lymph node dissection
MFS	metastasis-free survival
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCBI RefSeq	National Center for Biotechnology Information reference sequence
NCCN	National Comprehensive Cancer Network
NK-1	neurokinin-1
NMIBC	nonmuscle invasive bladder cancer
NYHA	New York Heart Association
OCT	optical coherence tomography
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PD-L1	programmed death-ligand 1
PFS	progression-free survival

Abbreviation	Term/Definition
PK	pharmacokinetics
pNx	post-lymphadenectomy or no lymphadenectomy
PPES	palmar-plantar erythrodysesthesia syndrome
PR	partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	once a day
QED	QED Therapeutics, Inc.
QLQ-C30	quality of life questionnaire core 30
QOL	quality of life
QT	measure of time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RNU	radical nephroureterectomy
RPTD	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
TdP	Torsades de Pointes
T_{max}	time at which the maximum observed concentration (C_{max}) occurs
UBC	urothelial carcinoma of the bladder/urinary bladder cancer
UC	urothelial carcinoma
ULN	upper limit of normal
UTUC	upper tract urothelial carcinoma
WBC	white blood cell
WOCBP	woman of childbearing potential
WHO	World Health Organization

1 SYNOPSIS

Name of Sponsor/Company: QED Therapeutics, Inc.

Name of Investigational Product: Infigratinib (also known as BGJ398, BBP-831, and infigratinib phosphate; hereafter referred to as infigratinib)

Name of Active Ingredient: Infigratinib

Title of Study: Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations (PROOF 302)

Study centers: This is a multicenter study involving approximately 165 study centers worldwide.

Medical Monitor: PPD MD

Studied period (years):	**Phase of development:** 3
Estimated date first subject enrolled: December 2019 Estimated date last subject completed: 2024	

Objectives and Endpoints:

Objectives	Endpoints
Primary:	
• To determine if treatment with infigratinib improves centrally reviewed disease-free survival (DFS) compared with placebo treatment in subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations after nephroureterectomy, distal ureterectomy, or cystectomy	• Centrally reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier
Secondary:	
• To compare DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence in subjects treated with infigratinib vs placebo	• Investigator-reviewed DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, from date of randomization to any recurrence or death due to any cause, whichever occurs earlier
• To compare metastasis-free survival (MFS) of subjects treated with infigratinib vs placebo	• Investigator-reviewed MFS, from date of randomization to metastatic recurrence or death due to any cause, whichever occurs earlier
• To compare OS in subjects treated with infigratinib vs placebo	• OS (from date of randomization to death)
• To compare investigator-reviewed DFS in subjects treated with infigratinib vs placebo	• Investigator-reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier
• To characterize the safety and tolerability of infigratinib when administered as postoperative adjuvant monotherapy	• Type, frequency, and severity of adverse events and serious adverse events, laboratory abnormalities, and other safety findings
Exploratory:	
• To compare QOL in subjects treated with infigratinib vs placebo	• QOL as measured by the EQ-5D-5L and the EORTC QLQ C30

• To evaluate the PK of infigratinib	• PK parameters (trough and maximum plasma concentration).
• To evaluate the overall genomic landscape in subjects with invasive urothelial carcinoma	• Determine the prevalence of genomic alterations and their correlations with available clinicopathologic and demographic features in subjects with invasive urothelial carcinoma.
• To evaluate biomarkers related to the biology of urothelial carcinoma and their potential association with efficacy, disease recurrence, and resistance to study medication.	• Genomic and proteomic assessments of tumor tissue and cell-free DNA samples from baseline to disease recurrence and the determination of the prognostic and/or predictive value of biomarkers.

Abbreviations: DFS=disease-free survival; EORTC=European Organization for Research and Treatment of Cancer; EQ-5D-5L=EuroQOL 5-dimensions, 5-levels questionnaire; FGFR3=fibroblast growth factor receptor 3; MFS=metastasis-free survival; PK=pharmacokinetics; QLQ=quality of life questionnaire; QOL=quality of life; OS=overall survival.

Study Design: This is a Phase 3 multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy of infigratinib in approximately 218 adult subjects with invasive urothelial carcinoma with susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations (mutations, and gene fusions or rearrangements; hereafter referred to collectively as "FGFR3 alterations") who are within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and ineligible for or refuse cisplatin-based (neo)adjuvant chemotherapy or with residual disease after neoadjuvant therapy. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach. Subjects with invasive urothelial carcinoma includes subjects with invasive upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of the bladder (UBC).

Subjects who meet eligibility criteria will be randomly assigned (1:1) to receive oral infigratinib or placebo administered once daily for the first 3 weeks (21 days) of each 28-day cycle for a maximum of 52 weeks (13 cycles), or until local/regional or contralateral invasive or metastatic recurrence (whichever occurs first) is confirmed by BICR, or until other criteria specified in the protocol are met, whichever occurs first.

Subjects will be evaluated for tumor recurrence radiographically, by urine cytology, and for subjects with UTUC (ie, subjects with a bladder), cystoscopy will also be performed. Radiography, urine cytology, and cystoscopy will continue until metastatic recurrence by blinded independent central review (BICR) or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Use of anticancer therapy will be collected for all subjects, including from the time of study treatment discontinuation, regardless of reason for discontinuation. After metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred, subjects will be followed for survival status and use of anticancer therapy until 1 year after the final disease-free survival (DFS) event goal is reached (ie, End of Study [EOS]). After the EOS (1 year after the DFS primary analysis), subjects will continue to be followed for overall survival (OS) (under a separate protocol) for approximately 14 years, or until all of the subjects die or drop from this follow up, whichever is earlier, referred to as long-term OS follow up.

Subjects should remain on study treatment until local/regional or contralateral invasive or metastatic recurrence is confirmed by BICR. If BICR confirms recurrence (local/regional or contralateral invasive or metastatic recurrence, whichever occurs first), the subject must be permanently discontinued from study treatment. BICR diagnosis of a local/regional or contralateral invasive or metastatic recurrence, independently from and undiagnosed by local team, will not be communicated to the clinical site.

An interim analysis for adaptation and futility for centrally reviewed DFS will be conducted after approximately 35 confirmed DFS events by BICR (independent of investigator assessment) (ie, half of the planned number) have been reached. Based on the results of the interim analysis on DFS, if a sample size increase is deemed necessary using the promising zone approach, the sample size/centrally reviewed DFS event goal will be increased by a maximum of 50% (328/105). If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly time-wise when the adjusted event goal is reached. The details of the sample size adaptation method will be prespecified in the adaptation plan.

Subjects will be stratified according to lymph node involvement (yes vs no), prior neoadjuvant cisplatin chemotherapy (yes vs no), Stage (pT2 vs >pT2), and disease (UTUC vs UBC).

Number of subjects (planned): Approximately 218 subjects are initially planned for study participation. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach. No more than 15% of the population will be enrolled with UBC, and ≤25% of UTUC subjects will have Stage pT2 UTUC (limit will be based on stratification). The number of subjects refusing cisplatin-based perioperative therapy will be capped at approximately 10% of the total population (approximately 22 subjects).

Diagnosis and criteria for inclusion: To be eligible for the study, subjects must meet all of the following criteria:

1. Are ≥18 years of age (≥20 years of age in Taiwan) of either sex.
2. Have signed informed consent.
3. Are randomized within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy.
   Note: at the time of definitive surgery, lymph node dissection (LND) should be performed in cases of suspected lymph node invasion based on preoperative imaging or intraoperative findings. In other cases, LND is to be performed in accordance with surgeon preferences/local standard practices. Additional details on recommended standards for LND are provided in the protocol.
4. Have histologically or cytologically confirmed, invasive urothelial carcinoma with susceptible FGFR3 alterations. Variant histology is allowed provided urothelial carcinoma is predominant (>50%). Neuroendocrine (including small and large cell), sarcomatoid, and plasmacytoid variants are excluded (any component):
   a. Regarding samples and documentation of FGFR3 alterations:
      i. FGFR3 mutation is confirmed if: FGFR3 gene is mutated in Exon 7 (R248C, S249C), Exon 10 (G370C, A391E, Y373C), or Exon 15 (K650M/T, K650E/Q)
      OR
      ii. FGFR3 gene fusion or FGFR3 rearrangement is confirmed based on the following genomic criteria:
         (1) Any fusion/rearrangement with a literature-derived known partner gene regardless of strand or frame.
         (2) Fusion/rearrangements in the same strand that are in frame with a novel partner gene.
         (3) Fusion/rearrangements with one breakpoint in the intron 17 - exon 18 hotspot region and the other breakpoint in an intergenic region or another gene. This rule excludes 3′ duplications comprising only exon 18.
      iii. The amino acid numbers for the FGFR3 mutations refer to the functional FGFR3 isoform 1 (NP_000133.1) that is the NCBI Refseq ID used to report genetic alterations in FGFR3 by the FoundationOne® CDx test (F1CDx, Foundation Medicine, USA).
      iv. Written documentation of central laboratory determination by F1CDx testing of FGFR3 alterations is required for study eligibility.
      v. For subjects who require molecular prescreening to confirm the presence of the FGFR3 alteration to meet the inclusion criteria, a tumor sample with a pathology report must be sent to Foundation Medicine USA for F1CDx testing. (Instructions for optimal tumor specimens are provided in the protocol).
         (1) The tumor sample to be used should be from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy).

(2) An archival biopsy of confirmed invasive urothelial carcinoma (≥pT2) can be used if (1) tissue from definitive surgery cannot be submitted, (2) the biopsy sample is not older than 4 months prior to surgery date and (3) the subject did not receive any type of systemic anticancer treatment since the biopsy was obtained. If more than one biopsy is available, the most recent one is to be sent.

b. If status post neoadjuvant chemotherapy, pathologic stage at surgical resection must be Stage ≥ ypT2 and/or yN+. Prior neoadjuvant therapy is defined as at least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m^2/cycle. Subjects who received less than this or non-cisplatin-based neoadjuvant treatment are not excluded. If enrolled, they will be stratified as having received no neoadjuvant chemotherapy.

c. If not status post neoadjuvant chemotherapy, is ineligible to receive cisplatin-based adjuvant chemotherapy based on Galsky (2011):
   i. Creatinine clearance ≤60 mL/minute, or
   ii. Common Terminology Criteria for Adverse Events (CTCAE version 5.0) Grade ≥2 hearing loss, or
   iii. CTCAE Grade ≥2 neuropathy.

d. Subjects who refuse cisplatin-based chemotherapy or who are ineligible to receive cisplatin-based chemotherapy based on Galsky (2011), must also meet the following criteria:
   i. UTUC should be Stage ≥pT2 pN0-2 (post-lymphadenectomy or no lymphadenectomy [pNx]), or pN+, M0
   ii. UBC should be Stage ≥pT3 or pN+, M0.

e. Must have a centrally reviewed negative postoperative computed tomography (CT) (defined as lymph nodes with short axis <1.0 cm and without growth and no distant metastases according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or negative biopsy within 28 days before randomization to confirm absence of disease at baseline.

5. If have had adverse events (AEs) associated with prior surgery or neoadjuvant chemotherapy, they have stabilized or resolved to Grade ≤2 before randomization.
6. Have Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
7. If a woman of childbearing potential, 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 ≥6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for ≥12 months, and there is no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

   Women of childbearing potential and males whose sexual partners are women of childbearing potential must agree to use barrier contraception and a second form of contraception (Clinical Trials Facilitation Group 2020) while receiving study drug and for 1 month 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 (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. (Highly effective contraception methods are specified in the protocol.)

   Sexually active males must use a condom during intercourse while taking study drug and for 1 month after the last dose of 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 study drug via seminal fluid. Study subjects must agree to refrain from donating sperm and eggs during the study and for 1 month following their last dose of study drug.
8. Are willing and able to comply with study visits and study procedures.

Criteria for exclusion: To be eligible for the study, a subject must not meet any of the following criteria:

1. Presence of positive invasive surgical margins following nephroureterectomy, distal ureterectomy, or cystectomy. In subjects not eligible for further surgery, radiotherapy, or other efficacious treatment, microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease are allowed.
2. Have received Bacillus Calmette-Guerin (BCG) or other intravesical therapy for nonmuscle invasive bladder cancer (NMIBC) within the previous 30 days.

3. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing antiepileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.
   Prior anticancer or other therapies are restricted as follows:
   a. Prior adjuvant treatment for urothelial cancer is not allowed.
   b. Prior neoadjuvant therapy (eg, chemotherapy, immunotherapy, or investigational) is allowed if inclusion criterion #4 is met.
      Prior neoadjuvant chemotherapy must have been completed within a period of time that is greater than the cycle length used for that treatment before the first dose of study drug.
   c. Prior biologic, immunotherapy, or investigational therapy should have been completed within a period that is ≥5 half-lives or 30 days, whichever is shorter, before the first dose of study drug.
4. Are planning to receive other systemic therapies intended to treat invasive urothelial carcinoma while on this study.
5. Have previously or currently is receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor.
6. Have a history of primary malignancy within the past 3 years other than (1) invasive UBC or UTUC (ie, disease under study), (2) noninvasive urothelial carcinoma, (3) any adequately treated in situ carcinoma or non-melanoma carcinoma of the skin, (4) any other curatively treated malignancy that is not expected to require treatment for recurrence during participation in the study, or (5) an untreated cancer on active surveillance that may not affect the subject's survival status for ≥3 years based on clinician assessment/statement and with medical monitor approval. For any other cancers that do not meet the criteria above, and for which the natural history or treatment do not have the potential to interfere with the safety or the efficacy assessments of the study, written approval is required by the medical monitor.
7. Have current evidence of corneal keratopathy or retinal disorder including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, macular degeneration, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, vasculature, myocardium, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, small renal cyst or stone calcifications, and asymptomatic coronary calcification.
9. Have impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis (eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis), unless well controlled.
11. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, or Seville oranges or products containing juice of these fruits within 7 days before the first dose of study drug; have taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.
12. Have insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) <1,000/mm^3 (1.0×10^9/L).
    b. Platelets <75,000/mm^3 (<75×10^9/L).
    c. Hemoglobin<8.5 g/dL; transfusion support is allowed if >1 week before randomization and hemoglobin remains stable.
13. Have insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) of the testing laboratory (for subjects with documented Gilbert syndrome, direct bilirubin must be ≤1.5× ULN and enrollment requires approval by the medical monitor).
    b. AST/SGOT and ALT/SGPT >2.5× ULN of the testing laboratory.
    c. Serum creatinine >1.5 × ULN or a calculated (using the Cockcroft-Gault [C-G] formula [Cockcroft 1976]) or measured creatinine clearance of <30 mL/min.

14. Have amylase or lipase >2.0 × ULN.
15. Have abnormal calcium or phosphorus:
    a. Inorganic phosphorus higher than 1.02 × ULN of the testing laboratory.
    b. Total serum calcium (can be corrected) higher than 1.02 × ULN of the testing laboratory.
16. Have clinically significant cardiac disease including any of the following:
    a. New York Heart Association (NYHA) Class ≥2B; subjects with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the NYHA classification.
    b. Uncontrolled hypertension (refer to European Society of Cardiology and European Society of Hypertension guidelines [Williams 2018]).
    c. Presence of CTCAE (version 5.0) Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality.
    d. Unstable angina pectoris or acute myocardial infarction ≤3 months before the first dose of study drug.
    e. QTcF >470 msec (males and females). Note: If the QTcF is >470 msec in the first electrocardiogram (ECG), a total of 3 ECGs separated by ≥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.
    f. History of congenital long QT syndrome.
17. Have had a recent (≤3 months before the first dose of study drug) transient ischemic attack or stroke.
18. If female, are pregnant or nursing (lactating), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.
19. Have a known allergy/hypersensitivity reaction to any components of the study drug.
20. Have any other concurrent disease or condition that, in the view of the investigator, would interfere with study participation.

Investigational product, dosage and mode of administration: Subjects randomly assigned to infigratinib will receive hard gelatin capsules for oral administration of infigratinib 125 mg once daily (administered as one 100-mg capsule and one 25-mg capsule) using a 3 weeks on (Days 1-21) /1 week off (Days 22-28) dosing schedule. Subjects with mild/moderate renal or hepatic impairment should have their dose adjusted as described in the protocol.

Reference therapy, dosage and mode of administration: Subjects randomly assigned to placebo will receive placebo matching in appearance the investigational product (infigratinib), which will be provided as hard gelatin capsules for oral use and will be administered once daily on a 3 weeks on (Days 1-21) /1 week off (Days 22-28) dosing schedule. Subjects with mild/moderate renal or hepatic impairment should have their dose adjusted as described in the protocol.

Duration of treatment: Up to 52 weeks

Criteria for evaluation:

Efficacy: Assessments will consist of CT/magnetic resonance imaging (MRI) scans performed at baseline within 28 days before randomization, every 3 months up to 24 months after start of treatment, and annually thereafter or until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Scan images will be sent for BICR. Cystoscopy (for subjects with a bladder) and urine cytology will be performed at Screening; 3 (C4), 6 (C7), 9 (C10), and 12 (C13) months; at C13D28 or End of Treatment (EOT); every 6 months up to 24 months after start of treatment, and then annually or until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. After metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred, subjects will be followed up for use of anticancer therapy and survival status approximately every 6 months up to 1 year, then annually thereafter until 1 year after the final DFS event goal is reached. Use of anticancer therapy will be collected for all subjects, including from the time of study treatment discontinuation, regardless of reason for discontinuation. For subjects started on a non-study related anticancer therapy after discontinuing from study treatment, imaging assessment of disease status should continue , until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Subjects who come off treatment before the end of the year of treatment for reasons other than recurrence (as stated above) should continue efficacy assessments according to the Schedule of Assessments, including survival follow-up for 1 year after final DFS event goal is reached (ie, EOS). After the EOS (1 year after the DFS primary analysis), subjects will continue to be followed for long-term OS follow-up for approximately 14 years (under a separate protocol).

QOL: Subject quality of life (QOL) will be evaluated at Screening and at every visit through the first 6-month follow-up visit after discontinuation of study drug using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and EuroQOL 5 dimensions, 5 levels questionnaire (EQ-5D-5L).

PK: Blood samples will be collected on Cycle 1 Day 1 predose and 4 hours (±30 min) postdose; on Cycle 1 Day 21 predose and 4 hours (±30 min) postdose; and on Cycle 2 and all subsequent cycles on Day 21 predose and 4 hours (±30 min) postdose. Plasma concentrations of infigratinib and its active metabolites will be measured. The pharmacokinetic (PK) parameters of C_{trough} and C_{max} will also be calculated.

Safety: Assessments will be performed at Screening and visits throughout the treatment period: adverse events (AEs and serious AEs [SAEs]), clinical laboratory tests (blood and urine), physical examinations, vital signs, ECGs (screening, C1D1, C2D1, and C13D28 or EOT only), ECOG performance status, and ophthalmic assessments. Retinal optical coherence tomography (OCT) scan images will be read locally and the scans will be sent to the OCT imaging vendor. AEs and SAEs will be assessed until 30 days post EOT.

Statistical methods:

Sample Size: Approximately 218 subjects will be initially randomly assigned to treatment in this study in a double-blind fashion. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach. The study will start with a group sequential design with 1 interim analysis at approximately 35 confirmed DFS events by BICR (independent of investigator assessment) (50% of the initial event goal). A Haybittle-Peto boundary will be used for the efficacy boundary with a fixed one-sided alpha of 0.00005 spent at the interim analysis for centrally reviewed DFS, and the rest of the alpha (one-sided alpha=0.025) spent at the primary centrally reviewed DFS analysis. Though an efficacy boundary is specified for the interim centrally reviewed DFS analysis, the trial will not stop at the interim analysis if the efficacy boundary is crossed. A Lan DeMets spending function approximating O'Brien-Fleming boundaries will be used for the non-binding futility boundary. Assuming disease will recur in 46% of subjects in the first 2 years and a 5% yearly recurrence rate in the third year and beyond for the placebo group, the required sample size with initial group sequential design is approximately 218 subjects to reach 70 confirmed DFS events by BICR (independent of investigator assessment). This is assuming with 3-year uniform enrollment, 1-year follow-up, 10% yearly drop-out rate, and a hazard ratio (HR) of 0.5. The sample size will provide approximately 80% power to detect a difference in DFS assuming an HR of 0.5, based on a log-rank test controlling type I error at one-sided 0.025.

At the interim analysis, the study uses an adaptive design promising zone approach to adjust sample size and event goal as needed. The details of the sample size adaptation method will be prespecified in the adaptation plan. If no sample size adaption is needed at the interim analysis, the study is projected to reach the planned number of confirmed DFS events by BICR (70 events) 4 years from the randomization of the first subject. If a sample size increase is deemed necessary based on the interim result and the promising zone approach, the sample size/event goal will be increased by maximum of 50% (328/105). If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly time-wise when the adjusted event goal is reached, and the boundary to test centrally reviewed DFS when the adjusted event goal is reached will be based on the original boundary from the initial group sequential design.

Efficacy Analyses: The primary efficacy analysis will be conducted on the intent-to-treat (ITT) population, which will include all subjects who are randomly assigned to treatment. Subjects will be analyzed according to the treatment arm to which they are randomly assigned.

For the primary efficacy endpoint, CHW statistics based on stratified log-rank test (using randomization stratification factors except disease type [UTUC or UBC]) will be used to control type I error in case of sample size increase at the interim analysis. Conventional stratified log-rank test will be used for the inference on centrally reviewed DFS if sample size is not adjusted at interim. Repeated confidence interval (CI) will be provided for the estimated HR based on stratified Cox proportional hazard model.

For the secondary efficacy endpoints DFS (including intraluminal low-risk [noninvasive, low-grade, or high-grade] recurrence), MFS, and OS, a fixed sequence testing procedure will be followed to control the family-wise type I error at a level of one-sided 0.025.

DFS including intraluminal low-risk (noninvasive, low -grade, or high-grade), recurrence will be tested first if the test on centrally reviewed DFS is significant, followed by the test on MFS if both DFS and DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence are significant. OS will be tested finally if DFS, DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, and MFS are all significant.

A Haybittle-Peto boundary will be used for the secondary efficacy endpoints. A fixed one-sided type I error with alpha=0.00005 will be spent at the interim analysis, and the rest of the type I error will be spent at the time of the primary analysis.

For DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence and MFS, 1 interim analysis will be conducted at the time of interim analysis for centrally reviewed DFS, and the primary analysis will be conducted at the primary analysis for centrally reviewed DFS when the DFS event goal is reached. There will be 2 interim analyses for OS, one at the interim centrally reviewed DFS analysis and the other one at the primary centrally reviewed DFS analysis. The primary analysis for OS will be conducted at approximately 1 year after the DFS event goal is reached. For OS analyses, a fixed one-sided type I error with alpha=0.00005 will be spent at each of the interim analyses, and the rest of the type I error will be spent at the time of the primary OS analysis. After EOS (1 year after the primary DFS analysis), subjects will continue to be followed for long-term OS follow up (under a separate protocol) for approximately 14 years or all of the subjects die or drop from this follow up, whichever is earlier. The data for this long-term OS follow-up will be reported in a separate study report.

The same analysis methodology described for centrally reviewed DFS will be applied for statistical analyses for DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, MFS, and OS with corresponding efficacy boundaries.

Sensitivity analyses may be conducted to evaluate the potential effect on efficacy outcomes due to enrollment of subjects refusing cisplatin-based chemotherapy (yes vs no) and reasons why a subject did not receive cisplatin-based chemotherapy (ineligible or refusal) in the 2 treatment arms (active vs placebo), using the Cox regression model with this factor as a covariate. The number of subjects refusing cisplatin-based perioperative therapy will be capped at approximately 10% of the total population (approximately 22 subjects). If sufficient numbers of subjects are enrolled with a component of variant histology, or with microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease, sensitivity analysis will be conducted to account for variations in response. Further details are provided in the Statistical Analysis Plan (SAP).

Safety Analyses: All reported AEs will be assigned to a system organ class and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent AEs (all, serious, related, and deaths within 30 days) will be tabulated by treatment arm graded using CTCAE (version 5.0). Summary tables also will be provided for treatment-emergent AEs leading to study drug modification (discontinuation, hold or reduction).

Interim Analysis: One formal interim analysis of centrally reviewed DFS will be performed when a total of 35 confirmed DFS events by BICR (independent of investigator assessment) has occurred.

At the interim analyses, the study will not be stopped for efficacy if the efficacy boundary for centrally reviewed DFS is crossed.

The study may be stopped due to futility at the interim DFS analysis if the futility boundary for testing centrally reviewed DFS is crossed. The futility stopping boundary is non-binding to allow for additional considerations.

If a sample size increase is deemed necessary based on the interim result on centrally reviewed DFS using the promising zone approach, the sample size/event goal will be increased by a maximum of 50% (328/105). The details of sample size adaptation method will be prespecified in a separate adaptation plan.

Other Information: An independent Data Monitoring Committee (DMC) will review safety and efficacy data at the interim analysis and make recommendations regarding sample size adaptation.

In addition, the DMC will periodically review safety data at regularly scheduled meetings, according to a prespecified DMC charter.

Full details of the planned statistical analyses will be included in the SAP.

2 SCHEDULE OF ASSESSMENTS

Table 2 is a schedule of assessments to be performed during the study. Table 3 outlines detailed sampling times for pharmacokinetic (PK), urine and blood plasma cell-free DNA (cfDNA), and other laboratory parameters. All data obtained from these assessments must be supported in the subject's source documentation.

Molecular prescreening for susceptible fibroblast growth factor receptor 3 (FGFR3) genetic alterations (mutations, and gene fusions or rearrangements; hereafter referred to collectively as "FGFR3 alterations") testing can be conducted any time before the Screening visit.

All baseline/screening assessments, including screening cystoscopy (for subjects with a bladder) and imaging assessments must be conducted within 28 days before randomization. Baseline scans must be sent for blinded independent central review (BICR) to confirm absence of residual or metastatic disease before randomization. In the event that subjects have a baseline/screening laboratory assessment that excludes them from the study, the baseline/screening laboratory assessment can be repeated to re-check their eligibility.

Whenever feasible, vaccinations should be administered at least 30 days prior to randomization.

Baseline/Screening assessments that are conducted within 3 days before the first treatment can be used to satisfy the Day 1 requirement. Every effort must be made to follow the schedule outlined.

Unless otherwise indicated, for Treatment Period there is a minus-3-day window on assessments (study visits on C1D1, C1D4, C1D7, C1D14 and C2D1) or a minus-5-day window (study visits on C4D1, C7D1, C10D1, and C13D1) on assessments to take into account scheduling over weekends and holidays. For study visits on Day 21 of all cycles (C1 to C13) there is a minus-2-day window. For postbaseline imaging assessments, a ±7-day window is allowed, except for the first postbaseline assessment (+7-day window permitted). The end of treatment (EOT) visit is to be conducted no later than 5 days from the decision to discontinue study drug.

For visits that occur every 6 months after the EOT or the End of Study (EOS) visit, a ±7-day window is allowed. For Survival Follow-up visits that occur annually after EOT or the EOS, a ±14-day window is allowed (see Section 9.9 for details on long-term overall survival [OS] follow-up after the EOS).

Table 2: Schedule of Assessments

Assessment	Molecular Prescreening [b]	Screening [b]	Treatment Period Clinic Visits (Cycle and Day) [a]							30-Day Post-Treatment Follow-Up	Every 6 Months after EOT [c] and at EOS	Survival Follow-Up [d]
			C1 D1	C2 D1	C4 D1	C7 D1	C10 D1	C13 D1	C13 D28 or EOT [c]			
Visit Window (days) [e]		**–28 to −1**	**-3**	**-3**	**-5**	**-5**	**-5**	**-5**	**±5**	**±5**	**±7**	**±14**
Informed consent for molecular prescreening	X											
Prescreening FGFR3 alteration testing by F1CDx [b]	X											
FGFR3 alteration documentation		X										
PD-L1 testing [f]			X [f]									
Informed consent [g]		X										
Inclusion/exclusion criteria [g]		X										
Demographics		X										
ECOG performance status		X	X	X	X	X	X	X	X			
Medical history		X										
Diagnosis & extent of cancer		X										
Prior medication and antineoplastic therapy		X										
Ophthalmic assessment [h]		X		X	X	X	X	X	X			
Physical examination [i]		X	X	X	X	X	X	X	X		X	
Weight and BMI (height at screening only)		X	X	X	X	X	X	X	X		X	
Vital signs		X	X	X	X	X	X	X	X		X	
12-Lead ECG [j]		X	X	X					X			
QOL assessment [k]			X	X	X	X	X	X	X		X [k]	
Blood samples:												
Hematology [l,m]		X	Refer to Table 3 for specific schedule						X			
Clinical chemistry [l,m]		X	Refer to Table 3 for specific schedule						X			
Coagulation		X	As clinically indicated									
Pharmacokinetics			Refer to Table 3 for specific schedule									
cfDNA			Refer to Table 3 for specific schedule [n]								X [n]	

Assessment	Molecular Prescreening [b]	Screening [b]	Treatment Period Clinic Visits (Cycle and Day) [a]							30-Day Post-Treatment Follow-Up	Every 6 Months after EOT [c] and at EOS	Survival Follow-Up [d]
			C1 D1	C2 D1	C4 D1	C7 D1	C10 D1	C13 D1	C13 D28 or EOT [c]			
Visit Window (days) [e]		**–28 to −1**	**-3**	**-3**	**-5**	**-5**	**-5**	**-5**	**±5**	**±5**	**±7**	**±14**
Urine samples:												
Urinalysis		X (subjects with a bladder)	As clinically indicated (all subjects)									
Cytology		X			X	X	X	X	X		X	
cfDNA			Refer to Table 3 for specific schedule [n]								X	
Pregnancy test in WOCBP [o]		X	Monthly (refer to Table 3 for schedule)						X			
Chest, Abd/Pelvis CT or MRI scan [p]		X			X	X	X	X	X		X (every 3M) [p]	
Cystoscopy (subjects with a bladder) [q]		X			X	X	X	X	X		X	
Randomization [r]		X										
Administer study drug (3 weeks on [Days 1-21] /1 week off [Days 22-28] [s]			X									
AEs		X [t]	X (Refer to Table 3 for additional schedule)						X	X		
Concomitant medications			X (Refer to Table 3 for additional schedule)						X	X		
Antineoplastic therapies since discontinuation of study treatment										X	X	X
Newly obtained tumor sample (if medically feasible)				Collect upon any disease recurrence [u]								
Survival follow up [d]											X	X

Abbreviations: Abd=abdomen; AE=adverse event; BICR=blinded independent central review; BMI=body mass index; C=cycle; cfDNA=cell-free DNA; CRF=case report form; CT=computed tomography; D=day; DFS=disease-free survival; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EDC=electronic data capture; EORTC=European Organization for Research and Treatment of Cancer; EOS=end of study; EOT=end of treatment; EQ-5D-5L=EuroQOL 5 dimensions, 5 levels questionnaire; F1CDx=FoundationOne CDx test (from Foundation Medicine USA); FGFR3=fibroblast growth factor receptor 3; ICF=informed consent form; M=months; MRI=magnetic resonance imaging; OCT=optical coherence tomography; OS=overall survival; PD-L1=programmed death-ligand 1; PK=pharmacokinetics; QLQ-Core 30=Quality Of Life Questionnaire Core 30; QOL=quality of life; UTUC=upper tract urothelial carcinoma; SAE=serious adverse event; WOCBP=women of childbearing potential.

[a] Additional assessments, including sample collection for clinical laboratory assessments, PK and blood and urine cfDNA assessments, pregnancy testing, and collection of AEs and concomitant medications will be as detailed in Table 3.

[b] Molecular Prescreening: If F1CDx data are not available from testing that occurred as part of the subject's standard of care, molecular prescreening assessments can be done (after signing Molecular Prescreening ICF) any time before the initiation of the Screening visit. Further details are provided in Section 9.1.
Screening: All baseline/screening assessments, including baseline imaging assessments and screening cystoscopy (for subjects with a bladder) must be conducted within 28 days before randomization. Baseline/screening assessments that are conducted within 3 days before the first treatment can be used to satisfy the C1D1 requirement. Every effort must be made to follow the schedule outlined.

[c] After EOT, subjects will be followed up every 6 months until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. The EOT visit should be no later than 5 days after treatment discontinuation. See footnote p regarding schedule of imaging assessments.

[d] After metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred, subjects will be followed up for survival every 6 months for 1 year, then annually thereafter (via phone or office visit) for 1 year after the final DFS event goal is reached (ie, EOS). See Section 9.9 for details on long-term OS follow-up (under a separate protocol).

[e] C1D1 has a minus-3-day window to account for scheduling over weekends and holidays. During study treatment, there is a minus-3-day window on C2D1 assessments and a minus-5-day window on C4D1, C7D1, C10D1, and C13D1 assessments to take into account scheduling over weekends and holidays, if not explicitly specified otherwise. For postbaseline imaging assessments, a ±7-day window is allowed, except for the first postbaseline assessment (+7-day window is permitted).

[f] If local PD-L1 test has been completed and status is available, enter the status information in EDC. If local PD-L1 is not already known, PD L1 testing can be initiated at C1D1 or at any time after the subject is deemed eligible. See Section 10.3 for additional details for PD-L1 testing.

[g] Written informed consent is required before performing any study-specific tests or procedures and may be obtained at any time before such test or procedure. Results of standard-of-care tests or examinations and review of inclusion/exclusion criteria performed before obtaining informed consent and within 28 days before randomization may be used for screening assessments rather than repeating such tests. If the subject did not receive platinum-based chemotherapy in the perioperative setting (see inclusion criterion #4, Section 6.1), the reason must be documented in the CRF.

[h] Ophthalmic assessment (performed by an ophthalmologist) will also be done as clinically indicated. Ophthalmic assessment includes visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure, retinal OCT, and dilated fundoscopy. Additional examination methods such as specular microscopy and corneal pachymetry will be done as clinically indicated. Retinal OCT scans will be read locally and images will be provided to the OCT imaging vendor. Refer to the Study Manual for details regarding image collection and transfer or shipment. Ophthalmic assessment will be conducted at C13D28 or EOT visit unless performed within previous 4 weeks.

[i] Full physical examination at screening, C1D1, and C13D28/EOT; abbreviated or symptom-directed physical examination at C2D1, C4D1, C7D1, C10D1, C13D1, every 6 months after EOT, and at the EOS visit.

[j] For each subject, 12-lead ECGs will be done at Screening; predose on Day 1 of Cycles 1 and 2; and at C13D28 or EOT visit.

[k] QOL assessments should be conducted before study drug administration, AE evaluation, and disease status notification, and preferably in order of EQ-5D-5L then EORTC QLQ-C30. Subjects should complete QOL assessments for 18 months; for subjects who complete all 52 weeks of study drug treatment, the last assessment will be at the first 6-month follow-up visit after discontinuation of study drug. Assessments do not need to be administered at the EOT visit if they were completed within the previous 7 days at a regularly scheduled visit.

[l] Laboratory tests will be collected and analyzed on the scheduled day, even if study drug treatment is being withheld. Laboratory tests must be conducted within the windows specified in the protocol.

[m] Hematology will be assessed at C1D1, C2D21, C4D21, C7D21, C10D21, C13D21, and C13D28 or EOT (refer to Table 3).
Clinical chemistry will be assessed at C1D1, C1D4, C1D7, C1D14, C1D21; Cycles 2-13 (Day 21); and C13D28 or EOT (refer to Table 3).

The schedules for these clinical laboratory tests coincide, as closely as possible, with the blood draws specified for PK and cfDNA (refer to Table 3). Every attempt should be made to collect the clinical chemistry sample at the same time as the PK sample taken at 4 hours after study drug administration.

[n] At the time of local/regional or contralateral invasive or metastatic recurrence, a blood and urine sample will be collected for analysis of cfDNA.

[o] Serum or urine pregnancy test within 7 days before the first dose of study drug; thereafter, pregnancy tests should be conducted monthly (at study visit on Day 21 of each cycle [per Table 3]) and may be serum or urine based on standard at the institution. Where required while the subject is receiving study drug, more frequent urine pregnancy tests may be conducted.

[p] Baseline CT/MRI scans must be performed within 28 days before randomization and must be submitted for BICR to confirm absence of residual or metastatic disease before randomization. For an individual subject, whichever modality (CT or MRI) is used at screening, that same modality should be used for radiographic assessment throughout the study. Refer to the Study Manual for details regarding image collection and transfer or shipment. For postbaseline imaging assessments, a ±7-day window is allowed, except for the first postbaseline assessment (+7-day window permitted). Perform CT/MRI scans every 3 months for a total of 24 months since start of treatment, then annually until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Subjects who discontinue study drug for reasons other than metastatic recurrence by BICR (as stated in the previous sentence) will continue to have radiographic assessments every 3 months for a total of 24 months since start of treatment, then annually until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. A radiographic assessment should be conducted at the EOT visit, unless taken within the previous 4 weeks. CT/MRI scans indicating unequivocal recurrence (as defined in Table 8) must be read locally and submitted for BICR as well as any supporting report (including pathology and cytology reports) if a biopsy was conducted at the time of recurrence. Refer to the Study Manual for details regarding image collection and transfer or shipment.

[q] Perform cystoscopy (for UTUC subjects with a bladder) at Screening, within 28 days before randomization, and at C4D1, C7D1, C10D1, C13D1, and C13D28 or EOT, and then every 6 months for a total of 24 months since start of treatment; then annually until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Subjects who discontinue study drug for reasons other than recurrence (as stated in the previous sentence) will continue to have cystoscopy/cytology as described until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Conduct cystoscopy/cytology at the EOT visit, unless done within the previous 4 weeks.

[r] Randomization will occur after the subject completes the Screening visit and is deemed eligible for study (including documented medical monitor approval) and before C1D1. Treatment starts within 1 week of randomization. Note: only under certain unforeseen circumstances that are not caused by noncompliance or inappropriate planning [eg, adverse weather], randomization may occur after day 120 from definitive surgery but window for randomization and dosing should be 127 days total (120 days +7 days).

[s] Study drug may be dispensed at study visits on Day 1 of C1, C2, C4, C7, C10, and C13 and/or monthly at study visits per local standard practice.

[t] Only report protocol-mandated procedure-related AEs. See Sections 10.5.1.3 and 10.5.1.4 for details on collection and reporting of AEs and SAEs.

[u] Histologic/cytologic confirmation is the preferred criterion to determine unequivocal recurrence, and new lesions should be biopsied to confirm recurrence when safe and feasible. All CT/MRI scans and biopsy reports (including pathology and cytology reports) must be submitted for BICR assessment.

Table 3: Schedule of Assessments: Pharmacokinetic and Blood and Urine cfDNA Sample Collection, Laboratory Parameters, and Adverse Event and Concomitant Medication Assessments

		Parameters						
		PK[a]		cfDNA[a]				
Cycle	Day	Predose (hrs before dose)	Postdose (hrs ±30 min)	Blood and Urine (predose)	Clinical Chemistry[b]	Hematology[b]	Pregnancy Test[c]	AEs and Conmeds
1	1	0	4	X	X	X		X
1	4				X			
1	7				X			
1	14				X			
1	21[d]	0	4	X	X		X	X
2	21[d]	0	4		X	X	X	X
3	21[d]	0	4	X	X		X	X
4	21[d]	0	4		X	X	X	X
5	21[d]	0	4	X	X		X	X
6	21[d]	0	4		X		X	X
7	21[d]	0	4	X	X	X	X	X
8	21[d]	0	4		X		X	X
9	21[d]	0	4	X	X		X	X
10	21[d]	0	4		X	X	X	X
11	21[d]	0	4	X	X		X	X
12	21[d]	0	4		X		X	X
13	21[d]	0	4	X	X	X	X	X
13	28(or EOT)[e]	If within 24 hrs of last dose	NA	If not done within 28 days prior	X	X	X	X

Abbreviations: AEs=adverse events; C=cycle; cfDNA=cell-free DNA; Conmeds=concomitant medications; D=day; eCRF=electronic case report form; EOT=end of treatment; hrs=hours; NA=not applicable; PK=pharmacokinetic(s).

NOTE 1: On the days of PK and cfDNA sampling, subjects should not take their study drug dose at home; subjects should take their study drug with them to the study center where dosing will be supervised and administration time recorded.

NOTE 2: If a subject is not on study drug, then no PK or cfDNA sample will be collected. PK and cfDNA sampling will resume once the subject is back on study drug.

[a] On PK sampling days after C1D1, the time of the last study drug dose (ie, time of infigratinib/placebo administration on the previous day) before the predose PK sample will be recorded in the eCRF. For any subject who permanently discontinues study drug, attempts should be made to collect PK and blood (2 tubes, 16-20 mL) and urine cfDNA samples from the subject at the time of discontinuation, if the samples can be collected within 24 hours of last dose.

[b] Samples for clinical laboratory tests (including hematology, clinical chemistry, and pregnancy) will be collected and analyzed on the scheduled day even if study drug is being withheld; where applicable, every attempt should be made to collect samples for clinical laboratory tests on the same day as PK and cfDNA sample collection (window is minus-3 days for C1D1, C1D4, C1D7, and C1D14). Every attempt should be made to collect the clinical chemistry sample at the same time as the PK sample taken at 4-hours after study drug administration.

[c] Pregnancy test may be serum or urine based on standard at the institution. Where required while the subject is receiving study drug, more frequent urine pregnancy tests may be conducted.

[d] A minus-2-day window before Day 21 is allowed (specifically on Days 19, 20, or 21).

[e] Blood (2 tubes, 16-20 mL) and urine cfDNA samples will be collected at C13D28 or EOT if not done within 28 days before. At the time of local/regional or contralateral invasive or metastatic recurrence, blood (2 tubes, 16-20 mL) and urine samples will be collected for analysis of cfDNA. Sample for PK to be collected if within 24 hours of last dose of study drug.

3 BACKGROUND

3.1 Overview of Disease Pathogenesis, Epidemiology and Current Treatment

3.1.1 Upper Tract Urothelial Carcinomas

In 2018, it was estimated that 150,350 new patients would be diagnosed with urinary system cancer: 81,190 urinary bladder; 65,340 kidney and renal pelvis; and 3820 ureter and other urinary organs. Excluding non-urothelial kidney cancers, approximately 5% to 10% of all urothelial carcinomas are upper tract urothelial carcinomas (UTUCs). The incidence of UTUC is 2 to 3 times greater in men than women (Siegel 2018; Roupret 2015).

In contrast to invasive urinary bladder cancer (UBC), UTUC has a more aggressive clinical course. At the time of diagnosis, 60% of patients with UTUC have invasive cancer compared to 15% to 25% of patients with UBC (Margulis 2009; Roupret 2015). Thirty-six percent (36%) have regional disease and 9% have distant disease (Raman 2010). A large retrospective review of 1363 patients with UTUC who underwent radical nephroureterectomy (RNU) at 12 centers demonstrated that 28% of the total population had recurrence outside of the bladder after RNU (Margulis 2009).

Standard-of-care neoadjuvant, adjuvant, and metastatic disease treatment is based on urothelial histology common to UBC and UTUC. Neoadjuvant and adjuvant treatment regimens containing cisplatin in combination with other cytotoxic agents are administered for 3 to 4 cycles. These regimens are: dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (DDMVAC); gemcitabine and cisplatin; and cisplatin, methotrexate, and vinblastine (CMV; National Comprehensive Cancer Network [NCCN] Guidelines Version 3 2018; European Society of Medical Oncology [ESMO] Guidelines [Bellmunt 2014]).

The peak incidence of UTUC occurs predominantly in 70- to 90-year-old patients who, if eligible for RNU, have 1 remaining kidney following surgery and often have other significant co-morbid conditions making cisplatin-based treatment a challenge (Roupret 2015). Renal function before and after RNU greatly limits the number of patients with UTUC who are eligible for platinum-based neoadjuvant or adjuvant therapy. Retrospective review of 336 patients with UTUC treated with RNU at the Cleveland Clinic using an estimated glomerular filtration rate (eGFR) cutoff of 60 mL/min/1.73 m^2 determined the percentage of patients eligible for platinum-based therapy. The median age was 72 years and the median preoperative eGFR was 59 mL/min/1.73m^2. Before RNU, 48% of patients were eligible for platinum-based therapy and after RNU 22% were eligible; for patients with Stage pT2 to pT4 and/or pN1 to pN3 disease these proportions were 40% and 24%, respectively (Lane 2010; Birtle 2018).

The POUT study, a large randomized trial in UTUC supports the use of standard-of-care adjuvant platinum-based chemotherapy (Birtle 2020). Patients with histologically confirmed Stage pT2 to T4, N0-3, M0 UTUC, World Health Organization (WHO) performance status 0-1, ≤90 days post RNU were randomly assigned (1:1) to 4 cycles gemcitabine and cisplatin (or gemcitabine and carboplatin if their glomerular filtration rate (GFR) was 30-49 mL/min) versus surveillance. There were 260 patients (131 chemotherapy and 129 surveillance patients) in the

intent-to-treat (ITT) population. The distribution of patients by stage was: 28% Stage pT2; 66% pT3; and 91% pN0. The 3-year disease-free survival (DFS) was 71% for chemotherapy patients (95% confidence interval [CI]: 61, 78) and 46% for surveillance patients (95% CI: 36, 56). The metastasis-free survival (MFS) also favored the chemotherapy patients (HR=0.48 [95% CI: 0.31, 0.74; p=0.0007]). Subgroup analysis demonstrated benefit was greater for patients who received gemcitabine and cisplatin (HR 0.35 [95% CI: 0.20,0.61]) compared to patients who received gemcitabine and carboplatin (HR 0.66 [95% CI: 0.35,1.26]). The independent Data Monitoring Committee (DMC) recommended stopping enrollment because the study met the early stopping criteria for efficacy. Patients continue to be followed for OS.

3.1.2 Invasive Urinary Bladder Carcinomas

Approximately 20% of patients with urothelial carcinoma have invasive UBC at the time of diagnosis and only 15% to 25% of Stage T2 or higher invasive UBC tumors have activating FGFR3 alterations (Roupret 2015). Nonetheless, invasive UBC has a poor prognosis and approximately 50% of patients with invasive UBC will develop metastatic disease; 5-year mortality is approximately 50% (Knowles 2015). Phase 3 trials have demonstrated a survival benefit for neoadjuvant cisplatin-based chemotherapy; however, patients with residual disease following neoadjuvant therapy have a poor prognosis (Grossman 2003). In addition, studies suggest that patients with invasive UBC are unlikely to receive neoadjuvant or adjuvant cisplatin-based chemotherapy, in part due to cisplatin ineligibility (Porter 2011). Moreover, postoperative complications can preclude the use of adjuvant cisplatin-based therapy (Donat 2009). Therefore, patients with invasive UBC harboring FGFR3 alterations and either residual disease following neoadjuvant therapy or who are ineligible to receive or refuse cisplatin-based adjuvant chemotherapy will be permitted to enroll into this study. Given the small patient population, it is expected that ≤15% of enrolled patients will have invasive UBC. (Note: No more than 15% of the population will be enrolled with UBC and ≤25% of UTUC patients will have Stage pT2 UTUC [limit will be based on stratification]). The number of subjects refusing cisplatin-based perioperative therapy will be capped at approximately 10% of the total population (approximately 22 subjects).

3.1.3 Overview of the FGFR Family and FGFR Genetic Alterations in Human Malignancies

The fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases (RTKs) consists of 4 members (FGFR1, FGFR2, FGFR3, FGFR4) which serve as high affinity receptors for 22 different fibroblast growth factors (FGFs).

Several lines of evidence support the association and the involvement of FGFRs in human cancer, where genetic alterations leading to abnormal activation and/or deregulated expression of FGFs and FGFRs family members has been found in diverse tumor types.

Somatic activating mutations in FGFR3 have been identified in solid tumors, with high frequency in bladder carcinomas (Cappellen 1999), where FGFR3 overexpression is also reported (Tomlinson 2007). Activating point mutations of FGFR3 have been identified in approximately 40% of bladder tumors overall. Eleven different missense mutations in Exons 7,

10 and 15, have been identified (Knowles 2008). Some of these mutations lead to constitutive activation of the kinase activities of the receptor and downstream signaling, and activation of FGFR family members occurs also as fusion proteins that result from chromosomal rearrangements (eg, translocations) with other genes (Katoh 2019). FGFR1, FGFR2, and FGFR3 gene fusions or translocations (ie, rearrangements) have been identified in diverse cancer types including cholangiocarcinoma, breast cancer, prostate cancer, thyroid cancer, lung squamous cell carcinoma, bladder cancer, oral cancer, head and neck squamous cell carcinoma, and glioblastoma at low frequency (Wu 2013). As noted above, FGFR3 alterations occur in up to two-thirds of patients with UTUC (Sfakianos 2015; Moss 2017; Bagrodia 2019).

3.2 Overview of Infigratinib

Infigratinib (also known as BGJ398, BBP-831, and infigratinib phosphate) is an orally bioavailable, potent, and selective ATP-competitive inhibitor of FGFRs 1-3, which has demonstrated antitumor activity in nonclinical in vitro and in vivo tumor models harboring FGFR genetic alterations. Infigratinib is a tyrosine kinase inhibitor and its chemical name is 3-(2,6-dichloro-3,5- dimethoxyphenyl)-1-{6-[4-(4-ethylpiperazin-1-yl)phenylamino]-pyrimidin-4-yl}-1-methylurea phosphate1 (1:1).

Please refer to the current Investigator's Brochure for the most recent information on infigratinib.

3.3 Nonclinical 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 4 to 5 nM for FGFR1, FGFR2, and FGFR3. Infigratinib is less potent in inhibiting FGFR4, with an IC_{50} of 168 nM.

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 urothelial cancer with FGFR3 mutations or FGFR3 fusions (Wesche 2011; Guagnano 2012; Konecny 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 or on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, infigratinib did lead to increases in serum FGF23 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.

3.4 Clinical Experience with Infigratinib

Please refer to the current Investigator's Brochure for the most recent clinical safety and efficacy information on infigratinib.

This section focuses on results from the single agent, first-in-human Phase 1 study in subjects with advanced solid malignancies for which no further standard therapy existed (CBGJ398X2101). A total of 208 subjects were treated in this study. Infigratinib was evaluated at 9 different dose levels and 3 different dose schedules, ranging from 5 mg/day to 150 mg/day (CBGJ398X2101 Clinical Study Report). Eight dose levels were administered on the once daily (QD) continuous 28-day cycle schedule and 1 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 QD 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 before 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 QD on a 3 weeks on (Days 1-21)/1 week off (Days 22-28) 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 and 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 overall response rate (ORR) (95% confidence interval [CI]) and disease control rate (DCR) (95% CI) were 13.9% (9.10, 19.94) and 49.1% (41.47, 56.83), respectively. The median progression free survival (PFS) for all subjects treated at the MTD/RPTD was 3.12 months (95% CI: 2.10, 3.65 months).

3.4.1 Clinical Pharmacokinetics and Phase 1 Data

The PK of infigratinib and its active metabolites (BHS697, CQM157) have been evaluated following single and repeat daily doses in a Phase 1 study (CBGJ398X2101).

Following a single dose, median T_{max} was approximately 3-4 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 cytochrome P450 3A4 (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 vitro studies indicated that infigratinib inhibits CYP3A4; therefore, a clinical drug-drug interaction study (QBGJ389-106) was conducted to assess the effects of multiple doses of infigratinib on midazolam (a sensitive CYP3A4 substrate). Midazolam exposure in terms of AUC_{inf} and C_{max} was minimally reduced (11% and 1%, respectively). For the active metabolite, 1-hydroxymidazolam, exposure increased by 19% and 26% for AUC_{inf} and C_{max}, respectively. Overall, these results indicate that infigratinib had a small effect on the metabolism of midazolam and can be considered a weak CYP3A4 inhibitor. As such, infigratinib is not expected to have a clinically relevant effect on drugs metabolized by CYP3A4. However, due to the weak inhibition, drugs that are CYP3A4 substrates and have a narrow therapeutic index should be co-administered with caution.

3.4.2 Clinical Safety

The majority of Study CBGJ398X2101 subjects (99.0%) evaluable for safety experienced ≥1 adverse event (AE), with a Grade 3/4 AE reported in 58.7%, regardless of study treatment relationship (CBGJ398X2101 Clinical Study Report; Pal 2018). The incidence of Grade 3/4 AEs was similar at the MTD (52.6%). The majority of these subjects (95.7%) experienced ≥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 subjects, all grades), regardless of study treatment relationship were: hyperphosphatemia (65.4%), constipation (39.9%), decreased appetite (37.5%), fatigue (36.1%), stomatitis (34.1%), and nausea (32.2%). The most common AEs suspected to be study treatment related (occurring in ≥30% of all subjects, all grades) were: hyperphosphatemia (63.5%) and stomatitis (33.7%).

The most commonly reported Grade 3/4 AEs (in ≥4% of all subjects), regardless of study treatment relationship were: hyperlipasemia (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 subjects) were: hyperlipasemia (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% subjects died due to disease progression, 2 subjects died due to sepsis, and 1 subject each died due to respiratory failure, cardiac arrest, and unknown reason.

At least 1 serious adverse event (SAE) (occurring in ≥5% subjects) of any grade, regardless of study treatment 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 subjects. The most commonly reported SAEs, by preferred term (occurring in ≥5% subjects) were: general physical health deterioration (2.9%); pneumonia (2.9%); vomiting (2.9%); dyspnea (2.4%); and, hypercalcemia (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 subjects, by preferred term were: visual impairment, hypercalcemia, hypercreatininemia, hyperlipasemia, and palmar-plantar erythrodysethesia syndrome (PPES) in 1.0% each. Twenty-one subjects (10.1%) discontinued treatment due to AEs that were suspected to be related to study treatment. The common suspected related AEs leading to study treatment discontinuation were: visual impairment, hypercalcemia, hypercreatininemia, hyperlipasemia, and PPES in 1.0% each.

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

Overall, Grade 3 hematology abnormalities were reported in 13.9%, of which, 2 SAEs of anemia were reported in 2 subjects (1 subject 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 subjects.

Eye-related AEs were reported in a total of 44.7% of subjects. 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.

3.4.3 Clinical Efficacy

Efficacy data for all subjects in the dose escalation and dose expansion parts of Study CBGJ398X2101 are available in the Investigator's Brochure. The following efficacy data presented are for subjects with urothelial carcinoma participating in the Arm 4 expansion part (ie, subjects with advanced/metastatic urothelial carcinoma, originating in the bladder, urethra, ureter, or renal pelvis with FGFR3 mutations).

Arm 4 of the expansion part of Study CBGJ398X2101 included 67 subjects with advanced/metastatic urothelial carcinoma with FGFR3 mutations or FGFR fusions who had either progressed on or were intolerant of platinum-based chemotherapy, or had contraindications to platinum-based chemotherapy (Pal 2018). Permitted FGFR3 mutations included mutations in exon 7 (R248C, S249C), exon 10 (G372C, A393E, Y375C), or exon 15 (K652M/T, K652E/Q). These amino acid numbers refer to the functional FGFR3 isoform 3 (NP_001156685.1). All FGFR3 fusions were included. Subjects were treated with oral infigratinib 125 mg/day for 21 days followed by 7 days without treatment as 28-day cycles.

All 67 subjects were evaluable for response. Seventeen subjects (25.4%) had responses (1 CR and 16 PR). Forty-three (43) subjects (64.2%) had disease control (CR + PR + stable disease [SD]). Sixteen subjects (23.9%) had progressive disease and 8 subjects (11.9%) had an indeterminate response. One subject with an indeterminate response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria actually had a pathologic CR; however, due to changing imaging modalities between assessments, the response was reported as unknown (Pal 2018). The subject had primary bladder cancer and a histologically confirmed metastasis in the humerus. During infigratinib treatment, the subject had surgical resection of a suspected

pathologic fracture of the humerus. Histologic assessment revealed no evidence of residual disease.

3.5 Rationale

3.5.1 Study Rationale and Purpose

UTUC comprises approximately 5% to 10% of all urothelial carcinomas (Roupret 2015). At the time of diagnosis, 60% of patients with UTUC have invasive cancer (Roupret 2015), 36% have regional disease and 9% have distant disease (Raman 2010), and 28% have recurrence outside of the bladder after RNU (Margulis 2009). The peak incidence of UTUC occurs in 70- to 90-year-old patients (Shariat 2011; Roupret 2015). To reduce the morbidity and mortality in patients with UTUC, neoadjuvant or adjuvant treatment is needed. The POUT study, a large randomized trial in UTUC supports the use of standard-of-care adjuvant cisplatin-based chemotherapy (Birtle 2020). Because many patients with UTUC will have 1 remaining kidney following RNU and frequently have other significant co-morbid conditions, cisplatin-based therapy is not well tolerated (NCCN Guidelines Version 3.2018; ESMO Guidelines [Bellmunt 2014]). Renal function before and after RNU greatly limits the number of patients with UTUC who are eligible for platinum-based neoadjuvant or adjuvant therapy. Therefore, targeted therapies are needed (Lane 2010).

Despite demonstrated survival benefit for neoadjuvant treatment of invasive UBC, many patients with invasive UBC are unlikely to receive (neo)adjuvant cisplatin-based chemotherapy, due in part to cisplatin ineligibility (Porter 2011). In addition, residual disease following neoadjuvant therapy is associated with a poor prognosis (Grossman 2003). Therefore, there remains an unmet need for a substantial proportion of patients with invasive UBC who are ineligible to receive cisplatin-based adjuvant chemotherapy or who have residual disease following neoadjuvant therapy. The proportion of cancer patients who refuse chemotherapy in general varies between 3% and 19% (Frenkel 2013; Rehman 2013). Whereas the NCCN Guidelines for Bladder Cancer (Version 5.2020) recommend treatment with cisplatin-based peri-operative chemotherapy, there are no other recommended treatments with Level 1 evidence for neoadjuvant or adjuvant treatment for patients who refuse this therapy. Thus, for these patients, treatment options are limited to active surveillance or participation in clinical studies. To avoid unnecessarily excluding patients who are otherwise eligible but refuse treatment with cisplatin-based chemotherapy even after being informed of the limited options, these patients will be allowed to enroll in the study.

The most frequent genetic alterations in UTUC affect the FGFR3 gene and occur in up to two-thirds of UTUC (Sfakianos 2015; Moss 2017; Bagrodia 2019). FGFR3 alterations are also identified in invasive UBC, although at a far lower rate (<20%) (Knowles 2015).

Infigratinib is rationally designed to target cancers with susceptible FGFR3 alterations. Phase 2 infigratinib data derived from Arm 4 of the expansion part of Study CBGJ398X2101 included 67 subjects with advanced/metastatic urothelial carcinoma with susceptible FGFR3 alterations who had either progressed on or were intolerant of platinum-based chemotherapy, or had contraindications to platinum-based chemotherapy. Seventeen subjects (25.4%) had responses

(1 CR and 16 PR). Forty-three (43) subjects (64.2%) had disease control (CR + PR + SD). Sixteen subjects (23.9%) had progressive disease and 8 subjects (11.9%) had an indeterminate response. In addition, 1 subject with an indeterminate response by RECIST criteria actually had a pathologic CR (Pal 2018). Eight (8) of the 67 subjects had advanced UTUC and 4 of 8 (50%) subjects had confirmed responses (1 CR and 3 PR) (Dizman 2019). These Phase 2 data demonstrate significant activity in advanced/metastatic urothelial carcinoma with FGFR3 mutations and support the use infigratinib in the adjuvant setting where subjects with less tumor burden are more likely to benefit for a targeted therapy. This Phase 3 study addresses this unmet need for an adjuvant therapy for subjects with UTUC who are ineligible or refuse to receive cisplatin-based adjuvant chemotherapy or who have residual disease following neoadjuvant chemotherapy. Although the population of subjects with susceptible FGFR3-altered invasive UBC is much smaller, subjects with invasive UBC who fit the same criteria will be permitted to enroll in the trial.

3.5.2 Rationale for the Study Design

This is a Phase 3 multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy of infigratinib in adult subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations who are within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and ineligible for or refuse cisplatin-based (neo)adjuvant chemotherapy or who have residual disease following neoadjuvant therapy. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach (Mehta 2011). Subjects with invasive urothelial carcinoma includes subjects with invasive UTUC and UBC.

Subjects will be stratified according to lymph node involvement, prior neoadjuvant cisplatin chemotherapy, Stage (pT2 vs >pT2), and disease (UTUC vs UBC), and then randomly assigned (1:1) to receive oral infigratinib or placebo administered QD for the first 3 weeks (21 days) of each 28-day cycle for a maximum of 52 weeks (13 cycles), or local/regional or contralateral invasive or metastatic recurrence (whichever occurs first) is confirmed by BICR, or other criteria specified in Section 8.1.1 are met, whichever occurs first.

The use of a placebo control is justified because there is no standard-of-care adjuvant therapy for patients with invasive urothelial carcinoma who are ineligible to receive cisplatin-based adjuvant chemotherapy or who have residual disease following neoadjuvant therapy (NCCN Guidelines Version 3.2018; ESMO Guidelines [Bellmunt 2014]). Placebo comparator was chosen over surveillance to reduce unbalanced dropout in the comparator arm and to allow for determination of background rates of AEs, including ophthalmic events, in the population under study.

Subjects who refuse cisplatin-based chemotherapy will be informed of available treatment options during a well-balanced risk-benefit discussion between the investigator and the subject; this will also be specified in the informed consent form (ICF) to ensure that subjects are fully informed and aware that they may be deferring a standard treatment by enrolling in this trial. The reason that a subject did not receive cisplatin-based chemotherapy in the perioperative setting will be clearly documented in the electronic case report form (eCRF).

Stratification before randomization is essential to ensure balance of significant prognostic variables between the infigratinib and placebo-treated groups.

The surveillance plan is consistent with standard-of-care follow-up procedures (Table 2; NCCN Guidelines Version 3.2018; ESMO Guidelines [Bellmunt 2014]).

An interim analysis will be conducted after approximately 35 confirmed DFS events by BICR (independent of investigator assessment) have occurred. Based on the results of the interim analysis, if a sample size increase is deemed necessary using the promising zone approach, the sample size/event goal will be increased by a maximum of 50% (328/105). If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly time-wise when the adjusted event goal is reached. The details of the sample size adaptation method will be prespecified in the adaptation plan.

3.5.3 Rationale for Dose and Regimen Selection

In this study, subjects randomly assigned to the infigratinib group will receive 125 mg QD of infigratinib on a 3 weeks on (Days 1-21)/1 week off (Days 22-28) schedule. This dose level and regimen is based on experience from the Phase 1 CBGJ398X2101 trial (Section 3.4.1). Subjects with mild/moderate renal or hepatic impairment should have their study drug dose adjusted because the relative potency-adjusted steady state AUC of infigratinib and its metabolites is increased in these subjects compared with that for subjects with normal organ function. Refer to Section 7.2.1 for dosing recommendations and the current Investigator's Brochure for recent clinical safety updates.

3.6 Benefit/Risk Assessment of Study Participation

Subjects enrolled in this study have high unmet medical need, as described in Section 3. Current US and European Union (EU) guidelines do not recommend perioperative chemotherapy for patients who are not candidates for cisplatin (NCCN Guidelines Version 3, 2018; ESMO Guidelines [Bellmunt 2014]; Milowsky 2016). Participation in Study QBGJ398-302 offers the possibility of adjuvant treatment with infigratinib for these subjects. Study subjects will be randomly assigned (1:1) to either infigratinib or placebo.

Infigratinib, which targets FGFR3 genetic alterations, has shown preliminary evidence of efficacy in subjects with urothelial carcinoma (Section 3.4.3) and has an acceptable safety profile in this study population (Section 3.4.2). Reported adverse effects across the infigratinib development program are consistent with its mechanism of action (eg, hyperphosphatemia, etc.), and can be adequately managed/reversed through dose modification/supportive care, thus minimizing risk to study subjects who receive infigratinib.

Subjects will be closely monitored for safety. Safety assessments that will be performed at Screening and visits throughout the treatment period include: adverse events (AEs and SAEs), clinical laboratory tests (blood and urine), physical examinations, vital signs, and electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, and ophthalmic assessments. In addition, AEs/SAEs will be collected up to 30 days after the last study dose.

This study offers subjects an opportunity to receive adjuvant therapy who would otherwise not be eligible for such treatment, outside of possibly another investigational treatment. Subjects, regardless of the treatment group to which they are randomly assigned, will receive close medical monitoring and care throughout their participation in the study. Subjects are required to comply with the study visit schedule and procedures in order to receive this potentially efficacious/beneficial investigational adjuvant therapy with infigratinib, and also to monitor, manage, and mitigate its safety risks.

4 OBJECTIVES AND ENDPOINTS

Table 4 presents the study objectives and endpoints defined in Section 10.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary:	
To determine if treatment with infigratinib improves centrally reviewed disease-free survival (DFS) compared with placebo treatment in subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations after nephroureterectomy, distal ureterectomy, or cystectomy	Centrally reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier
Secondary:	
To compare DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence in subjects treated with infigratinib vs placebo	Investigator-reviewed DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, from date of randomization to any recurrence or death due to any cause, whichever occurs earlier
To compare metastasis-free survival (MFS) of subjects treated with infigratinib vs placebo	Investigator-reviewed MFS, from date of randomization to metastatic recurrence or death due to any cause, whichever occurs earlier
To compare OS in subjects treated with infigratinib vs placebo	OS (from date of randomization to death)
To compare investigator-reviewed DFS in subjects treated with infigratinib vs placebo	Investigator-reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier
To characterize the safety and tolerability of infigratinib when administered as postoperative adjuvant monotherapy	Type, frequency, and severity of adverse events and serious adverse events, laboratory abnormalities, and other safety findings
Exploratory:	
To compare QOL in subjects treated with infigratinib vs placebo	QOL as measured by the EQ-5D-5L and the EORTC QLQ C30
To evaluate the PK of infigratinib	PK parameters (trough and maximum plasma concentration)
To evaluate the overall genomic landscape in subjects with invasive urothelial carcinoma	Determine the prevalence of genomic alterations and their correlations with available clinicopathologic and demographic features in subjects with invasive urothelial carcinoma.
To evaluate biomarkers related to the biology of urothelial carcinoma and their potential association with efficacy, disease recurrence, and resistance to study medication.	Genomic and proteomic assessments of tumor tissue and cell-free DNA samples from baseline to disease recurrence and the determination of the prognostic and/or predictive value of biomarkers.

Abbreviations: DFS=disease-free survival; EORTC=European Organization for Research and Treatment of Cancer; EQ-5D-5L=EuroQOL 5-dimensions, 5-levels questionnaire; FGFR3=fibroblast growth factor receptor 3; MFS=metastasis-free survival; OS=overall survival; PK=pharmacokinetics; QLQ-C30=Quality of Life Questionnaire Core 30; QOL=quality of life.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a Phase 3 multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy of infigratinib in approximately 218 adult subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations who are within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and ineligible for or refuse cisplatin-based adjuvant chemotherapy or with residual disease following neoadjuvant therapy. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach. Subjects with invasive urothelial carcinoma includes subjects with invasive UTUC and UBC.

Prior neoadjuvant therapy is defined as at least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m^2/cycle. Subjects who received non-cisplatin-based neoadjuvant treatment should be considered as having received no neoadjuvant chemotherapy.

A study schematic is presented in Figure 1

Subjects who meet eligibility criteria will be randomly assigned 1:1 to receive oral infigratinib or placebo administered QD for the first 3 weeks (21 days) of each 28-day cycle for a maximum of 52 weeks (13 cycles), or until BICR confirmed local/regional or contralateral invasive or metastatic recurrence (whichever occurs first) (see Section 10.1 for definitions of recurrence), or until other criteria specified in Section 8.1.1 are met, whichever occurs first.

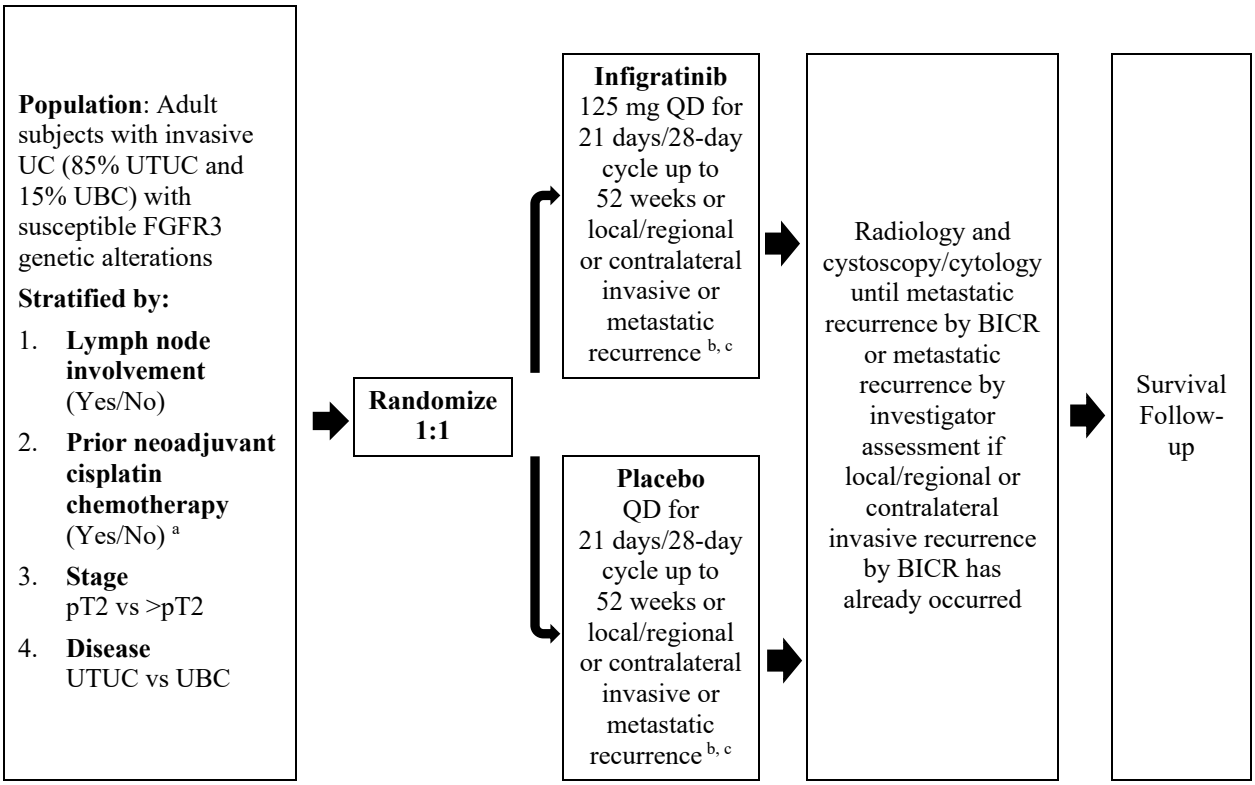
Subjects will be evaluated for tumor recurrence radiographically every 3 months for the first 24 months after the start of treatment, and annually thereafter or until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Cystoscopy (for subjects with a bladder) and urine cytology/cfDNA will be performed at 3 (C4), 6 (C7), 9 (C10), and 12 (C13) months, then every 6 months up to 24 months after start of treatment, and then annually until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. After metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred, subjects will be followed up for survival status and use of anticancer therapy approximately every 6 months (via phone or office visit) up to 1 year, then annually thereafter until 1 year after the final DFS event goal is reached (ie, EOS) (Section 9.9). (See Section 9.9 for details on long-term OS follow-up after EOS). Use of anticancer therapy will be collected for all subjects, including from the time of study treatment discontinuation, regardless of reason for discontinuation. For subjects started on a non-study related anticancer therapy after discontinuing from study treatment, imaging assessment of disease status should continue until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred.

Subjects should remain on study treatment until local/regional or contralateral invasive or metastatic recurrence is confirmed by BICR. If BICR confirms recurrence (local/regional or contralateral invasive or metastatic recurrence, whichever occurs first), the subject must be permanently discontinued from study treatment. BICR diagnosis of a local/regional or contralateral invasive or metastatic recurrence, independently from and undiagnosed by local team, will not be communicated to the clinical site (additional details are provided in Section 8.1.1).

An interim analysis will be conducted after approximately 35 confirmed DFS events by BICR (independent of investigator assessment) have occurred, ie, half of the planned number of 70 confirmed DFS events by BICR (independent of investigator assessment) (see Section 11.2). Based on results of the interim analysis, if a sample size increase is deemed necessary using the promising zone approach, the sample size/event goal will be increased by a maximum of 50% (328/105). If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly time-wise when the adjusted event goal is reached. The details of the sample size adaptation method will be prespecified in the adaptation plan.

Subjects will be stratified according to lymph node involvement (yes vs no), prior neoadjuvant cisplatin chemotherapy (yes vs no), Stage (pT2 vs >pT2), and disease (UTUC vs UBC). Staging is described by Amin (2017).

Figure 1: Study Design



Abbreviations: BICR=blinded independent central review; FGFR3=fibroblast growth factor receptor 3; QD=once daily; UBC=urothelial carcinoma of the bladder; UC=urothelial carcinoma; UTUC=upper tract urothelial carcinoma.

a Prior neoadjuvant cisplatin chemotherapy is defined as at least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m^2/cycle. Subjects who received less than this or non-cisplatin-based neoadjuvant treatment will be considered as having received no neoadjuvant chemotherapy.
b Subjects with mild/moderate renal or hepatic impairment should have their dose adjusted; see Section 7.2.1 for dosing recommendations.
c Refer to Section 8.1.1 for guidance on treatment when recurrence is not confirmed by BICR.

5.2 Number of Subjects

Approximately 218 subjects with histologically confirmed invasive urothelial carcinoma with susceptible FGFR3 alterations within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and who are ineligible for or refuse cisplatin-based adjuvant chemotherapy or with residual disease following neoadjuvant therapy are planned for study participation. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach.

5.3 Time on Study and End of Study Definition

End of study is defined as 1 year after the final number of confirmed DFS events by BICR is reached (planned number of confirmed DFS events is 70). The expected duration of the study is approximately 5 years.

After the EOS (1 year after the DFS primary analysis), subjects will continue to be followed for OS (under a separate protocol) for approximately 14 years, or all of the subjects die or drop from this follow up, whichever is earlier, referred to as long-term OS follow-up (Section 9.9).

The duration of time spent on study treatment will vary for individual subjects. Subjects will receive study treatment for a maximum of 52 weeks (13 cycles), or until BICR-confirmed local/regional or contralateral invasive or metastatic recurrence (whichever occurs first), or until other criteria specified in Section 8.1.1 are met, whichever occurs first. Subjects who complete 52 weeks of treatment and subjects who discontinue study treatment for any reason (except withdrawal of consent) will remain in the study and will be followed up until metastatic recurrence, including after initiation of a non-study anticancer therapy, as described in Section 9.8. Use of anticancer therapy will be collected for all subjects, including from the time of study treatment discontinuation, regardless of reason for discontinuation. All subjects will be followed up for survival status and use of anticancer therapy for 1 year after the final number of DFS events are reached (ie, EOS) (see Section 9.9). After the final DFS goal is reached, subjects will continue to be followed for long-term OS follow up for approximately 14 years as described above and in Section 9.9.

6 STUDY POPULATION

6.1 Inclusion Criteria

To be eligible for the study, a subject must meet all of the following criteria:

1. Are ≥18 years of age (≥20 years of age in Taiwan) of either sex.

2. Have signed informed consent.
3. Are randomized within 120 days following nephroureterectomy, distal ureterectomy or cystectomy. Note: at the time of definitive surgery, lymph node dissection (LND) should be performed in cases of suspected lymph node invasion based on preoperative imaging or intraoperative findings. In other cases, LND is to be performed in accordance with surgeon preferences/local standard practices. Additional details on recommended standards for LND are provided in Appendix 4 (Section 17.4).
4. Have histologically or cytologically confirmed, invasive urothelial carcinoma with susceptible FGFR3 alterations. Variant histology is allowed provided urothelial carcinoma is predominant (>50%). Neuroendocrine (including small and large cell), sarcomatoid, and plasmacytoid variants are excluded (any component).

    a. Regarding samples and documentation of FGFR3 alterations (see also Section 10.3):

        i. FGFR3 mutation is confirmed if: FGFR3 gene is mutated in Exon 7 (R248C, S249C), Exon 10 (G370C, A391E, Y373C), or Exon 15 (K650M/T, K650E/Q)

        OR

        ii. FGFR3 gene fusion or FGFR3 rearrangement is confirmed based on the following genomic criteria: if:

            (1) Any fusion/rearrangement with a literature-derived known partner gene regardless of strand or frame.

            (2) Fusion/rearrangements in the same strand that are in frame with a novel partner gene.

            (3) Fusion/rearrangements with one breakpoint in the intron 17 - exon 18 hotspot region and the other breakpoint in an intergenic region or another gene. This rule excludes 3′ duplications comprising only exon 18.

        iii. The amino acid numbers for the FGFR3 mutations refer to the functional FGFR3 isoform 1 (NP_000133.1) that is the NCBI Refseq ID used to report genetic alterations in FGFR3 by the FoundationOne® CDx test (F1CDx, Foundation Medicine, USA).

        iv. Written documentation of central laboratory determination by F1CDx of FGFR3 alterations is required for study eligibility.

        v. For subjects who require molecular prescreening to confirm the presence of the FGFR3 alteration to meet the inclusion criteria, a tumor sample with a pathology report must be sent to Foundation Medicine USA for F1CDx testing. (See Appendix 5 [Section 17.5] for instructions for optimal tumor specimens).

            (1) The tumor sample to be used should be from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy).

(2) An archival biopsy of confirmed invasive urothelial carcinoma (≥pT2) can be used if (1) tissue from definitive surgery cannot be submitted, (2) the biopsy sample is not older than 4 months prior to surgery date and (3) the subject did not receive any type of systemic anticancer treatment since the biopsy was obtained. If more than one biopsy is available, the most recent one is to be sent.

b. If status post neoadjuvant chemotherapy, pathologic stage at surgical resection must be Stage ≥ ypT2 and/or yN+. Prior neoadjuvant therapy is defined as at least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m^2/cycle. Subjects who received less than this or non-cisplatin-based neoadjuvant treatment are not excluded. If enrolled, they will be stratified as having received no neoadjuvant chemotherapy.

c. If not status post neoadjuvant chemotherapy, is ineligible to receive cisplatin-based adjuvant chemotherapy based on Galsky (2011):

   i. Creatinine clearance ≤60 mL/minute, or

   ii. Common Terminology Criteria for Adverse Events (CTCAE version 5.0) Grade ≥2 hearing loss, or

   iii. CTCAE Grade ≥2 neuropathy.

d. Subjects who refuse cisplatin-based chemotherapy or who are ineligible to receive cisplatin-based chemotherapy based on Galsky (2011), must also meet the following criteria:

   i. UTUC should be Stage ≥pT2 pN0-2 (post-lymphadenectomy or no lymphadenectomy [pNx]) , or pN+, M0.

   ii. UBC should be Stage ≥pT3 or pN+, M0.

e. Must have a centrally reviewed negative postoperative computed tomography (CT) (defined as lymph nodes with short axis <1.0 cm and without growth and no distant metastases according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or negative biopsy within 28 days before randomization to confirm absence of disease at baseline.

5. If have had AEs associated with prior surgery or neoadjuvant chemotherapy, they have stabilized or resolved to Grade ≤2 before randomization.

6. Have Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

7. If a woman of childbearing potential, 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 ≥6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for ≥12

months, and there is no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

Women of childbearing potential and males whose sexual partners are women of childbearing potential must agree to use barrier contraception and a second form of contraception (Clinical Trials Facilitation Group 2020) while receiving study drug and for 1 month 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 (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. (Highly effective contraception methods are specified in Appendix 3 [Section 17.3].)

Sexually active males must use a condom during intercourse while taking study drug and for 1 month after the last dose of 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 study drug via seminal fluid.

Study subjects must agree to refrain from donating sperm and eggs during the study and for 1 month following their last dose of study drug.

8. Are willing and able to comply with study visits and study procedures.

6.2 Exclusion Criteria

To be eligible for the study, a subject must not meet any of the following criteria:

1. Presence of positive invasive surgical margins following nephroureterectomy, distal ureterectomy, or cystectomy. In subjects not eligible for further surgery, radiotherapy, or other efficacious treatment, microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease are allowed.
2. Have received Bacillus Calmette-Guerin (BCG) or other intravesical therapy for nonmuscle invasive bladder cancer (NMIBC) within the previous 30 days.
3. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or 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. See Appendix 2 (Section 17.2).
   Prior anticancer or other therapies are restricted as follows:

   a. Prior adjuvant treatment for urothelial cancer is not allowed.

   b. Prior neoadjuvant therapy (eg, chemotherapy, immunotherapy, or investigational) is allowed if inclusion criterion #4 is met.
      Prior neoadjuvant chemotherapy must have been completed within a period of time that is greater than the cycle length used for that treatment before first dose of study drug.

c. Prior biologic, immunotherapy, or investigational therapy should have been completed within a period that is ≥5 half-lives or 30 days, whichever is shorter, before the first dose of study drug.

4. Are planning to receive other systemic therapies intended to treat invasive urothelial carcinoma while on this study.
5. Have previously or currently is receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor.
6. Have a history of primary malignancy within the past 3 years other than (1) invasive UBC or UTUC (ie, disease under study), (2) noninvasive urothelial carcinoma, (3) any adequately treated in situ carcinoma or non-melanoma carcinoma of the skin, (4) any other curatively treated malignancy that is not expected to require treatment for recurrence during participation in the study, or (5) an untreated cancer on active surveillance that may not affect the subject's survival status for ≥3 years based on clinician assessment/statement and with medical monitor approval. For any other cancers that do not meet the criteria above, and for which the natural history or treatment do not have the potential to interfere with the safety or the efficacy assessments of the study, written approval is required by the medical monitor.
7. Have current evidence of corneal keratopathy or retinal disorder including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, macular degeneration, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, vasculature, myocardium, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, small renal cyst or stone calcifications, and asymptomatic coronary calcification.
9. Have impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis (eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis), unless well controlled.
11. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, or Seville oranges or products containing juice of these fruits within 7 days before the first dose of study drug; have taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.
12. Have insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) <1,000/mm^3 (1.0×10^9/L).
    b. Platelets <75,000/mm^3 (<75×10^9/L).

c. Hemoglobin <8.5 g/dL; transfusion support is allowed if >1 week before randomization and hemoglobin remains stable.

13. Have insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) of the testing laboratory (for subjects with documented Gilbert syndrome, direct bilirubin must be ≤1.5 × ULN and enrollment requires approval by the medical monitor).
    b. AST/SGOT and ALT/SGPT >2.5 × ULN of the testing laboratory.
    c. Serum creatinine >1.5 × ULN or a calculated (using the Cockcroft-Gault [C-G] formula [Cockcroft 1976]) or measured creatinine clearance of <30 mL/min.
14. Have amylase or lipase >2.0 × ULN.
15. Have abnormal calcium or phosphorus:
    a. Inorganic phosphorus higher than 1.02 × ULN of the testing laboratory.
    b. Total serum calcium (can be corrected) higher than 1.02 × ULN of the testing laboratory.
16. Have clinically significant cardiac disease including any of the following:
    a. New York Heart Association (NYHA) Class ≥2B; subjects with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the NYHA classification.
    b. Uncontrolled hypertension (refer to European Society of Cardiology and European Society of Hypertension guidelines [Williams 2018]).
    c. Presence of CTCAE v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality.
    d. Unstable angina pectoris or acute myocardial infarction ≤3 months before the first dose of study drug.
    e. Average QTcF >470 msec (males and females). Note: If the QTcF is >470 msec in the first ECG, a total of 3 ECGs separated by ≥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.
    f. History of congenital long QT syndrome.
17. Have had a recent (≤3 months before the first dose of study drug) transient ischemic attack or stroke.
18. If female, are pregnant or nursing (lactating), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.
19. Have a known allergy/hypersensitivity reaction to any components of the study drug.
20. Have any other concurrent disease or condition that, in the view of the investigator, would interfere with study participation.

7 TREATMENTS

7.1 Treatments Administered

Subjects will receive hard gelatin capsules of infigratinib (or matching placebo) for oral use at a dose of 125 mg QD (administered as one 100-mg capsule and one 25-mg capsule) QD using a 3 weeks on (Days 1-21)/1 week off (Days 22-28) schedule for each 28-day treatment cycle. Treatment with study drug will continue for a maximum of 52 weeks (13 cycles; Cycle 1 [C1] through Cycle 13 [C13]), or until local/regional or contralateral invasive or metastatic recurrence (whichever occurs first) is confirmed by BICR, or until other criteria specified in Section 8.1.1 are met, whichever occurs first. Subjects with mild/moderate renal or hepatic impairment should have their dose adjusted; see Section 7.2.1 for dosing recommendations. Study drug may be dispensed at study visits on Day 1 of C1, C2, C4, C7, C10, and C13 and/or monthly at study visits per local standard practice.

7.2 Information on Dosing with Study Drug

7.2.1 Subject Instructions for Dosing

Subjects with mild or moderate renal impairment (creatinine clearance 30 mL/min to ≤89 mL/min) should be administered a starting dose of 100 mg QD infigratinib on a 3 week on (21 day)/1 week off (7 day) schedule. Subjects with mild (total bilirubin >ULN to 1.5×ULN or AST >ULN) and moderate hepatic impairment (total bilirubin >1.5 to 3×ULN with any AST) should be administered a starting dose of 100 and 75 mg QD of infigratinib, respectively, on a 3 weeks on (21 day)/1 week off (7 day) schedule. For subjects with combined hepatic and renal impairment, the lower of the 2 starting doses should be administered.

Subjects should be instructed to take the daily dose of study drug in the morning, at approximately the same time each day (24±4-hour interval). Subjects will take their first dose of study drug at the study center on Cycle 1 Day 1 (C1D1). On the days of PK sampling, subjects should not take their study drug dose at home; subjects should bring their study drug with them to the study center where dosing of study drug will be supervised and administration time recorded. Administration may fall outside of the ±4-hour interval on the days of PK sampling. On PK sampling days after C1D1, the time of the last study drug dose (ie, time of study drug administration on the previous day) before the predose PK sample will be recorded in the eCRF.

Study drug 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 study drug in the morning (other than on a day of PK sampling), he/she should not take the dose more than 4 hours after the usual time and should continue treatment the next day. Any such 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 study drug, re-dosing is not permitted the same day. Dosing should resume the next day. If vomiting occurs on a PK sampling day within the first

4 hours postdosing, this event is to be noted on the Dose Administration page of the eCRF, as well as on the AE page, as appropriate.

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 (eg, omeprazole), H_2-antagonists (eg, ranitidine) and antacids. Proton pump inhibitors are prohibited due to their long pharmacodynamic (PD) effect and should be replaced with H_2-antagonists or antacids. Study drug should be taken ≥2 hours before or 10 hours after dosing with H_2-antagonists. Antacids, locally-acting acid neutralizing agents, are to be separated from study drug doses by 2 hours.

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

If a subject is not taking study medication (eg, study treatment is on hold for an AE), then no PK sample will be collected. PK sampling will resume once the subject is back on study medication.

If study drug is on hold for ≤14 days, and the criteria for restarting treatment are met, study treatment can be restarted on any day of the cycle between D1 to D21. Study drug should not be restarted on D22 through D28 of a cycle; if criteria for treatment restart fall on a day between D22 and D28, treatment restart must wait until D1 of the next cycle.

7.2.2 Description of Test Article

Study drug (test article) will be supplied as hard gelatin capsules for oral use at dose strengths of 25 and 100 mg or matching placebo. Excipients will include microcrystalline cellulose, lactose monohydrate, hypromellose 2910, crospovidone, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule. Infigratinib and the matching placebo will be manufactured under Good Manufacturing Practice (GMP) for investigational use.

The study center pharmacist or designee will dispense the correct number and dose strength of capsules to ensure the subject receives sufficient drug for each 28-day treatment cycle. Study drug will be dispensed to the subject by authorized trained study center personnel only.

7.2.3 Packaging and Labeling

Study drug capsules will be packaged in high-density polyethylene (HDPE) bottles with intact induction seal child-resistant closures. Medication labels will be in the local language and comply with the legal requirements of each country. Labels will include storage conditions for the drug.

7.2.4 Study Drug Accountability, Handling, and Disposal

Study drug capsules will be received by designated personnel at the study center, handled and stored safely and properly, and kept in a secured location to which only the investigator and

designated study center personnel have access. Upon receipt, study drug 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 study drug in a drug accountability log. Subjects will be asked to return all used and unused bottles of study drug 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 and/or study personnel, and captured in a subject drug accountability log. This information must be captured in the source document at each subject visit. Drug accountability will be completed by the field monitor during study center visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will provide access to all used and unused bottles of study drug, packaging, drug labels, and a copy of the completed drug accountability log to the field monitor.

At study close-out, study drug can be destroyed at the study center if permitted by local regulations. Alternatively, the study drug can be destroyed at a third-party depot.

7.2.5 Dose Modifications for Study Drug

Subject management and treatment decisions will be based upon Investigator evaluations.

7.2.5.1 Dose Modifications and Delays

For subjects who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the subject to continue the study treatment. For these subjects, the dosing guidelines outlined below will be followed. All dose modifications related to tolerability should be based on the worst preceding toxicity as described in Table 6 (AEs considered possibly related to study drug) and Table 7 (skin toxicity). In addition, per investigator's medical judgment, dose modification (hold) can be applied for subject's safety (eg, perioperatively); the medical monitor must be consulted for dose modifications that are not related to tolerability issues. Dosage changes must be recorded on the Dose Administration page of the eCRF.

The following guidelines should be applied.

- Each subject may be allowed up to 3 study drug dose reductions according to protocol-specified dose modifications for AEs. Prospective sponsor medical monitor approval is required for the third dose reduction (Table 5). Note: the minimum daily dose allowed in the study is 50 mg.
- Treatment-related toxicity will be managed as detailed in Table 6, and additional guidelines in the protocol, or following institutional guidelines. Management of related toxicity, including during a period of study treatment hold, will continue until the toxicity is stable at Grade ≤1, returns to baseline, or in accordance with the assessment of the treating physician.
- 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 permanently discontinue the study drug for a study-related AE or an abnormal laboratory value must be followed up as described in Section 7.2.5.2.
- Study drug must be permanently discontinued for a delay of >14 days due to a treatment-related toxicity and may only be restarted with written permission of the medical monitor if (1) the delay is not due to an AE that requires permanent study drug discontinuation as provided in Table 6, and (2) the subject has not met other criteria requiring study drug discontinuation as provided in Section 8, and (3) it is the investigator's opinion that no safety concerns are present. In situations where a delay of >14 days is needed for a treatment-related AE requiring permanent study drug discontinuation (see Table 6), with prospective sponsor medical monitor approval, the delay may be extended to a maximum of 28 days before permanent treatment discontinuation is required.
- If study drug is on hold for ≤14 days, and the criteria for restarting treatment are met, study treatment can be restarted on any day from D1 to D21 of a cycle. Study drug should not be restarted on D22 to D28 of a cycle; in such cases, treatment restart must wait until D1 of the next cycle.

Table 5: Dose Reduction Scheme

Dose Reduction	Starting Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3 [a]
Study drug	125 mg or matching placebo	100 mg or matching placebo	75 mg or matching placebo	50 mg or matching placebo

[a] Dose reduction to 50 mg requires prospective sponsor medical monitor approval. Details are provided in the text above.

NOTE: The minimum daily dose of study drug allowed in the study is 50 mg.

Table 6: Criteria for Interruption and Re-initiation of Study Drug for Adverse Events Considered to be Possibly Related to Study Drug

Worst Toxicity CTCAE[a] (version 5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
CARDIAC DISORDERS	
Cardiac – Prolonged QTcF Interval	
Grade 2: Average QTc 481 - 500 msec	Maintain dose level of study drug. Two additional ECGs separated by ≥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 according to the 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: Average QTc ≥501 msec; >60 msec change from baseline	Hold dose of study drug. 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, hypomagnesemia and decreased blood oxygenation. • Subjects should receive appropriate electrolyte replacement and should not receive further study drug until electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved to <481 msec, subjects may be re-treated at 1 lower dose level at the investigator's discretion. If not determined to be clinically significant, the subject may resume at the current dose. 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, ECG monitoring will be performed according to the visit schedule for subsequent cycles. • 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.

Worst Toxicity CTCAE[a] (version 5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
	• Subjects who experience recurrent QTcF ≥501 msec after 1 dose reduction will be discontinued from study treatment.
Grade 4: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue study drug.
INVESTIGATIONS-HEMATOLOGY	
Neutrophil Count Decreased (Neutropenia)	
Grade 3 (ANC <1000 - 500/mm^3 [<1.0 - 0.5 × 10^9/L])	Hold dose of study drug until resolved to CTCAE Grade ≤1 or baseline, then • If resolved within ≤7 days, maintain dose level of study drug. • If resolved between >7 days and 14 days, ↓ 1 dose level of study drug. • If not resolved within ≤14 days, discontinue study drug.
Grade 4 (ANC <500/mm^3 [<0.5 × 10^9/L])	Hold dose of study drug until resolved to CTCAE Grade ≤1, then ↓ 1 dose level of study drug. If not resolved within ≤14 days, discontinue study drug.
Febrile Neutropenia	
Grade 3 (ANC <1000/mm^3 with a single temperature of >38.3°C [101.0°F] or a sustained temperature of ≥38.0°C [100.4°F] for >1 hour)	Hold dose of study drug until resolved to CTCAE Grade ≤ 1, then • If resolved within ≤14 days, ↓ 1 dose level of study drug. • If not resolved within 14 days, discontinue study drug
Grade 4	Discontinue study drug.
Anemia	
Grade 3 (hemoglobin <8.0 g/dL [<4.9 mmol/L; <80 g/L]; transfusion indicated)	Hold dose of study drug until resolved or corrected to CTCAE Grade ≤1 or baseline, then maintain dose level.
Grade 4	Hold dose of study drug until resolved or corrected to CTCAE Grade ≤1 or baseline, then ↓ 1dose level.
Platelet Count Decreased (Thrombocytopenia)	
Grade 3 (platelet <50,000 - 25,000/mm^3 [<50 - 25 × 10^9/L])	Hold dose of study drug until resolved to CTCAE Grade ≤1 or baseline, then • If resolved within ≤7 days, maintain dose level of study drug. • If resolved between >7 days and 14 days, ↓ 1 dose level of study drug. • If not resolved within ≤14 days, discontinue study drug.

Worst Toxicity CTCAE[a] (version 5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
Grade 4 (platelet <25,000/mm^3 [<25 × 10^9/L])	Hold dose of study drug until resolved to CTCAE Grade ≤1 or baseline, then ↓ 1 dose level. • If not resolved within ≤14 days, discontinue study drug.
INVESTIGATIONS – RENAL	
Serum Creatinine	
Creatinine clearance <30 mL/min (calculated or measured)	Hold dose of study drug until creatinine clearance is ≥45 mL/min regardless of grade.
Serum creatinine increase Grade 2 (≥1.5 -3.0 × ULN or 1.5 - 3.0 × baseline)	Hold dose of study drug until resolved to Grade ≤1 or baseline, then: • If resolved within ≤7 days, maintain dose level of study drug. • If resolved between >7 days and 14 days, ↓ 1 dose level of study drug • If not resolved within ≤14 days, discontinue study drug.
Serum creatinine increase 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.
Serum creatinine increase Grade ≥3 (>3.0 × ULN or >3.0 × baseline)	Discontinue study drug.
INVESTIGATIONS – HEPATIC	
Blood Bilirubin Increased (for subjects with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only)	
Grade 2 (bilirubin > 1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	Hold dose of study drug until resolved to CTCAE Grade ≤1, then: • If resolved within ≤7 days, maintain dose level of study drug. • If not resolved within ≤7 days, ↓ 1 dose level of study drug.
Grade ≥3 (bilirubin >3.0 × ULN if baseline was normal; >3.0 × baseline if baseline was abnormal)	Discontinue study drug. Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of study drug and continue treatment at the discretion of the investigator.
AST or ALT Increased	
Grade 3 (>5.0 – 20.0 × ULN if baseline was normal; >5.0 – 20.0 × baseline if baseline was abnormal)	Hold dose of study drug until resolved to CTCAE Grade ≤1 or baseline, then: • If resolved within ≤7 days, ↓ 1 dose level of study drug. • If not resolved within ≤7 days, discontinue study drug.
Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue study drug.

Worst Toxicity CTCAE[a] (version 5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
AST or ALT and Bilirubin Increased	
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 study drug until both transaminases and bilirubin resolved to CTCAE Grade ≤1 or baseline, then: • If resolved within ≤7 days, ↓ 1 dose level of study drug. • If not resolved within ≤7 days, discontinue study drug.
AST or ALT >5.0 × ULN and total bilirubin >2.0 × ULN	Discontinue study drug
LABORATORY/METABOLIC DISORDERS	
Amylase and/or Lipase Increase	
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 (amylase or lipase >2.0 - 5.0 × ULN with signs or symptoms; >5.0 × ULN and asymptomatic)	Hold dose of study drug until resolved to CTCAE Grade ≤2, then: • ↓ 1 dose level of study drug. • If not resolved within ≤14 days, discontinue study drug. For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, study drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to Grade ≤2.
Grade 4 (amylase or lipase >5.0 × ULN and with signs or symptoms)	For any Grade 4 lipase or amylase elevation, study drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to Grade ≤2.
Hypophosphatemia	
Serum phosphate <LLN - 2.0 mg/dL (0.6 mmol/L)	Maintain dose level of study drug; decrease or hold dose of phosphate binder and optimize standard diet or medical therapy as clinically indicated to increase phosphate level.
Serum phosphate <2.0 - 1.0 mg/dL (<0.6 - 0.3 mmol/L)	Hold dose of study drug until resolved to >2.0 mg/dL (>0.6 mmol/L), then: • ↓ 1 dose level of study drug. • If not resolved within ≤14 days, discontinue study drug.
Serum phosphate <1.0 mg/dL (<0.3 mmol/L) (life threatening consequences)	Discontinue study drug.
Hyperphosphatemia	
General Comment:	Optimize dose and schedule of phosphate lowering therapy in accordance with the package insert, or local or institutional guidelines.
Serum phosphate >5.5 - ≤7.5 mg/dL	Maintain dose level of study drug and optimize phosphate-lowering therapy as clinically indicated.

Worst Toxicity CTCAE[a] (version 5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
Serum phosphate >7.5 mg/dL for >7 days despite maximal phosphate-lowering therapy Or, single serum phosphate >9.0 mg/dL regardless of duration or dose of phosphate-lowering therapy	• Hold dose of study drug until resolved to serum phosphate ≤5.5 mg/dL. • Restart study drug at the same dose level with maximal phosphate binder dosing if the subject did not receive maximal phosphate binder dosing for serum phosphate >7.5 mg/dL for >7 days. • ↓ 1 dose level of study drug if the subject had received maximal phosphate-lowering therapy for serum phosphate >7.5 mg/dL for >7 days or if subject had a one-time serum phosphate of >9.0 mg/dL. Restart study drug with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during study drug dose interruptions for hyperphosphatemia and that serum phosphate values be monitored frequently, eg, every 2-3 days. • Phosphate binder dosing should be held during the week off of study drug each cycle (Days 22-28) unless serum phosphate is not normalized and during study drug dose interruptions for non-hyperphosphatemia AEs.
Serum phosphate with life-threatening consequences; urgent intervention indicated (eg, dialysis)	Discontinue study drug.
Hypercalcemia	
Serum calcium Grade 2 Corrected serum calcium (>11.5 - 12.5 mg/dL [>2.9 - 3.1 mmol/L]) Ionized calcium (>1.5 - 1.6 mmol/L) symptomatic	Hold dose of study drug until resolved to Grade 1 or baseline, then: • If resolved within ≤7 days after suspending study drug, maintain dose level. • If resolved between >7 days and 14 days, ↓ 1 dose level. • If not resolved within ≤14 days, discontinue study drug.
Serum calcium Grade ≥3 Corrected serum calcium (>12.5 - 13.5 mg/dL [>3.1 - 3.4 mmol/L]) Ionized calcium (>1.6 - 1.8 mmol/L), hospitalization indicated	Discontinue study drug.
GASTROINTESTINAL SYSTEM DISORDERS	
Pancreatitis	
Grade 2 (asymptomatic enzyme elevation with radiologic findings only)	Hold dose of study drug until resolved to CTCAE Grade <2, then: • ↓ 1 dose level of study drug. • If not resolved within ≤14 days, discontinue study drug. For recurrent Grade 2 asymptomatic radiologic pancreatitis despite dose reduction, discontinue study drug.
Grade 3 or Grade 4	Discontinue study drug.
Diarrhea	
General Comment:	Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea.

Worst Toxicity CTCAE[a] (version 5.0) Grade (Unless Otherwise Specified)	**Dose Modifications any Time During a Cycle of Therapy**
Grade 1 (increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline)	Maintain dose level of study drug, initiate antidiarrheal treatment.
Grade 2 (increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living [ADL])	• Hold dose of study drug until resolved to CTCAE Grade ≤1. • Optimize antidiarrheal treatment. • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of study drug until resolved to CTCAE Grade ≤1, then ↓ study drug by 1 dose level.
Grade 3 (increase of ≥7 stools/day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL)	• Hold dose of study drug until resolved to CTCAE Grade ≤1. • Optimize antidiarrheal treatment. • ↓ study drug by 1 dose level. • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal antidiarrheal treatment, discontinue study drug.
Grade 4	Discontinue study drug.
Vomiting	
Grade 2 (outpatient IV hydration; medical intervention indicated) not controlled by optimal anti-emetic therapy	Hold dose of study drug until Grade ≤1, then ↓ 1 dose level. • If not resolved within ≤14 days, discontinue study drug.
Grade 3 (tube feeding, TPN, or hospitalization indicated) not controlled by optimal anti-emetic therapy or Grade 4	Discontinue study drug.
EYE DISORDERS (CONFIRMED BY OPHTHALMOLOGIC EXAMINATION)	
Retinal Disorders	
Grade 2 or 3 central serous retinopathy and central serous retinopathy-like events	Hold dose of study drug until resolved to Grade ≤1 and continue ophthalmic evaluations. • If resolved within ≤14 days, ↓ study drug by 1 dose level. • If not resolved within ≤14 days, discontinue study drug.
Grade ≥1 retinal vein occlusion, Grade 4 central serous retinopathy and central serous retinopathy-like events	Discontinue study drug.
Other Ocular/Visual Toxicity	
Grade ≥3	Hold dose of study drug until resolution to Grade ≤1. • If resolution within ≤14 days, ↓ 1 dose level. • If not resolved within ≤14 days, discontinue study drug.
OTHER CLINICALLY SIGNIFICANT AEs	
Grade 3	Hold dose of study drug until resolved to CTCAE Grade ≤1, then ↓ 1 dose level of study drug. • If not resolved within ≤14 days, discontinue study drug.
Grade 4	Discontinue study drug.

Abbreviations: ADL=activities of daily living; AE=adverse Event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CT= computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; IV=intravenous;

LLN=lower limit of normal; QT=measure of time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle; QTc=QT interval corrected for heart rate; QTcF=QTc corrected by Fridericia's formula; ULN=upper limit of normal.

[a] CTCAE (v5.0) general guidelines:
Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

NOTE: All dose modifications should be based on the worst preceding toxicity. Subjects may have a third dose reduction only with prospective approval of the sponsor medical monitor.

7.2.5.2 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 least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Clinical experts or specialists, such as an ophthalmologist, endocrinologist, dermatologist, should be consulted as deemed necessary. Further guidelines and dose modifications for the management of specific study drug-induced toxicities (hyperphosphatemia, diarrhea) are provided in Table 6. All subjects must be followed up for AEs and SAEs for 30 days following last dose of study drug.

7.2.6 Anticipated Risks and Safety Concerns for Infigratinib

Eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Guidelines for prophylactic or supportive treatment for expected toxicities, including management of study drug-induced AEs (eg, hyperphosphatemia, renal toxicities) are provided in Table 6 and Section 7.5. For more information, refer to the nonclinical toxicity and/or clinical data presented in the infigratinib Investigator's Brochure.

Treatment of AEs or lab abnormalities should follow the protocol where specified, otherwise local institutional guidelines with regard to safety management should apply.

7.3 Randomization and Blinding

Subjects will be randomly assigned in a 1:1 ratio to 1 of the 2 treatment arms. Subjects must be randomly assigned to study treatment within 120 days of completing surgery and start treatment within 1 week of randomization. (Note: only under certain unforeseen circumstances that are not caused by noncompliance or inappropriate planning [eg, adverse weather], randomization may occur after day 120 from definitive surgery but window for randomization and dosing should be 127 days total (120 days +7 days). Randomization will be stratified by lymph node involvement (yes vs no), prior neoadjuvant cisplatin chemotherapy (yes vs no), Stage (pT2 vs >pT2), and disease type (UTUC vs UBC). The number of subjects refusing cisplatin-based perioperative therapy will be capped at approximately 10% of the total population (approximately 22 subjects), no more than 15% of the population will be enrolled with UBC, and ≤25% of UTUC subjects will have Stage pT2 UTUC (limit will be based on stratification). Documented medical monitor approval is required before randomization. Interactive Response Technology (IRT) will be used to assign subjects to treatment based on the stratification factors entered into the system. Site personnel will be given a unique subject number for each subject, consisting of a unique center number followed by a sequential subject number suffixed to it.

This is a double-blind study. Subjects, Investigators, study monitors, and the study team will be blinded to the treatment administered, except for a designated QED Clinical Supply representative. Staff associated with tracking, assaying, and analyzing PK samples may have access to the PK-related information only, and the contract research organization (CRO) analyzing PK samples for concentration will be unblinded to study treatment.

Treatment assignment may be unblinded by the sponsor/designee to satisfy expedited safety reporting requirements of regulatory authorities. If an SAE report meets expedited safety reporting criteria, the sponsor's safety representative or designee will unblind the study treatment for the respective patient for regulatory reporting purposes.

Emergency unblinding: Treatment unblinding by the investigator should be conducted in an emergency only when knowledge of the treatment assignment will affect the management of a subject who experiences a treatment-emergent AE. The investigator will have the ability to perform emergency unblinding. The knowledge of the actual treatment the unblinded subject received should be concealed from any site-level (including any party involved in subject assessment, for example, ophthalmologist) or sponsor (and their representative) personnel involved in managing subject's data, in order to protect ongoing data acquisition and interpretation.

The sponsor recognizes, however, that unblinding for nonemergency situations will be of increasing concern to many sites as additional treatment options become available for subjects who have recurrence of their urothelial carcinoma by BICR. For such subjects, single-subject unblinding in nonemergency situations may be performed by the study team only with medical monitor approval for the purpose of facilitating subsequent treatment decisions, including assessment of eligibility for other clinical trials.

The process of unblinding in these circumstances will require written request submitted to medical monitor (sponsor or representative) with reason for the unblinding request. The nonemergency unbinding may occur only with written approval by the medical monitor.

Including for these cases of nonemergency unblinding, the knowledge of the actual treatment the unblinded subject received should be concealed from any site-level (including any party involved in subject assessment, for example, ophthalmologist) or sponsor (and their representative) personnel who continue to manage patient's data in order to protect ongoing data acquisition and interpretation

The investigator must notify the medical monitor or designee after determining it is necessary to unblind a subject's treatment assignment. The investigator must also indicate in source documents and in the eCRF that the blind was broken and provide the date and reason for breaking the blind. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

In order to limit the number of individuals with access to the unblinded information, Investigators or dedicated study personnel should handle this information with highest confidentiality. Any documentation regarding the treatment assignment should be kept in an envelope, securely stored, and not attached to the subject's files in order to allow for unbiased/blinded continuation of subject's evaluation, and the information should not be communicated or distributed to any personnel other than those who need to know for subject management.

Unblinding of study treatment should not result in withdrawal of the subject from the study, and these subjects will continue to be followed per the protocol.

The investigator can unblind treatment via the IRT system. The investigator should document all occurrences of unblinding in the study file and the reason for unblinding should be documented.

If the investigator would like to discuss the subject's treatment assignment (once known) with the sponsor, the site may liaise with the unblinded Global Study Manager (GSM). The investigator is to communicate directly with the unblinded GSM via email at: proof302unblinded@prahs.com. The unblinded GSM will then convey any discussions to the medical monitor in a "blinded" fashion for any case that requires medical input. If there is an urgent question pertaining to subject management, the site should call the medical monitor but not disclose treatment assignment or unblinding status unless specifically requested.

7.4 Compliance

The investigator or responsible site personnel should instruct the subject to take study drug 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 on the appropriate eCRF as outlined in the Case Report Completion Guidelines. Subject re-training for dosing non-compliance should be conducted and documented, as needed.

Subjects will be instructed to return all used and unused bottles of study drug to the study center at the end of each cycle and at the end of the study or at the time of discontinuation of study drug. Compliance will be assessed by the investigator and/or study personnel, and compliance information will be captured in the Drug Accountability Form. This information must be captured in the source document at each subject visit.

7.5 Supportive Care Guidelines

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

7.5.1 Hematopoietic Growth Factors

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

7.5.2 Management of Hyperphosphatemia

Hyperphosphatemia is a recognized on-target effect of potent and selective inhibitors of the FGFR pathway. While on study drug, 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. Phosphorus will be checked at screening and starting on Cycle 1 Day 4. Subjects who 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 study drug. Once the subject has had hyperphosphatemia, the subject should

remain on a low phosphate diet, if possible, and take phosphate binder on the days study drug is taken even, if the serum phosphorus is normalized. Unless otherwise specified by the local prescribing information or institutional practice, the following regimen should be used to manage hyperphosphatemia:

- For serum phosphorus >5.5 – ≤7.5 mg/dL
  - Start sevelamer 800 mg 3-times per day with meals
  - Increase the dose of sevelamer up to 1200 mg every 8 hours
- For serum phosphorus >7.5 mg/dL
  - Increase the dose of sevelamer up to 1600 mg (2 tablets per meal) every 8 hours
  - Consider adding acetazolamide, 2 to 3 tablets (250 mg) per day

During the study drug cycle, subjects do not need to be on a low phosphate diet or take a phosphate binder during their 1 week off study treatment period (Days 22-28 of cycle) unless serum phosphate is not normalized. Other dose modifications for hyperphosphatemia are provided in Table 6, but should be modified as per country or institutional practice.

7.5.3 Management of Diarrhea

Study drug dose modification recommendations are provided in Table 6. 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/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with >1 antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study treatment should be temporarily interrupted or dose reduced (Table 5).

7.5.4 Management of Alopecia, Palmar-Plantar Erythrodysesthesia Syndrome, Paronychia, and Stomatitis

Recommendations for management (not required per protocol) of stomatitis (adapted from Rugo 2017), PPES, paronychia (adapted from Segaert 2005), and alopecia are provided in Table 7. These recommendations and the additional information provided below, which includes management of dry skin and dry mouth/xerostomia (adapted from Lacouture 2020), are guidelines only and institutional guidelines should be followed where applicable.

In addition, as a general guideline, if toxicity is tolerable and treated, study treatment may be continued for Grade 1 and Grade 2 AEs and interrupted for Grade 3 AEs; rechallenge at a reduced dose may be initiated when dermatologic events improve to Grade ≤1 or baseline or for a well-tolerable Grade 2 toxicity.

Table 7: Management of Skin Toxicity

SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Alopecia	
Grade 1	Continue study drug • Minoxidil 5% (OTC) solution or foam once daily to scalp
Grade 2	Continue study drug • Minoxidil 5% (OTC) solution or foam twice daily to scalp • Fluocinonide 0.05% solution daily to scalp
Palmar-plantar erythrodysesthesia syndrome	
Grade 0/1	Continue study drug • Urea 20% or ammonium lactate 12% lotions BID to hands and feet
Grade 2	Continue study drug • Urea 20% or ammonium lactate 12% BID to hands and feet • Fluocinonide 0.05% cream BID to hands and feet
Grade 3	Hold study drug until resolved to Grade ≤1 • Urea 20% or ammonium lactate 12% BID to hands and feet • Fluocinonide 0.05% cream BID to hands and feet
Paronychia	
Grade 1	Continue study drug • Clindamycin 1% solution around and under nails TID • Soak for 15 minutes daily in white vinegar in tap water (1:1) • Topical povidone iodine 2%–10% applied BID
Grade 2	Continue study drug • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg BID or TMP/SMX DS BID for 14 days • Soak for 15 minutes daily in white vinegar in tap water (1:1) • Topical povidone iodine 2%–10% applied BID • Dermatology consultation
Grade 3	Hold study drug until resolved to Grade ≤1 • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg BID or TMP/SMX DS BID for 14 days • Dermatology consultation
Stomatitis	
Grade 1/2	Continue study drug • Dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5 mL) TID.
Grade 3	Hold study drug until resolved to Grade ≤1 • Dexamethasone elixir 0.5 mg/5 mL swish and spit 1 teaspoon (5 mL) TID. • Clotrimazole 10 mg lozenges 3-5 times/day

Abbreviations: BID=2 times daily; OTC=over-the-counter; TID=3 times daily; TMP/SMX DS=sulfamethoxazole and trimethoprim.

Additional guidelines for specific skin toxicities:

- Alopecia: hair camouflaging methods (such as TOPPIK™) may be considered. Alopecia typically reverses when treatment is discontinued.

- PPES: Prevention strategies for PPES include prophylactic removal of hyperkeratotic areas, application of moisturizing cream containing urea ≥10%, pedicures, and cushioning of callused areas. Other preventive tactics include avoiding activities that cause force or rubbing on the hands and feet during the first 6 weeks of treatment and limiting contact with harsh chemicals and sources of heat (eg, saunas, sun exposure).

- Stomatitis: Preventive strategies may include dental work to eliminate existing tooth and gum disease before starting treatment and education regarding the importance of thorough and frequent cleaning of the oral cavity. Avoiding salty, spicy, or citrus-based foods, and hot beverages may help prevent stomatitis.

- Dry skin: Subjects should be advised to moisturize skin and avoid excessive exposure to detergents and soaps containing fragrances. Urea preparations have been shown to prevent transepidermal water loss, and salicylic acid preparations are helpful due to their keratolytic, bacteriostatic, and fungicidal properties. Exfoliation of scaly areas of xerosis is recommended. More severe grade 3 xerosis, which can result in asteatotic dermatitis, can be treated with low-potency topical steroids (eg, hydrocortisone 2.5% cream or ointment, triamcinolone 0.1% cream).

- Dry mouth/xerostomia: The importance of good oral hygiene, regular dentist visits, and other strategies for preventing oral disease should be stressed. Toothpaste with high fluoride content is recommended to prevent cavities. Treatment may include systemic and topical salivary stimulants (eg, cevimeline and pilocarpine, and intraoral topical agents, such as chewing gums and saliva stimulants and substitutes).

7.5.5 Management of Dry Eye and Blurred Vision

For management of dry eyes and/or blurred vision, the following supportive measures can be implemented singly or in combination and as advised in consultation with an ophthalmologist:

1) Artificial tears, 4 times per day.

2) Artificial tears without preservative, 6 times per day.

3) Ointments (any over-the-counter or Vaseline®).

4) Steroid drops (prescription; may help with corneal haze).

5) Punctal plugs (requires ophthalmologist management).

7.6 Prior and Concomitant Medications

At Screening, subjects are to be asked about their history of prior medication (including prior antineoplastic therapy); Investigators are to check for use of any disallowed prior medications, as outlined in the Exclusion Criteria for the study (Section 6.2).

For each subject enrolled in the study, all anticancer therapies ever taken for urothelial carcinoma and other medications taken within 28 days of first dose of study drug are to be recorded on the appropriate page of the eCRF.

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.

Cancer medications taken by the subject after last dose of study drug are to be recorded on the appropriate page of the eCRF. Non-medication cancer therapies and surgeries are to be recorded on the appropriate page of the eCRF.

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

7.6.1 Permitted Concomitant Therapy Requiring Caution and/or Action

Details for specific medications that require action and/or caution while on study in subjects potentially taking infigratinib are provided in Appendix 1 (Section 17.1). 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. These agents include, but are not limited to, proton pump inhibitors (eg, omeprazole), H_2-antagonists (eg, ranitidine) and antacids. Proton pump inhibitors are prohibited due to their long PD effect and should be replaced with H_2-antagonists or antacids. Study drug should be taken ≥2 hours before or 10 hours after dosing with H_2-antagonists. Antacids, locally-acting acid neutralizing agents, are to be separated from study drug doses by 2 hours.

Infigratinib a substrate of CYP3A4. If anticoagulation is required, heparin and/or low-molecular-weight heparins or direct thrombin inhibitors and/or Factor Xa inhibitors that are not metabolized by CYP3A4 (eg, dabigatran, edoxaban) to be used. Anticoagulants that are CYP3A4 substrates and have a narrow therapeutic index (eg, warfarin sodium or any other coumadin-derivative anticoagulants or certain direct thrombin inhibitors [eg, argatroban] or Factor Xa inhibitors [eg, rivaroxaban]) should be used with caution and frequency of monitoring increased. Refer to Section 7.6.2 for further information on CYP3A4.

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, with the following considerations:

- Ondansetron has a known risk for Torsade de Pointes (TdP), and therefore should be used with caution. Palonosetron may be used as an alternative.

- Aprepitant (brand name: Emend®) is both a sensitive substrate and a moderate CYP3A4 inhibitor and is prohibited with infigratinib. Similarly, the use of other agents in the neurokinin-1 (NK-1) receptor antagonist class (casopitant and fosaprepitant) is limited by drug interactions and is prohibited with infigratinib.

Preliminary data have shown that infigratinib has no effect on cardiac conduction or ECG intervals (see current version of the infigratinib Investigator's Brochure). Medications that have the possible, conditional, or established risk of QTc prolongation or causing TdP are allowed but

should be used with caution while on study. Investigators at their discretion may co-administer such medications, but subjects should be carefully monitored.

See Appendix 1 (Section 17.1) for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

Subjects with newly detected NMIBC or low-grade/noninvasive UTUC can be treated with non-systemic standard therapy, such as BCG instillation, intravesical treatment, and mitomycin gel.

7.6.2 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 (eg, CYP, BCRP).

Details for specific medications prohibited while on study are provided in Appendix 2 (Section 17.2). The rationale for the restricted medications is provided below.

Other investigational therapies must not be used while the subject is on the study. Other than study drug, anticancer therapy (eg, chemotherapy, biologic or radiation therapy, surgery) must not be given to subjects while the subject is on the study drug. If such agents are required, then the subject must be discontinued from study drug but will continue in the study with all described study-related assessments, including assessment for recurrence (conducted until metastatic recurrence [see Section 9.8]) as well as use of other anticancer therapy and survival. Exceptions are nonsystemic treatments for low-grade/noninvasive UTUC or NMIBC, such as intravesical treatment, mitomycin gel, or BCG instillation.

Proton pump inhibitors are prohibited; see Section 7.6.1 for rationale.

Strong and moderate inhibitors of CYP3A4 such as the ones listed in Appendix 2 (Section 17.2) are prohibited because infigratinib is a likely substrate of this isoenzyme; these include the anti-emetic aprepitant (brand name: Emend) and other agents in the NK-1 receptor antagonist class (casopitant and fosaprepitant), as described in Section 7.6.1.

Strong and moderate inducers of CYP3A4 are prohibited because their usage may decrease the exposure of infigratinib. Therefore, agents such as those listed in Appendix 2 (Section 17.2) 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 before the first dose of study drug 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. Chinese herbal medicines and Chinese patent medicines for the treatment of cancer are not allowed during the treatment period.

7.6.3 COVID-19 Vaccinations

The effect of coronavirus disease 2019 (COVID-19) vaccines has not been studied in combination with infigratinib; hence the safety and efficacy of either agent when used in combination are unknown (ie, vaccination before, during, or after infigratinib treatment has not been studied, and the efficacy and safety of COVID-19 vaccines in the presence of infigratinib, as well as the efficacy and safety of infigratinib in the presence of a COVID-19 vaccine, are unknown).

There is no detailed or conclusive information on studies conducted with the COVID-19 vaccines in subjects receiving any anticancer therapies, or in patients with cancer. In general, COVID-19 vaccines may be administered before, during, and after study participation, if determined to be safe in the clinical judgement of the treating physician/study investigator. The treating physician/study investigator should assess the risk for each individual study subject for receiving the vaccine in the context of the study.

Whenever feasible, vaccinations should be administered at least 30 days prior to randomization

All applicable guidelines should be followed, and vaccinations should adhere to the manufacturer's guidelines for eligibility and contraindications to receive the vaccine (Garassino 2020; ASCO 2021; Pergam 2021). Subjects vaccinated for COVID-19 should be closely monitored, and any observed AEs/SAEs should be reported as outlined in Section 10.5.1.

7.7 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 Concomitant Therapy 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 (eg, CYP, BCRP) (in Appendix 2 [Section 17.2]).

8 SUBJECT DISCONTINUATION AND STUDY TERMINATION

8.1 Subject Discontinuation

8.1.1 Discontinuation of Study Drug

Discontinuation of study treatment does not represent withdrawal from the trial.

If study treatment is permanently discontinued for reasons other than subject's withdrawal of consent, the subject will remain in the study to be evaluated for all study prespecified assessments (such as safety follow-up, efficacy, etc.) See Section 2 for data to be collected at the time of discontinuation of study treatment and follow-up.

Subjects must be discontinued from study drug for:

- Local/regional or contralateral invasive or metastatic recurrence (whichever occurs first) by BICR:
  - Subjects should remain on study treatment until local/regional or contralateral invasive or metastatic recurrence is confirmed by BICR.
  - All subjects' imaging (CT/magnetic resonance imaging [MRI] scans) will be read locally and submitted for BICR read, together with any supporting report (including pathology and cytology reports) if a biopsy was conducted (for example, if recurrence was suspected). A central read should be requested at the time of investigator-assessed disease recurrence for confirmation by BICR.
  - If BICR confirms recurrence (local/regional or contralateral invasive or metastatic recurrence, whichever occurs first), the subject must be permanently discontinued from study treatment.
  - If locally diagnosed local/regional or contralateral invasive or metastatic recurrence is not confirmed by BICR, treatment continuation is allowed at Investigator's decision.
  - BICR diagnosis of a local/regional or contralateral invasive or metastatic recurrence, independently from and undiagnosed by local team, will not be communicated to the clinical site.
- Pregnancy.
- 52-week treatment phase completed.
- AE that leads to substantial changes in individual risk-benefit considerations.
- Delay of study drug administration of >14 days (exclusive of scheduled dose interruption, with exceptions noted in Section 7.2.5.1).
- Death.

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

- New medical condition that does not allow continuation of study drug compliance.
- Protocol deviation, including non-compliance with dosing regimen and retroactive failure to fulfill study entry criteria.
- Lost to follow-up (defined as no contact after 3 documented attempts by telephone followed by 1 attempt via letter [eg, certified mail, if available]).
- Subject request; if a subject withdraws consent from study treatment, it is required to document if the subject agrees or not 1) with continuation with study assessments; 2) to be followed for long-term follow-up and initiation of new anticancer therapies.
- Investigator request
- Use of other investigational therapies.

- Use of anticancer therapy (eg, chemotherapy, biologic or radiation therapy, surgery) other than the study drug. Exceptions are non-systemic treatments for low-grade or noninvasive UTUC or NMIBC, such as intravesical treatment, mitomycin gel, or BCG instillation.

The investigator must notify the sponsor/representatives if a subject is discontinued prematurely from study drug for any reasons, including reasons other than radiological or pathologic local/regional or contralateral invasive or metastatic recurrence. Subject's withdrawal from treatment must be documented and must also capture subject's permission or not to be followed for long-term follow up and anticancer therapy initiation. At the time of discontinuation of study drug, subjects are to complete the EOT visit (no later than 5 days after treatment discontinuation), the 30-day Follow-up visit (according to Table 2 and Section 9.7), and subsequent follow-up visits and assessments, according to Table 2, Section 9.8, and Section 9.9.

The reason for treatment discontinuation is to be documented in the eCRF including identifying one reason as the primary reason for treatment discontinuation. The investigator should make every effort to determine why a subject is lost to follow-up or withdraws consent and record this information in the eCRF. Further, if a subject is discontinued from treatment due to protocol deviation or Investigator's request, specifics are to be recorded in the eCRF.

8.1.2 Discontinuation from Study

Subjects have the right to withdraw from the study at any time without prejudice. Pending the criteria for which the subject withdraws consent, as listed below, those specified assessments 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.

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

- Subject's formal withdrawal of informed consent. If a subject withdraws consent from study participation, the level of withdrawal must be documented. Below are the possible levels of subject's withdrawals:
    - Full withdrawal: withdrawal from all study treatments, procedures, assessments, and any type of follow-up (survival, new anticancer therapy, etc.)
    - Withdrawal from all study assessments or procedures; survival follow-up is permitted, together with collection of data related to initiation of new anticancer therapy.
    - Withdrawal from survival follow-up (subject or family cannot be contacted; public record data can be reviewed).
    - If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested, and the investigator must document this in the study records and notify the sponsor immediately.
- Investigator request.
- Lost to follow-up (defined as no contact after 3 documented attempts by telephone followed by 1 attempt via certified letter).
- Discontinuation of the study by the sponsor.

- Protocol deviation.
- Study complete.
- Death.
- Other.

The reason for discontinuation from the study is to be documented in the eCRF, including the exact level of subject's withdrawal from the study. The investigator should make every effort to determine why a subject is lost to follow-up or withdraws consent and record this information in the eCRF. Further, if a subject is withdrawn due to protocol violation or Investigator's request, specifics are to be recorded in the eCRF.

8.2 Study Termination

The study can be terminated at any time for any reason by QED Therapeutics, Inc. (QED). Should this be necessary, every effort is to be made to ensure that the subject completes certain assessments, depending on where they are in the study. If a subject is still on study drug, the subject is to complete the EOT visit. If the subject has already discontinued study drug, he/she is to complete the 30-day Safety follow-up visit (if not already completed). EOS reasons will be recorded for all subjects.

The investigator may be informed of additional procedures to be followed to ensure adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

9 STUDY VISITS AND PROCEDURES

See Section 2 for the Schedule of Assessments (Table 2 and Table 3).

9.1 Molecular Prescreening

Written documentation of the FGFR3 alteration by FoundationOne CDx (F1CDx) through Foundation Medicine USA (FoundationOne CDx 2020). is required for study eligibility.

The sponsor must review all cases for which written documentation of the FGFR3 alteration by F1CDx was obtained as part of routine clinical care for adherence to the study protocol. If F1CDx testing is not performed as part of routine clinical care, molecular prescreening is required to confirm the presence of FGFR3 alteration from tissue (subjects must provide written consent before the molecular prescreening). Molecular prescreening by F1CDx should be performed using the tumor sample from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy) because this tumor provides the most current readout of FGFR3 status (see Appendix 5 [Section 17.5] for instructions for optimal tumor specimens). If the surgical specimen is not available, an archival biopsy sample can be used when:

- Biopsy sample is also confirmed invasive urothelial carcinoma (≥pT2).

- Subject did not receive systemic anticancer therapy after the biopsy was obtained.
- The biopsy is collected ≤4 months before the definitive surgery.
- The most recent biopsy is submitted (if >1 biopsy procedure was performed).

The sponsor must review all cases where an archival biopsy sample that is not from the definitive surgical resection is used to assess FGFR3 alterations by F1CDx (including when a biopsy sample is used to determine the FGFR3 alteration by F1CDx that was obtained as part of routine clinical care). Sites must consult with QED if the pre-surgical biopsy sample is the only sample available to submit to the central laboratory for molecular prescreening to ensure adherence with the above criteria.

Tumor samples for molecular prescreening will be sent to Foundation Medicine USA (with a corresponding pathology report) Results of the analysis will be communicated to each respective study center. The results of molecular prescreening will be used to validate F1CDx as a companion diagnostic for the identification of patients with invasive urothelial carcinoma who may benefit from treatment with infigratinib following the detection of FGFR3 alterations.

If written documentation by F1CDx of the FGFR3 alteration from the tumor sample obtained from the definitive surgical resection is not available before obtaining prescreening consent, molecular prescreening is required and the subjects must provide written informed consent for molecular prescreening (Section 13.3). Molecular prescreening assessments and confirmation can be done any time before dosing.

For all subjects who undergo molecular prescreening, data collected as part of the assessment for FGFR3 alterations, including the following, will be collected and used for analysis of the exploratory objectives: (1) genetic alterations identified on the F1CDx gene panel as well as tumor mutational burden (TMB), and microsatellite instability (MSI); (2) pathologic disease stage of the sample tested; (3) sample type: biopsy (specify type such as core needle biopsy, excision biopsy, fine needle aspiration, cytology cell block) or resection from definitive surgery (specify type of surgery) and date of sample collection; (4) anatomic site of tumor collection; (5) UTUC or UBC; (6) prior neoadjuvant treatment (with date and name).

9.2 Main Study Informed Consent

Upon confirmation that a subject's tumor contains the required FGFR3 alteration (Section 10.3) the subject will sign the main study ICF to begin screening procedures (Section 13.3). Informed consent must be obtained before conducting any study-specific procedures. A copy of the ICF must be given to the subject or to the person signing the form. The investigator or designee must record the date when the study informed consent was signed in the medical records of the subject.

9.3 Screening (Day −28 to −1)

All baseline/screening assessments, including screening cystoscopy (for subjects with a bladder) and imaging assessments must be conducted within 28 days before randomization.

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

- Cystoscopy (for subjects with a bladder) and CT or MRI scan (chest, abdomen, and pelvis), unless available within 28 days before randomization. Baseline CT/MRI scans must be submitted for BICR to confirm absence of residual or metastatic disease prior to randomization. Images should be submitted in time to allow for return of the results before 120 days post-surgery. Refer to the Study Manual for details regarding image collection and transfer or shipment.
- Collection of written documentation of F1CDx determined FGFR3 alteration processed at Foundation Medicine USA.
- Inclusion/exclusion assessment (If the subject did not receive platinum-based chemotherapy in the perioperative setting [see inclusion criterion #4, Section 6.1], the reason must be documented in the case report form [CRF]).
- Demography.
- ECOG performance status.
- Relevant medical history/current medical conditions.
- Diagnosis and extent of cancer.
- Prior medication and antineoplastic therapy.
- Ophthalmic assessment (performed by an ophthalmologist).
- Full physical examination.
- Height and weight (body mass index [BMI] determination).
- Vital signs.
- 12-lead ECG.
- Blood draw for hematology, clinical chemistry, and coagulation assessments.
- Urine collection (urinalysis [micro- and macroscopic; for subjects with a bladder], and cytology [all subjects]).
- Pregnancy test (serum or urine pregnancy test at screening) for women of childbearing potential within 7 days before the first dose of study drug.
- Protocol-mandated procedure-related SAEs; see Section 10.5.1.3.
- Randomization after subject deemed eligible (including documented medical monitor approval) and treatment starts within 1 week of randomization.

In the event that subjects have a baseline/screening laboratory assessment that excludes them from the study, that assessment can be repeated to re-check their eligibility, if conducted within the 120 days from the definitive surgery.

9.4 Study Drug Dosing During Treatment Period (Days 1-28, Cycles 1-13)

Daily dosing of study drug using a 3 weeks on (Days 1-21)/1 week off (Days 22-28) schedule for each 28-day treatment cycle.

Study drug may be dispensed at study visits on Day 1 of C1, C2, C4, C7, C10, and C13 and/or monthly at study visits per local standard practice.

9.5 Study Visits During Treatment Period (Cycle 1 Day 1 to Cycle 13 Day 21)

The following assessments are to be performed during the Treatment Period as indicated below and as detailed in Table 2 and Table 3. Screening assessments conducted within 3 days before the first treatment can be used to satisfy the C1D1 requirement.

Throughout the treatment period, subjects will be monitored for AEs and concomitant medication use. Other safety assessments, including full or abbreviated/symptom-directed physical examinations; vital signs; ophthalmic assessments (performed by an ophthalmologist); laboratory measures (hematology, blood chemistry, coagulation, pregnancy) and urinalysis ; and 12-lead ECG will be conducted at the times indicated in Table 2 and Table 3. Laboratory tests will be collected and analyzed on the scheduled day, even if study drug is withheld.

The following assessments will be performed on C1D1, C2D1, C4D1, C7D1, C10D1, and C13D1, unless otherwise indicated:

- Quality of Life (QOL) assessments (before study drug administration).
- ECOG performance status.
- Ophthalmic assessment (C2D1, C4D1, C7D1, C10D1, C13D1, and if clinically indicated). Retinal optical coherence tomography (OCT) scan images will be read locally and images will be sent to the OCT imaging vendor. Refer to the Study Manual for details regarding image collection and transfer or shipment.
- Physical examination (full physical examination at C1D1, abbreviated or symptom-directed physical examination thereafter).
- Weight (and BMI determination).
- Vital signs.
- 12-lead ECG (predose on C1D1 and C2D1).
- If local programmed death-ligand 1 (PD-L1) testing is already known, record it (C1D1). If PD-L1 results are not known, and tissue was sent for testing, record the PD-L1 results as soon as available. While the PD-L1 results are not required for assessment of eligibility, testing for PD-L1 is required (it is not optional) (see Section 10.3 for additional details).
- Blood draw:
    - Hematology will be assessed at the following timepoints:.
        - Cycle 1 (Day 1).
        - Cycles 2, 4, 7, 10, and 13 (Day 21).
    - Clinical chemistry will be assessed at the following timepoints: Every attempt should be made to collect clinical chemistry sample at the same time as the PK sample taken at 4 hours post study drug administration.

  - Cycle 1 (Day 1, Day 4, Day 7, Day 14, and Day 21).
  - Cycles 2-13 (Day 21).
- Coagulation as clinically indicated.
- cfDNA will be assessed at the following timepoints (see Table 3 for details):
  - Cycle 1 Day 1 predose.
  - Cycle 1 Day 21 predose.
  - Cycle 3 and every other cycle thereafter (C5, C7, etc.) on Day 21 predose.

  In addition, attempts should be made to collect a blood sample from any subject who discontinues study drug due to an AE at the time of discontinuation, if the sample can be collected within 24 hours of last dose.

  If a subject is not on study medication, then no cfDNA will be collected. cfDNA sampling will resume once the subject is back on study medication.
- PK will be assessed at the following timepoints (see Table 3 for details):
  - Cycle 1 Day 1 predose and 4 hours (±30 min) postdose.
  - Cycle 1 Day 21 predose and 4 hours (±30 min) postdose.
  - Cycle 2 and all subsequent cycles on Day 21 predose and 4 hours (±30 min) postdose.

  In addition, attempts should be made to collect a blood sample from any subject who discontinues study drug due to an AE at the time of discontinuation, if the sample can be collected within 24 hours of last dose.

  If a subject is not on study medication, then no PK will be collected. PK sampling will resume once the subject is back on study medication.

- Urine collection:
  - Urinalysis (micro- and macroscopic), if clinically indicated.
  - Urine cytology on C4D1, C7D1, C10D1, and C13D1.
  - cfDNA will be assessed at the following timepoints (see Table 3 for details):
    - Cycle 1 Day 1 predose.
    - Cycle 1 Day 21 predose.
    - Cycle 3 and every other cycle thereafter (C5, C7, etc.) on Day 21 predose.
- Pregnancy test (blood or urine) for women of childbearing potential; monthly on Day 21 of C1 to C13.
- CT or MRI (chest, abdomen, and pelvis) scan on C4D1, C7D1, C10D1, and C13D1. All CT/MRI scans must be submitted for BICR. Refer to the Study Manual for details regarding image collection and transfer or shipment.
- Cystoscopy (for subjects with a bladder) on C4D1, C7D1, C10D1, and C13D1.

- Study drug may be dispensed at study visits on D1 of C1, C2, C4, C7, C10, and C13 and/or monthly at study visits per local standard practice; study drug administration will be as detailed in Section 9.4.
- All AEs (see Section 10.5.1.3) on D1 of C1, C2, C4, C7, C10, and C13 and on D21 of every cycle.
- Concomitant medication use on D1 of C1, C2, C4, C7, C10, and C13 and on D21 of every cycle.
- Newly obtained tumor sample (if medically feasible) upon any recurrence. Biopsy reports, including pathology and cytology, must be submitted for BICR, as well as imaging (CT/MRI scans) assessments. Refer to the Study Manual for details regarding report collection and transfer or shipment. With subject consent, tumor samples collected upon local/regional or contralateral invasive or metastatic recurrence as part of standard of care may be provided to the sponsor for exploratory objectives related to biomarkers of urothelial carcinoma biology and the potential association of biomarkers with efficacy, disease recurrence, and resistance to study medications.

Subjects will be dispensed study drug and instructed on daily dosing using a 3 weeks on (Days 1-21)/1 week off (Days 22-28) schedule for each 28-day treatment cycle (see Section 7.1).

9.6 Cycle 13 Day 28 or EOT Visit (±5 Days)

At Cycle 13 Day 28 or when the decision is made to discontinue treatment, subjects will complete an EOT visit, no later than 5 days after treatment discontinuation.

Assessments to be performed on C13D28 or EOT are as detailed in Table 2 and Table 3 and will include the following:

- QOL assessments (not needed if completed within the previous 7 days at a regularly scheduled visit).
- ECOG performance status.
- Ophthalmic assessment, unless performed within previous 4 weeks.
- Full physical examination.
- Weight (and BMI determination).
- Vital signs.
- 12-lead ECG.
- Blood draw for:
    - Hematology and clinical chemistry (every attempt should be made to collect clinical chemistry sample at the same time as the PK sample taken at 4-hours post study drug administration).
    - Coagulation (if indicated).

  - PK (if sample can be collected within 24 hours of last dose).
  - cfDNA (unless performed within 28 days); at the time of local/regional or contralateral invasive or metastatic recurrence, a blood sample will be collected for analysis of cfDNA.
- Urine collection:
  - Urinalysis, if clinically indicated.
  - Cytology (unless performed within 4 weeks).
  - cfDNA (unless performed within 28 days); at the time of local/regional or contralateral invasive or metastatic recurrence, a urine sample will be collected for analysis of cfDNA.
- Pregnancy test (blood or urine) for women of childbearing potential.
- CT or MRI (chest, abdomen, and pelvis) scan, unless performed within previous 4 weeks or subject prematurely discontinued treatment due to local/regional or contralateral invasive or metastatic recurrence. CT/MRI scans must be submitted for BICR. Refer to the Study Manual for details regarding image collection and transfer or shipment.
- Cystoscopy (for subjects with a bladder), unless performed within previous 4 weeks.
- All AEs.
- Concomitant medication use.
- Newly obtained tumor sample (if medically feasible) upon any recurrence. Biopsy reports, including pathology and cytology, must be submitted for BICR, as well as imaging (CT/MRI scans) assessments. Refer to the Study Manual for details regarding report collection and transfer or shipment. With subject consent, tumor samples collected upon local/regional or contralateral invasive or metastatic recurrence as part of standard of care may be provided to the sponsor for exploratory objectives related to biomarkers of urothelial carcinoma biology and the potential association of biomarkers with efficacy, disease recurrence, and resistance to study medications.

9.7 30-day Post-treatment Follow-up (±5 Days)

All subjects must complete safety follow-up assessments 30 days after the last dose of the study drug, as outlined in Table 2.

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.

9.8 Follow-up Every 6 Months (±7 Days) after EOT and at EOS

Subjects who prematurely discontinue treatment for reasons other than local/regional or contralateral invasive or metastatic recurrence (eg, for reasons detailed in Section 8.1.1) will be followed up until BICR-confirmed local/regional or contralateral invasive or metastatic recurrence and for 1 year after the final DFS event goal is reached (EOS). Note that all efficacy

assessments specified in Table 2 for the first year since start of treatment should continue according to the schedule if the subject prematurely discontinues treatment before BICR-confirmed local/regional or contralateral invasive or metastatic recurrence, ie, CT or MRI, cystoscopy (for subjects with a bladder), and urine cytology and cfDNA at C4D1, C7D1, C10D1, and C13D1. For subjects started on a non-study related anticancer therapy after discontinuing from study treatment, imaging assessment of disease status should continue, until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred.

After a subject completes 12 months of study treatment, the following assessments are to be conducted every 6 months (with the exception of CT or MRI scans; schedule for this assessment is noted below).

- QOL assessments until 18 months after start of treatment.
- Abbreviated or symptom-directed physical examination.
- Weight (and BMI determination).
- Vital signs.
- Blood draw for cfDNA.
- Urine cytology and cfDNA (every 6 months after EOT for an additional 12 months [24 months in total since start of treatment] and then annually until local/regional or contralateral invasive or metastatic recurrence).
- CT or MRI (chest, abdomen, and pelvis) scan every 3 months up to 24 months in total since start of treatment, then annually until metastatic recurrence confirmed by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred (subjects who complete 52 weeks of treatment without metastatic recurrence will continue to have radiographic assessments according to the schedule described until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred). All CT/MRI scans must be read locally and submitted for BICR as well as any supporting report (including pathology and cytology reports) if a biopsy was conducted at the time of recurrence. A patient discontinued from study treatment and started on a new anticancer therapy will continue to be assessed by imaging until metastatic recurrence is confirmed by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Refer to the Study Manual for details regarding image collection and transfer or shipment.
- Cystoscopy (for subjects with a bladder; every 6 months after EOT up to 24 months in total since start of treatment and then annually until local/regional or contralateral invasive or metastatic recurrence).
- Antineoplastic therapies since discontinuation of study treatment: to inquire at every study visit.

- Newly obtained tumor sample (if medically feasible) upon any recurrence. Biopsy reports, including pathology and cytology, must be submitted for BICR as well as imaging (CT/MRI scans) assessments. Refer to the Study Manual for details regarding report collection and transfer or shipment. With subject consent, tumor samples collected upon local/regional or contralateral invasive or metastatic recurrence as part of standard of care may be provided to the sponsor for exploratory objectives related to biomarkers of urothelial carcinoma biology and the potential association of biomarkers with efficacy, disease recurrence, and resistance to study medications.
- Survival follow up.

At the time of local/regional or contralateral invasive or metastatic recurrence, blood (2 tubes, 16-20 mL) and urine sample will be collected for analysis of cfDNA.

9.9 Survival Follow-up and New Antineoplastic Therapies

After either BICR-confirmed metastatic recurrence, or investigator-confirmed metastatic recurrence if BICR-confirmed local/regional or contralateral recurrence has already occurred, subjects will be followed up for survival status every 6 months for 1 year, then annually thereafter (via telephone or office visit) for 1 year (±14 days) after the final DFS event goal is reached (ie, EOS).

Antineoplastic therapies since discontinuation of study treatment should also be collected for 1 year (±14 days) after the final DFS event goal is reached (ie, EOS). Use of anticancer therapy will be collected for all subjects, including from the time of study treatment discontinuation, regardless of reason for discontinuation. For subjects started on a non-study related anticancer therapy after discontinuing from study treatment, imaging assessment of disease status should continue until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred.

If a subject requests withdrawal of consent specifically from survival follow-up, this request must be documented in the subject's medical record. In such cases, the site staff may use public information source (such as county records) to obtain information about survival status and only as appropriate per local regulations.

After the EOS (1 year after the DFS primary analysis), subjects will continue to be followed for OS (under a separate protocol) for approximately 14 years, or all of the subjects die or drop from this follow up, whichever is earlier, referred to as long-term OS follow up. The data for the long-term OS will be reported in a separate study report.

9.10 End of Treatment and End of Study

End of treatment: Subjects will stay on study drug until they complete 52 weeks of treatment or experience local/regional or contralateral invasive or metastatic recurrence (whichever occurs first), if no other reasons requiring permanent discontinuation of treatment are met (see Section 8.1.1).

End of Study: EOS is defined as 1 year after the time at which the final DFS event goal is reached. At the EOS, the investigator is to document the primary reason for EOS for each subject, as defined in Section 8.1.2.

See Section 9.9 for details on long-term OS follow-up after EOS.

10 STUDY ASSESSMENTS

10.1 Efficacy Assessments

Efficacy will be assessed by disease recurrence and OS. To assess disease recurrence, CT/MRI scans, cystoscopy (for subjects with a bladder), and urine cytology will be performed. Assessments are scheduled based on first dosing day of the dosing cycle and do not change due to dose interruptions and will be conducted as detailed in Table 2 and Table 3.

Chest, abdomen, and pelvic CT scans are required for all subjects at screening, unless available within 28 days before randomization. A contrast-enhanced MRI (if possible) of the chest, abdomen, and pelvis should be performed if a subject is known to have a contraindication to IV contrast at baseline or develops a contraindication during the trial. (Note that for individual subjects, the same modality [CT or MRI] should be used for radiographic assessments throughout the study). Details are provided in the Subject Scanning Guide. Scans must be sent for BICR to confirm absence of residual or metastatic disease prior to randomization. All postbaseline radiological assessments, including imaging obtained at unscheduled time points to determine disease recurrence, as well as imaging obtained for other reasons but captures radiologic recurrence, will be sent for BICR. Subject's imaging will be read locally and submitted for BICR as well as any supporting report (including pathology and cytology reports) if a biopsy was conducted at the time when recurrence was suspected. At the time of investigator-determined disease recurrence, a confirmatory BICR assessment should be requested. Refer to the Study Manual for details regarding image collection and transfer or shipment.

Subjects should remain on study treatment until local/regional or contralateral invasive or metastatic recurrence is confirmed by BICR. If BICR confirms recurrence (local/regional or contralateral invasive or metastatic recurrence, whichever occurs first), the subject must be permanently discontinued from study treatment. If locally diagnosed local/regional or contralateral invasive or metastatic recurrence is not confirmed by BICR, treatment continuation is allowed at Investigator's decision. BICR diagnosis of a local/regional or contralateral invasive or metastatic recurrence, independently from and undiagnosed by local team, will not be communicated to the clinical site (see Section 8.1.1).

If a subject discontinues treatment prematurely for reasons other than local/regional or contralateral invasive or metastatic recurrence, CT/MRI scans (chest, abdomen, and pelvis), cystoscopy (for subjects with a bladder), and urine cytology should continue to be taken at the intervals outlined in Table 2. For subjects started on a non-study related anticancer therapy after discontinuing from study treatment, imaging assessment of disease status should continue until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred.

For this study, definitions of recurrence are as follows:

- Local/regional or contralateral invasive recurrence: recurrence of the original diagnosis of invasive urothelial carcinoma (within the urinary tract, renal or ureter bed, urinary soft tissue or locoregional lymph nodes). This does not include local/regional recurrence of noninvasive, or low-grade, or high grade UTUC or NMIBC.

- Metastatic recurrence: Recurrence at any site or lymph node other than the urinary tract or local region of primary tumor.

- Intraluminal low-risk recurrence: Any local/regional or contralateral recurrence of noninvasive, low-grade, or high-grade UTUC or NMIBC.

These determinations will be recorded in the eCRF.

Acceptable criteria for the diagnosis of recurrence are listed in Table 8 under "Unequivocal Recurrence". For some recurrence sites, both histologic/cytologic and radiologic criteria for unequivocal recurrence are described. Histologic/cytologic confirmation is the preferred criteria to determine unequivocal recurrence, and new lesions should be biopsied to confirm recurrence when safe and feasible. Radiologic assessments completed to evaluate for disease recurrence must be submitted for BICR. Refer to the Study Manual for details regarding image collection and submission. New lesions meeting criteria for radiologic unequivocal recurrence, as well as highly suspicious lesions, should be biopsied to confirm recurrence when appropriate. Biopsy reports, including pathology and cytology reports, must be submitted for BICR (as well as radiological imaging as described above). Refer to the Study Manual for details regarding report collection and submission. For highly suspicious lesions or indeterminate lesions that are not amenable to biopsy, interval imaging surveillance should be performed as clinically indicated until disease recurrence is confirmed by biopsy or the subject has radiographic evidence of unequivocal recurrence according to Table 8. The frequency of surveillance imaging should be determined by the rate of tumor growth. For indeterminate or highly suspicious lesions that are followed using interval imaging surveillance, if recurrence is confirmed, the date of recurrence will be the *date of first recognition of the findings*. When both imaging and biopsy dates are available, the earlier date should be used as the date of recurrence.

Table 8: Definitions of Recurrence by Site

Site of Recurrence	Unequivocal Recurrence	Highly Suspicious Lesions	Indeterminate Lesions
Renal bed	Pathologic confirmation of disease (cytology or histology) OR Radiologic evidence of new focal defects on CT or MRI imaging that is consistent with recurrence or new tumor per RECIST v1.1, ie, its longest diameter is ≥1 cm.		
Ureteric bed	Pathologic confirmation of disease (cytology or histology) OR		

Site of Recurrence	Unequivocal Recurrence	Highly Suspicious Lesions	Indeterminate Lesions
	Radiologic evidence of new focal defects on CT or MRI imaging consistent with recurrence or new tumor per RECIST v1.1.		
Invasive Urinary Bladder Cancer (UBC):	Cystoscopic and TUR/biopsy confirmation of new lesions, stage T2, T3, or T4.		
Nonmuscle Invasive Bladder Cancer (NMIBC)	Cystoscopic and TUR/biopsy confirmation of new lesions, stage Ta, Tis, or T1.		
Upper Tract Urothelial Carcinoma (UTUC)	Histologically/cytologically confirmed high grade, invasive UTUC defined as pT1, T2, T3, and T4 OR Histologically/cytologically confirmed high grade noninvasive or low-grade noninvasive UTUC defined as pTa and pTis		
Lung and pleura	Pathologic confirmation of disease (cytology or histology) OR >3 non-calcified pulmonary nodules, all >1 cm or new innumerable nodules of any size; for solitary pulmonary nodules, >2 cm. Proof of neoplastic pleural effusion must be established by cytology or pleural biopsy.	Any number of nodules associated with thoracic adenopathy or not present at baseline	Any pulmonary nodules not meeting criteria for unequivocal recurrence or highly suspicious lesion
Liver	Pathologic confirmation of disease (cytology or histology) OR Abdominal CT or MRI demonstrating lesion ≥1 cm with confirmation of growth ≥5 mm or appearance of ≥1 new lesions on subsequent scans ≥4 weeks later. Proof of neoplastic abdominal ascites must be established by cytology or histology.	Nodules <10 mm in size that do not appear compatible with benign processes; lesions of any size not present on prior imaging	Any mass not meeting criteria for other 2 categories or that characteristically enhances compatible with benign processes
Central nervous system	Positive cerebral spinal fluid (CSF) cytology or biopsy OR Positive brain CT imaging or MRI imaging consistent with metastatic disease.		
Lymph Node	Pathologic confirmation of disease (cytology or histology) OR Lymph nodes ≥1.5 cm short axis, with confirmation of growth ≥5 mm or appearance of new lesions on subsequent scans ≥4 weeks later	Lymph nodes <1.5 cm short axis that increase in size on subsequent imaging but remain less than 1.5 cm	Lymph nodes that are stable ≥1 cm and <1.5 cm short axis

Site of Recurrence	Unequivocal Recurrence	Highly Suspicious Lesions	Indeterminate Lesions
Bone	Pathologic confirmation of disease (cytology or histology) OR ≥2 lesions of the bone on bone scan confirmed on CT or MRI. For solitary lesions, subsequent scan required to demonstrate growth or ≥ 1 new lesion ≥4 weeks apart	≥1 bone lesion with characteristic findings on imaging	Any bone lesion without characteristic findings or not meeting criteria for unequivocal recurrence or highly suspicious lesion
Other organs	Pathologic confirmation of disease (cytology or histology) OR CT or MRI demonstrating lesion that is ≥1 cm with confirmation of growth ≥ 5 mm or appearance of ≥1 new lesions on subsequent scans ≥ 4 weeks later	Nodules <10 mm in size that do not appear compatible with benign processes; lesions of any size not present on prior imaging	Any mass not meeting criteria for other 2 categories or that characteristically enhances compatible with benign processes

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; RECIST=Response Evaluation Criteria in Solid Tumors; TUR=transurethral resection.

All organ locations for recurrence up to 28 days from the first metastatic recurrence event will be reported on the eCRF and, for the purpose of analysis, will be considered part of the first recurrence.

10.2 Pharmacokinetic Assessments

Blood samples will be collected at the time points specified in Table 3. All blood samples will be taken from a central line, by direct venipuncture, or with an indwelling cannula inserted in a peripheral vein.

On the days of PK sampling, subjects should take their study drug at the clinic after the predose PK sample is taken. Subjects who forget and take their study drug at home will be excluded from PK analysis for that day and should not have blood samples collected for PK analysis. If a subject is not on study medication, then no PK will be collected. PK sampling will resume once the subject is back on study medication.

Complete dosing information, including the date and time of actual blood draw and time of the last study drug dose before the sampling, should be obtained on all sampling days and recorded on the appropriate blood collection eCRF. If any of the scheduled sampling times are missed or a sample is not drawn according to schedule, the actual collection date and time should be recorded, and the remaining samples should be collected on schedule whenever possible.

Refer to the Laboratory Manual for complete instructions on PK sample collection, processing, handling, storage and shipment.

Plasma concentrations of infigratinib and its active metabolites (BHS697, BQR917, and CQM157) will be measured by a central laboratory using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL. Concentrations below the LLOQ will be reported as below the quantification limit, and missing samples will be labeled accordingly.

PK parameters listed in Table 9 will be estimated for infigratinib and its active metabolites. Concentrations of metabolites will be reported and summary statistics (eg, mean, standard deviation, %CV) calculated, as appropriate.

Table 9: Pharmacokinetic Parameters

Term	Definition
C_{trough}	Trough observed plasma concentration (before drug administration)
C_{max}	Maximum observed plasma concentration after drug administration (defined as the 4-hour postdose concentration)

10.3 Assessment of Biomarkers and Eligible FGFR3 Alterations

Biomarker assessments will be performed to confirm subject eligibility and potentially aid in understanding the effects of infigratinib treatment on biomarkers of urothelial carcinoma and FGFR pathway regulation as related to clinical outcome.

Subjects must have written documentation of the FGFR3 alteration by F1CDx testing (through Foundation Medicine USA). The sponsor must review all written documentation of the FGFR3 alteration by F1CDx that was obtained as part of routine clinical care for adherence to the study protocol.

If F1CDx testing is not performed as part of routine clinical care, molecular prescreening is required to confirm the presence of FGFR3 alteration from tissue (subjects must provide written informed consent for the molecular prescreening). See Appendix 5 (Section 17.5) for details on the specimen requirements for F1CDx testing. F1CDx should be performed using the tumor sample from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy) because this tumor provides the most current readout of FGFR3 status. If the surgical specimen is not available, an archival biopsy sample can be used when prespecified criteria are met (see Section 9.1). The sponsor must review all cases where an archival biopsy sample is used to assess FGFR3 alterations (either locally as part of routine clinical care or centrally through molecular prescreening) for adherence to the study protocol. Molecular prescreening results (and any leftover tumor material) will be used to validate F1CDx as a companion diagnostic for the identification of patients with urothelial carcinoma who may benefit from treatment with infigratinib following the detection of FGFR3 alterations. The companion diagnostic validation may require a bridging study that will use leftover tumor samples from enrolled subjects collected during prescreening.

Subjects with an FGFR3 alteration identified as described below (in addition to all other inclusion/exclusion criteria) will be eligible for enrollment in the study. Subjects with susceptible FGFR alteration(s) other than the ones described below will be enrolled in the study only **following discussion between the investigator and the medical monitor.**

- **FGFR3 mutation** is confirmed if:
    - FGFR3 gene is mutated in Exon 7 (R248C, S249C), Exon 10 (G370C, A391E, Y373C), or Exon 15 (K650M/T, K650E/Q).

- **FGFR3 gene fusion/rearrangement** is confirmed based on the following criteria:
  - Any fusion/rearrangement with a literature-derived known partner gene regardless of strand or frame.
  - Fusion/rearrangements in the same strand that are in frame with a novel partner gene.
  - Fusion/rearrangements with one breakpoint in the intron 17 - exon 18 hotspot region and the other breakpoint in an intergenic region or another gene. This rule excludes 3′ duplications comprising only exon 18.
- The amino acid numbers for the FGFR3 mutations refer to the functional FGFR3 isoform 1 (NP_000133.1) that is the NCBI Refseq ID used to report genetic alterations in FGFR3 by the F1CDx test.

Assessment of the PD-L1 status is not an eligibility criterion, subjects are allowed to participate in the study regardless of the PD-L1 status results. Nevertheless, PD-L1 results are required and will be recorded in the eCRF. If PD-L1 status is not already known, the assessment will be initiated on subject's tumor sample from the definitive surgery or a biopsy (following the same rules for biopsy sample as described for the FGFR3 testing requirements in Section 9.1; refer to the Laboratory Manual for additional information). If PD-L1 status was not available at screening, the PD-L1 testing can be initiated at C1D1 or at any time after the subject is deemed eligible.

If PD-L1 status is not already known at the time of screening, tumor tissue collected prior to treatment with study drug will be assessed for PD-L1 protein expression using a Food and Drug Administration (FDA)-approved immunohistochemistry (IHC) assay (PD-L1 IHC 22C3 pharmDx) to support the exploratory objectives. If not already known, the PD-L1 IHC should be performed using the tumor sample from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy). If the surgical specimen is not available, a biopsy sample can be used instead. Refer to the Laboratory Manual for additional details regarding PD-L1 biomarker assessments. If tumor tissues or biopsy sample are not available, PD-L1 testing will not be expected.

Blood and urine samples for assessment of cfDNA will be collected as outlined in Table 2 and Table 3 to support exploratory objectives. These samples will be used for analysis of DNA to explore whether genetic alterations or other biomarkers found in tumor samples may also be observed in blood or urine, and if any biomarkers are prognostic or predictive of efficacy, disease recurrence, and/or resistance to study medications.

With subject consent, tumor samples collected upon local/regional or contralateral invasive or metastatic recurrence as part of standard of care may be provided to the sponsor for exploratory objectives related to biomarkers of urothelial carcinoma biology and the potential association of biomarkers with efficacy, disease recurrence, and resistance to study medications. Additional archival tumor samples (including leftover DNA from subjects who underwent molecular prescreening) may also be collected for biomarker assessments to support the exploratory objectives. Biomarker assessments using tumor tissue left over from FGFR3 prescreening and cfDNA derived from blood or urine may include (but are not limited to): (1) genetic analysis

including transcriptomic, whole genome sequencing, whole exome sequencing, or targeted gene sequencing; (2) protein analysis including proteome analysis and IHC.

QED designated laboratories(s) will be used for processing of all tumor, blood samples, and urine samples collected. The central laboratory will provide kits to collect and ship these samples to QED designated lab(s) for analysis. Refer to the Study Manual for additional instructions on the handling, storage and shipment of samples. Sample collection must be captured on the appropriate eCRF and requisition page(s).

If the subject consents to long-term storage, samples collected during molecular prescreening or as part of the main study may be stored for up to 15 years for additional future research related to infigratinib, cancer, or other study treatments. This may also include research to help develop ways to detect, monitor, or treat cancer. A decision to perform additional research studies would be based on outcome data or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.4 Quality of Life

Subject QOL will be evaluated using the EuroQOL 5 dimensions, 5 levels questionnaire (EQ-5D-5L), which measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, anxiety, and general health and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), which are reliable and valid measures of QOL in cancer subjects. QOL will be evaluated at the times outlined in Table 2. At each time point, the EQ-5D-5L is to be completed first, followed by the EORTC QLQ-C30.

The subject-reported assessments are for the purpose of exploring the subject's own perceptions about their symptoms and health-related QOL, and thus a proxy (ie, a caregiver or study personnel) should not complete the questionnaires. Additionally, the investigator must not influence the subject's assessments. Every effort should be made to maintain an unbiased assessment.

If a subject cannot complete the QOL instrument (questionnaire) because of illiteracy or other documented reason, the instrument should be omitted. Reasons for missing data will be documented and incorporated into the analysis as necessary.

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of general health states preferences and provides a simple descriptive profile and index value for health status and measures 5 dimensions of health including mobility, self-care, usual activities, pain/discomfort, anxiety, and general health is measured via a vertical visual analog scale (Rabin 2001). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

The subject-reported assessments are for the purpose of exploring the subject's own perceptions about their symptoms and health-related QOL and thus a proxy (ie, a caregiver or study personnel) should not complete the questionnaires. Additionally, the investigator must not

influence the subject's assessments. Every effort should be made to maintain an unbiased assessment.

At each scheduled assessment, the EQ-5D-5L should be administered before all other study procedures. If assessments were completed within the previous 7 days at a regularly scheduled visit, assessments do not need to be administered at the EOT visit.

Details of the algorithms that generate summary derived scores on each of the above health related QOL scales and the statistical approach for each will be provided in the Statistical Analysis Plan (SAP).

EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the QOL of cancer subjects (Aaronson 1993). It has been translated and validated into 8 languages. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scale scoring with anchors (1=very poor and 7=excellent).

10.5 Safety Assessments

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

10.5.1 Adverse Events

10.5.1.1 Definitions

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s).

An SAE is defined as one of the following:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Is medically significant, ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent 1 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 preplanned 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.

In addition, any suspected transmission of an infectious agent via a medicinal product will be considered an SAE at study centers in the EU.

10.5.1.2 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 (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug(s).

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

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

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

Overdose of study drug is to be reported as an AE when drug is administered or taken at a daily dose ≥200 mg and the overdose is associated with signs or symptoms potentially related to study drug (see also Section 10.5.1.5).

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

10.5.1.3 Recording Adverse Events

After a subject signs the molecular prescreening ICF and/or the main study ICF and until a subject is randomly assigned to study treatment, AEs will only be captured if they meet the definition of serious and are reported to be causally related with study procedures (eg, an invasive procedure such as biopsy). Any other appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) should be recorded as medical history.

Before randomization, any SAEs reported as causally related with study procedures will be captured on a paper SAE Report form. After randomization, all AEs and all SAEs will be captured and reported in the eCRF.

Conditions already present at the time of informed consent should be recorded in the Medical History eCRF.

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.

The following information is to be captured in the eCRF for each AE: severity grade (CTCAE version 5.0, Grade 1-5); duration (start and end date); relationship to study drug; action taken with respect to study drug; whether medication or therapy was given; outcome; and whether the event was 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.

10.5.1.4 Reporting Serious Adverse Events

Before randomization, any SAEs causally related with study procedures will be captured on a paper SAE Report Form and must be reported to Covance Safety immediately and under no circumstances later than 24 hours of learning of its occurrence via email: SAEintake@covance.com; or fax (please refer Study Manual for country-specific fax numbers).

After randomization, every SAE, regardless of suspected causality, occurring after the subject has been randomly assigned to study treatment through 30 days after the subject has taken his/her last dose of study drug must be reported on the SAE eCRF immediately and under no circumstances later than 24 hours of learning of its occurrence. If there are any issues with electronic data capture (EDC), please send a completed paper SAE report form to Covance Safety via email: SAEintake@covance.com or fax (please refer to the Study Manual for country-specific fax numbers). Any SAEs experienced after this 30-day period should only be reported to Covance Safety 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 initial SAE. 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 Covance Safety Associate may

urgently require further information from the investigator for Health Authority reporting. Covance Safety 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 according to national regulatory requirements in participating countries.

More detailed information on SAE Reporting can be found in the Study Manual.

10.5.1.5 Adverse Events of Special Interest

The following AEs, if otherwise not qualified as an SAE, are to be reported within 24 hours in the EDC system.

- Potential drug induced liver injury that meets the following criteria (elevation of bilirubin and ALT/AST that meet Hy's Law criteria [FDA Guidance for Industry 2009]):
    - Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin ≥2 × ULN (of which ≥35% is direct bilirubin)
    - Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice.
- Retinal detachment of Grade 3 or higher, regardless of relationship to study drug.
- Keratitis Grade 3 or higher with suspected relationship to study drug.
- Pathological fractures, defined as fractures potentially related or related to metastatic tumor to bone and/or study drug.
- Vascular calcifications with accompanying ischemic AEs.
- Overdose, defined as a daily dose ≥200 mg of study drug, and that is associated with an AE that is potentially related to study drug.

10.5.1.6 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 on the AE eCRF.

Once an AE is detected, it should be followed up 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 up according to standard of care until resolution or stability.

Also see Section 7.2.5.2 for follow up information on toxicities.

10.5.2 Pregnancies

All women of childbearing potential are to undergo pregnancy testing (blood or urine) at the times specified in Table 2 and Table 3. Female subjects must be discontinued from study drug in the event of pregnancy.

To ensure subject safety, each pregnancy in a subject or partner of a male subject occurring while the subject is on study drug (and for 30 days after the last study drug dose) must be reported to Covance Safety 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 entered on the Pregnancy Notification eCRF. Pregnancy follow-up should be documented on a paper Pregnancy Follow-up Form and reported to Covance Drug Safety (email: SAEintake@covance.com; fax: please refer to the Study Reference Manual for country-specific fax numbers).

Any SAE experienced by a subject during pregnancy must be reported on the applicable SAE Report Form and be reported as outlined in Section 10.5.1.4.

10.5.3 Laboratory Parameters

Clinical laboratory analyses are to be performed at the times specified in Table 2 and Table 3. Parameters included in the panel are listed in Table 10.

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 (eg, 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 10: Safety Laboratory Parameters

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, RBC counts, WBC counts with differentials, platelets
Biochemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), calcium (can be corrected), chloride, creatinine, BUN (or urea), potassium, sodium, magnesium, phosphorus Direct bilirubin, indirect bilirubin, total bilirubin, total protein, uric acid, amylase, lipase
Urinalysis	Macroscopic panel (dipstick) (blood, glucose, ketones, pH, protein, specific gravity). Microscopic panel (RBC, WBC)
Coagulation	PT or INR, PTT

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cell.

10.5.4 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 Table 2. 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.

10.5.5 Physical Examinations

A complete physical examination (including height and weight) must be performed at the Screening, C1D1, and C13D28/EOT visits; at all other times indicated in Table 2, abbreviated, symptom-based physical examinations are to be performed, as needed.

The complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information about the physical examination must be present in source documentation at the study center. Clinically significant findings that are present before randomization should be included in the Medical History eCRF. Significant new findings must be recorded on the AE eCRF.

10.5.6 Electrocardiograms

For each subject, 12-lead ECGs are to be performed at the times indicated in Table 2.

Clinically significant ECG findings must be discussed with the medical monitor prior to enrolling the subject. Clinically significant ECG abnormalities present before randomization should be reported on the Medical History eCRF page. Significant new findings post randomization from initiation of study drug until 30 days after permanent discontinuation of study drug must be recorded as an AE on the AE eCRF.

10.5.7 Ophthalmic Assessments

For each subject, ophthalmic examinations are to be performed by an ophthalmologist at the times indicated in Table 2 and with any new onset of visual disturbance. These assessments will include visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, intraocular pressure, retinal OCT, and dilated fundoscopy. Additional examinations such as specular microscopy and corneal pachymetry will be performed as clinically indicated.

Retinal OCT scan images will be read locally and the scans will be sent to the OCT imaging vendor. Refer to the study manual for details regarding image collection and transfer or shipment.

10.5.8 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed as detailed in Table 2. ECOG performance status describes a patient's level of functioning in terms of their ability to perform selfcare, daily activity and physical ability using the following scale:

- Grade 0: Fully active, able to carry on all predisease performance without restriction.
- Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
- Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
- Grade 3: Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
- Grade 4: Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
- Grade 5: Death.

10.5.9 Early Stopping Guidelines and Data Monitoring Committee

One formal interim analysis of DFS will be performed when approximately 35 confirmed DFS events by BICR (independent of investigator assessment) have occurred across both treatment arms in the ITT population.

At the interim analyses, the study will NOT be stopped for efficacy if the efficacy boundary for centrally reviewed DFS is crossed. A Haybittle-Peto (Haybittle 1971) boundary with a fixed one-sided alpha=0.00005 will be spent at the interim analysis, and the rest of the alpha (one-sided alpha=0.025) spent at the primary centrally reviewed DFS analysis.

The study may be stopped due to futility at the interim DFS analysis when the futility boundary for testing DFS is crossed. The futility stopping boundary is non-binding to allow for additional considerations. The methods of Lan and DeMets spending function approximating O'Brien and Fleming, boundaries will be used for the futility boundaries.

If a sample size increase is deemed necessary based on the interim result and the promising zone approach, the sample size/event goal will be increased by a maximum of 50% (328/105). The details of the sample size adaptation method will be prespecified in a separate adaptation plan.

An independent DMC will periodically monitor the interim data at regularly scheduled meetings, according to a prespecified DMC charter and at the interim analysis. The voting members of the committee will be external to the sponsor and must not be involved with the trial in any other capacity (ie, they cannot be trial Investigators) and must have no competing interests that could affect their role with respect to the trial.

The DMC will review the formal interim trial result when 35 confirmed DFS events by BICR are reached, consider the overall risk and benefit to trial participants and make recommendations to the Sponsor whether the trial should continue in accordance with the protocol, or whether sample size will need to be increased according to the prespecified rules in the adaptation plan, and regarding steps to ensure both subject safety and ethical and trial integrity of the trial.

In the event that the study is terminated early based on a DMC recommendation, QED will notify the appropriate regulatory authorities.

The DMC or QED study team may request an ad hoc meeting for any reason, including significant unexpected safety event or follow-up of an observation during a planned DMC meeting.

At each review, subject incidence rates of AEs (including all serious, treatment-related, serious treatment-related and events requiring the discontinuation of study drug) will be tabulated by system organ class, preferred term and severity grade. Listings and/or narratives of “on-study” deaths, deaths within 30 days of receiving study drug and serious and significant AEs, including any early discontinuations due to AEs will be provided.

Records of all meetings will be archived. The DMC will communicate major safety concerns and recommendations regarding study modification or termination to QED.

Further details will be provided in the DMC charter.

11 STATISTICAL METHODOLOGY

11.1 General Considerations

Data will be analyzed by QED and/or designated CRO.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The efficacy analyses will be conducted on the ITT population, defined as all subjects randomly assigned to study treatment; subjects will be analyzed according to their randomized treatment arm assignment. The safety analyses will be performed for all subjects who have received ≥1 dose of study drug according to the treatment they receive. Detailed definitions of the analysis populations will be provided in the SAP.

The study uses an adaptive design promising zone approach (Mehta 2011). The study will start with 218 subjects with a group sequential design with 1 interim analysis at approximately 50% of confirmed DFS events by BICR (35 events; independent of investigator assessment). A Haybittle-Peto boundary will be used for the efficacy boundary with a fixed one-sided alpha of 0.00005 spent at the interim analysis for centrally reviewed DFS, and the rest of the alpha (one-sided alpha 0.025) spent at the primary centrally reviewed DFS analysis. A Lan DeMets spending function approximating O'Brien-Fleming boundaries will be used for the non-binding futility boundary.

If no sample size adaption is needed at the interim analysis, the study is projected to reach the planned number of confirmed DFS events by BICR (70 events; independent of investigator assessment) 4 years from the randomization of the first subject. If a sample size increase is deemed necessary based on the interim result on centrally reviewed DFS using the promising zone approach, the sample size/event goal will be increased by a maximum of 50% (328/105). The details of the sample size adaptation method will be prespecified in the adaptation plan.

For the secondary efficacy endpoints DFS (including intraluminal low-risk [noninvasive, low-grade or high-grade] recurrence), MFS, and OS, a fixed sequence testing procedure will be followed to control the family-wise type I error at a level of one-sided 0.025.

DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence will be tested first if the test on DFS is significant, followed by the test on MFS if both DFS and DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence are significant. OS will be tested finally if DFS, DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, and MFS are all significant.

A Haybittle-Peto boundary will be used for the secondary endpoints. A fixed one-sided type I error with alpha=0.00005 will be spent at the interim analysis, and the rest of the type I error will be spent at the time of the primary analysis.

For DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence and MFS, 1 interim analysis will be conducted at the time of interim analysis for DFS, and the primary analysis will be conducted at the primary analysis for DFS when the DFS event goal is reached. There will be 2 interim analyses for OS, one at interim DFS analysis and the other one at primary DFS analysis. The primary analysis for OS will be conducted at approximately 1 year after the DFS event goal is reached. For OS analyses, a fixed one-sided type I error with alpha=0.00005 will be spent at each of the interim analysis, and the rest of the type I error will be spent at the time of the primary OS analysis. The analysis for long-term OS follow-up data will be descriptive.

The same analysis methodology described for centrally reviewed DFS will be applied for statistical analyses for DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, MFS, and OS with corresponding efficacy boundaries.

Any deviations in analysis from the protocol or SAP-specified analyses will be identified in the clinical study report.

Details on handling of missing data will be included in the SAP.

Sensitivity analyses may be conducted to evaluate the potential effect on efficacy outcomes due to enrollment of subjects refusing cisplatin-based chemotherapy (yes vs no) and reasons why a subject did not receive cisplatin-based chemotherapy (ineligible or refusal) in the 2 treatment arms (active vs placebo), using the Cox regression model with this factor as a covariate.

If sufficient numbers of subjects are enrolled with a component of variant histology, or with microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease, sensitivity analysis will also be conducted to account for variations in response. Further details are provided in the SAP.

11.2 Sample Size Determination

For the initial group sequential design, assuming disease will recur in 46% of subjects in the first 2 years and a 5% yearly recurrence rate in the third year and beyond for the placebo group, with 3-year uniform enrollment, 1-year follow-up, 10% yearly drop-out rate, and a hazard ratio (HR) of 0.5, the required sample size with initial group sequential design is approximately 218 subjects to reach 70 confirmed DFS events by BICR (independent of investigator assessment) in 4 years. The initial sample size will provide approximately 80% power to detect a difference in DFS assuming an HR of 0.5, based on a log-rank test controlling type I error at one-sided 0.025.

The sample size may be increased at the interim analysis based on the interim result on centrally reviewed DFS using the promising zone approach (Section 11.3.3). The maximum sample size increase would be 328 subjects (164 subjects per group) to reach 105 confirmed DFS events by BICR (independent of investigator assessment) at the final DFS analysis.

11.3 Statistical Hypothesis, Model, and Method of Analysis

11.3.1 Disposition of Subjects

The number of subjects randomly assigned to study treatment and screen failed subjects will be summarized. The number and percentage of subjects entering and completing treatment and study will be presented by treatment arm. Reason for discontinuation of treatment and study will also be summarized.

11.3.2 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, baseline characteristics, prior anticancer therapy, concomitant medication will be summarized by treatment arm.

11.3.3 Efficacy Analyses

The primary objective of the study is to compare the centrally reviewed DFS of subjects with invasive urothelial cancer with susceptible FGFR3 alterations treated with infigratinib vs placebo following nephroureterectomy, distal ureterectomy, or cystectomy.

The primary endpoint is centrally reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence (according to central review) or death due to any

cause, whichever occurs earlier. Criteria for recurrence are specified in Section 10.1. For subjects without a bladder who are alive and without recurrence (local/regional or contralateral invasive or metastatic) by BICR, DFS will be censored at the last radiology assessment. For subjects with a bladder who are alive and without recurrence, DFS will be censored at the last radiology assessment if the previous cystoscopy result within 6 months is negative for muscle invasive disease, otherwise DFS will be censored at the last complete recurrence assessment. Subjects who have no disease assessments after baseline or no death recorded will be censored on the randomization date.

Investigator-reviewed DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence is defined as the time from randomization to any recurrence as determined by the investigator, or death due to any cause, whichever occurs earlier. For subjects without documented recurrence and who are still alive, they will be censored at the last complete disease assessment (or, if no complete disease assessments are performed after the baseline visit or no death recorded, at the time of randomization day).

Investigator-reviewed MFS is defined as the time from randomization to any metastatic recurrence as determined by the investigator or death due to any cause, whichever occurs earlier. For subjects without documented metastatic recurrence and who are still alive, they will be censored at the last radiology assessment (or, if no radiology assessments are performed after the baseline visit or no death recorded, at the time of randomization day).

OS is defined as date of randomization to death. For subjects without documented death, they will be censored at the last known to be alive date.

The study uses an adaptive design promising zone approach. The study will start with 218 subjects using a group sequential design with 1 interim analysis at approximately 35 confirmed DFS events by BICR (independent of investigator assessment). A Haybittle-Peto boundary will be used for the efficacy boundary with a fixed one-sided alpha of 0.00005 spent at the interim analysis for centrally reviewed DFS, and the rest of the alpha (one-sided alpha 0.025) spent at the primary DFS analysis. A Lan DeMets spending function approximating O'Brien-Fleming boundaries will be used for the non-binding futility boundary.

If a sample size increase is deemed necessary based on the interim result and the promising zone approach, the sample size/centrally reviewed DFS event goal will be increased by a maximum of 50% (328/105).

If no sample size adaptation is needed at the interim analysis, the primary analyses of DFS will be performed when approximately 70 confirmed DFS events by BICR (independent of investigator assessment) have been reached. If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly time-wise when the adjusted event goal is reached, and the boundary to test DFS when the adjusted event goal is reached will be based on the original boundary from the initial group sequential design.

The primary efficacy analysis will be conducted on the ITT population, which will include all subjects who are randomly assigned to study treatment. Subjects will be analyzed according to the treatment arm to which they are randomly assigned.

For primary DFS analysis, CHW statistics (Cui 1999) based on stratified log-rank test (using randomization stratification factors except disease type [UTUC or UBC]) will be used to control type I error in case of a sample size increase at the interim analysis. Conventional stratified log-rank test will be used for the inference on centrally reviewed DFS if sample size is not adjusted at the interim analysis. Repeated confidence interval (Jennison 1989; Lehmacher 1999) will be provided for the estimated HR based on stratified Cox proportional hazards regression model. The disease type (UTUC or UBC) will be excluded from the stratified statistical analyses as a stratification factor due to small sample size in UBC (up to 15%).

In case of sample size re-estimation, the CHW method (Cui 1999) will be used to combine the independent increments of the stratified log rank statistics as shown below:

Let LR_1 denote the stratified log rank statistics calculated with respect to events in the infigratinib treatment group at the interim analysis and LR_2 is the log rank statistics with respect to events in the infigratinib treatment group calculated at the primary analysis using all the data available. The final test statistic for the primary analysis is

$$Z_{CHW} = \sqrt{w}\, Z_1 + \sqrt{1-w}\, Z_2$$

where $w = 0.5$ and

$$Z_1 = LR_1$$

$$Z_2 = \frac{\sqrt{D_2^*}\, LR_2 - \sqrt{D_1^*}\, LR_1}{\sqrt{D_2^* - D_1^*}}$$

where D_2^* is the event number at the primary analysis after sample size adjustment and $D_1^* = D_1$ which is the number of events at the interim analysis.

The p-value at the primary analysis is defined by $p_{CHW} = \Phi(Z_{CHW})$, where Φ is the cumulative probability based on standard normal distribution.

At the primary analysis, Z_{CHW} or p_{CHW} will be compared with the original group sequential design boundary to test whether centrally reviewed DFS is significant with the control of the family-wise type I error at a level of one-sided 0.025.

For the secondary efficacy endpoints DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, MFS and OS, a fixed sequence testing procedure will be followed to control the family-wise type I error at a level of one-sided 0.025.

DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence will be tested first if the test on centrally reviewed DFS is significant, followed by the test on MFS if both DFS and DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence are significant. OS will be tested finally if DFS, DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, and MFS are all significant.

A Haybittle-Peto boundary will be used for the secondary endpoints. A fixed one-sided type I error with alpha=0.00005 will be spent at the interim analysis, and the rest of the type I error will be spent at the time of the primary analysis.

For DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence and MFS, one interim analysis will be conducted at the time of interim analysis for centrally reviewed DFS, and the primary analysis will be conducted at the primary analysis for centrally reviewed DFS when the DFS event goal is reached. There will be 2 interim analyses for OS, one at interim centrally reviewed DFS analysis and the other one at primary centrally reviewed DFS analysis. The primary analysis for OS will be conducted at approximately 1 year after DFS event goal is reached. For OS analyses, a fixed one-sided type I error with alpha=0.00005 will be spent at each of the interim analyses, and the rest of the type I error will be spent at the time of the primary OS analysis. After the EOS (1 year after the DFS primary analysis), subjects will continue to be followed for long-term OS (under a separate protocol) for approximately 14 years, or all of the subjects die or drop from this follow up, whichever is earlier. The data for this long-term OS follow-up will be reported in a separate study report.

The same analysis methodology described for centrally reviewed DFS will be applied for statistical analysis for DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, MFS, and OS with corresponding efficacy boundaries.

Repeated CI will be provided based on Lehmacher (1999) in case of sample size increase. Otherwise it will be provided using Jennison (1989).

Sensitivity analyses may be conducted to evaluate the potential effect on efficacy outcomes due to subjects refusing cisplatin-based chemotherapy (yes vs no) and reasons why a subject did not receive cisplatin-based chemotherapy (ineligible or refusal) in the 2 treatment arms (active vs placebo), using the Cox regression model with this factor as a covariate; details will be provided in the SAP. The number of subjects refusing cisplatin-based perioperative therapy will be capped at approximately 10% of the total population (approximately 22 subjects).

If sufficient numbers of subjects are enrolled with a component of variant histology, or with microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease, sensitivity analysis will also be conducted to account for variations in response. Further details are provided in the SAP.

11.3.4 Pharmacokinetic Analyses

C_{trough} and C_{max} will be estimated from the PK concentration data collected (Section 10.2). PK concentration will be summarized as appropriate. Data may be used for population PK analysis and PK/PD analysis and results may be reported separately.

11.3.5 Biomarker Analyses

Summary statistics for genetic alterations among different groups of all prescreened subjects will be provided.

Biomarker analysis will be performed using available tumor samples in order to detect changes from baseline in the genetic profiles in tumor samples from treated subjects. The difference in biomarker results from samples taken before and during treatment may be explored.

In addition, correlation between genetic biomarkers, subject demographics, and clinical endpoints may also be explored. The SAP will provide more details of such descriptive analyses.

11.3.6 Analyses of Quality of Life Assessments

QOL assessments (EQ-5D-5L and EORTC QLQ-C30) will be analyzed using a random effects mixed model controlling for baseline scores and stratification factors to assess the difference in treatment arms. Two-sided 95% CI will be calculated for the difference between the 2 treatment arms.

In addition, descriptive summaries on the observed data (including change from baseline) will be summarized at each assessed time point. Compliance with QOL assessments will be reported.

11.3.7 Interim Analysis

One formal interim analysis of DFS will be performed when approximately 35 confirmed DFS events by BICR (independent of investigator assessment) have occurred. A Haybittle-Peto boundary will be used for the efficacy boundary with a fixed one-sided alpha of 0.00005 spent at the interim analysis for centrally reviewed DFS, and the rest of the alpha (one-sided alpha 0.025) spent at the primary DFS analysis. A Lan DeMets spending function approximating O'Brien-Fleming boundaries will be used for the non-binding futility boundary.

At the interim analyses, the study will not be stopped for efficacy if the efficacy boundary for DFS is crossed.

The study may be stopped due to futility at the interim DFS analysis if the futility boundary for testing DFS is crossed. The futility stopping boundary is non-binding to allow for additional considerations.

If a sample size increase is deemed necessary based on the interim result using the promising zone approach, the sample size/event goal will be increased by a maximum of 50% (328/105). The details of the sample size adaptation method based on interim analysis will be prespecified in the adaptation plan.

11.3.8 Safety Analyses

Safety analyses will be performed for all subjects who receive ≥1 dose of study drug according to the treatment they received.

11.3.8.1 Treatment Exposure

Duration of treatment will be summarized by treatment arm. In addition, the cumulative dose and the relative dose intensity (cumulative actual dose/planned cumulative dose) will be summarized. The number of subjects with dose interruptions or dose reductions will be tabulated by treatment arm.

11.3.8.2 Adverse Events

Study data will be monitored on an ongoing basis by the clinical study team to ensure subjects' safety. Additional safety reviews will be performed by the DMC periodically throughout the study. These reviews will include all available data on incidence of AEs, SAEs including deaths, and events leading to treatment discontinuation.

All reported AEs will be assigned to a system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA).

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

11.3.8.3 Other Safety Findings

Laboratory parameters for hematology and serum blood chemistry will be summarized at baseline, at each visit or selected visits, for the maximum and minimum observed postbaseline values, and the last observed value, along with the change from baseline. Tables of shifts in severity (by CTCAE version 5.0) from baseline for selected laboratory parameters also may be provided. Graphical representations of aggregate data may also be presented for parameters of interests.

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

12 DATA COLLECTION AND MANAGEMENT

12.1 Data Confidentiality

All records identifying the subject will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the eCRF. If the subject name appears on any other document or trial materials, then that information must be redacted before a copy of the document is supplied to the sponsor. Trial data

stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor, IRB/IEC/Research Ethics Board (IRB/IEC/REB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the trial are published, the subjects' identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Either year of birth or exact date of birth (depending on local privacy regulations) will be recorded to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

12.2 Study Center Monitoring

Before study initiation, at a study center initiation visit or at an Investigator's meeting, QED personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the study center regularly to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the subject's file. The exception is the QOL instrument (questionnaire) data collected in this study, which will be entered directly into a handheld device. The Investigator must also keep the original signed ICF (a signed copy is given to the subject).

The Investigator must give the field monitor access to all relevant source documents to confirm their consistency with the eCRF entries. QED monitoring standards require the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and full verification for drug accountability (as described in Section 7.2.4). Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

12.3 Data Collection

The designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. The Investigator and study center staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator's staff.

The Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

12.4 Database Management and Quality Control

QED personnel (or designated CRO) will review the data entered into eCRFs by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational study center via the EDC system. Designated Investigator study center staff are required to respond promptly to queries and to make any necessary changes to the data.

Prior medications, concomitant treatments, and post-treatment anticancer medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using MedDRA terminology.

PK and biomarker samples will be processed centrally and the results will be sent electronically to QED (or a designated CRO).

The occurrence of any protocol violations will be evaluated. Once the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Appropriate QED authorization is required prior to making any database changes to locked data.

After database lock, the investigator will receive an electronic CD-ROM copy of the subject data for archiving at the investigational study center.

12.5 Study Documentation, Record Keeping and Retention of Documents

Each participating study center will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the International Council for Harmonisation (ICH) E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a QED-sponsored study, each study center will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records,

clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the study center under the supervision of the investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The Investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

The Investigator must maintain all documentation relating to the study as outlined in local/regional requirements.

QED will retain records in accordance with ICH E6 GCP, Section C.05.012 of Division 5 of the Food and Drug Regulations (FDR), and other applicable regional regulatory requirements.

12.6 Audits and Inspections

Source data/documents must be available for inspection by QED, its designees or Health Authorities.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. Before study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to QED monitors, auditors, QED Clinical Quality Assurance representatives, designated agents of QED, IRBs/IECs/REBs and regulatory authorities as required.

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

13.3 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 (ie, all of the procedures described in the protocol). Study subjects will be informed in writing and orally before the start of the study about the nature and scope of the planned study procedures, in particular about the possible benefits and risks of participating in the study. Special attention will be given in the ICF for those subjects who refuse perioperative cisplatin-based chemotherapy in presenting what are the treatment alternatives versus participation in this clinical trial. The reason a subject did not receive cisplatin-based chemotherapy in the perioperative setting will be clearly documented in the eCRF. Consent will be documented by signature on the ICF. The process of obtaining informed consent should be documented in the subject source documents. The date when a subject's informed consent was 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.

QED will provide to Investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by QED before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the QED monitor after IRB/IEC/REB approval.

Women of childbearing potential and sexually active males should be informed that taking 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 and the requirement to refrain from donating sperm and eggs during the study and for 1 month following their last dose of study drug. 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.

13.4 Confidentiality of Study Documents and Subject Records

The Investigator must ensure pseudonymization of the subjects by replacing names with the study-specific subject identification number; subjects must not be identified by names in any documents submitted to QED. The names of study subjects and all other confidential information are subject to medical confidentiality and the provisions of the General Data Protection Regulation (GDPR) and other applicable regulations or laws. Subject data may only be passed on in pseudonymized form beyond the study center. Third parties do not have access to original documents. Signed ICFs and subject enrollment log kept at the study center to enable subject identification must be kept strictly confidential.

14 FINANCIAL CONSIDERATIONS AND INSURANCE

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of subjects at the study center before study start. Other aspects of finances (such as budgeting with study centers) and insurance will be provided in separate documents.

15 PUBLICATION POLICY

QED is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. QED assures that the key design elements of this protocol will be posted on the publicly accessible database, eg, www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials will be posted publicly according to local regulations.

QED follows the International Committee of Medical Journal Editors authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from QED or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, QED supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

Any data analysis carried out independently by the investigator must be submitted to QED before publication or presentation.

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17 APPENDICES

17.1 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 lists in Table 11 are based on the Indiana University School of Medicine's "Clinically Relevant" Table (Flockhart Table™; Flockhart 2007) and supplemented with the FDA Draft guidance and the online database Drugbank.ca.

Note: This is not an exhaustive list of medications. Investigator should use this list solely as a guide.

Table 11: Drugs to be Used with Caution While on Study

Category	Drug Names
CYP3A substrates with narrow therapeutic index	alfentanil, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus, terfenadine, warfarin sodium or any other coumadin-derivative anticoagulants, direct thrombin inhibitors (eg, argatroban), and Factor Xa inhibitors (eg, rivaroxaban)
Medications which alter the pH of the GI tract[a,b]	antacids, H_2-antagonists (eg, ranitidine)
Medications that have possible risk of TdP/QT prolongation	alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
Medications that have conditional risk of TdP/QT prolongation	amitriptyline, amisulpride, ciprofloxacin, clomipramine, desipramine, diphenhydramine, doxepin, fluoxetine, galantamine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, solifenacin, trazodone, trimethoprim-sulfa, trimipramine
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, cocaine, disopyramide, dofetilide, domperidone (off 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 (off US market), terfenadine (off US market), thioridazine, vandetanib
BCRP substrates	atorvastatin, irinotecan, methotrexate, rosuvastatin, simvastatin, sulfasalazine, topotecan

Abbreviations: BCRP=breast cancer resistance protein; CYP=cytochrome p450; GI=gastrointestinal; TdP=Torsades de Pointes

[a] Study drug should be dosed ≥2 hours before or 10 hours after dosing with a H_2 receptor agonist, or separated by 2 hours with acid neutralizing agents (antacids).

[b] Proton pump inhibitors are prohibited due to their long pharmacodynamic effect and should be replaced with H_2-antagonists or antacids.

Sources: FDA Guidance for Industry 2020; Flockhart 2007; drugbank.ca.

17.2 Appendix 2: List of Prohibited Medications

Table 12: List of Prohibited Medications and Substances[a] While on Study

Category	Drug Names
Moderate inhibitors of CYP3A4[b]	ACT-17882, ACT-539313, amprenavir, aprepitant, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, darunavir, darunavir/ritonavir, diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, FK1706, fluconazole, fosaprepitant, GSK2647544, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, netupitant, nilotinib, primidone, ravuconazole, Schisandra sphenanthera, tofisopam, verapamil, voxelotor
Moderate inducers of CYP3A4[b]	asunaprevir/beclabuvir/daclatasvir, bosentan, cenobamate, dabrafenib, efavirenz, elagolix, etravirine, lersivirine, lesinurad, lopinavir, lorlatinib, modafinil, nafcillin, PF-06282999, rifabutin, semagacestat, talviraline, telotristat ethyl, thioridazine, tipranavir/ritonavir
Strong inhibitors of CYP3A4[b]	boceprevir, ceritinib, clarithromycin, cobicistat (GS-9350), conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib, indinavir, indinavir/ritonavir, itraconazole, josamycin, ketoconazole, LCL161, lopinavir/ritonavir, mibefradil, mifepristone nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, troleandomycin, tipranavir/ritonavir, tucatinib, voriconazole grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits
Strong inducers of CYP3A4[b]	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampin, rifapentine, St. John's wort extract,
Medications which increase serum phosphate and/or calcium	calcium, parathyroid hormone, phosphate, vitamin D (including multivitamins containing vitamin D)
Medications which alter the pH of the GI tract	proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole)
Chinese herbal medicine and Chinese patent medicines for cancer treatments	Chinese herbal medicines and Chinese patent medicines for the treatment of cancer are not allowed during the treatment period.

Abbreviations: CYP=cytochrome p450; GI=gastrointestinal.

[a] This may not be an exhaustive list of prohibited medications. Use this list as a guide and refer to the prescribing information for any medication to determine unacceptable interactions and/or contact the sponsor.

[b] Sources: University of Washington 2021a; University of Washington 2021b.

17.3 Appendix 3: List of Highly Effective Methods of Contraception

The following is from the Clinical Trials Facilitation Group 2020 (Section 4.1).

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
    - oral
    - injectable
    - implantable [2]
- Intrauterine device (IUD) [2]
- Intrauterine hormone-releasing system (IUS) [2]
- Bilateral tubal occlusion [2]
- Vasectomised partner [2,3]
- Sexual abstinence [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see Clinical Trials Facilitation Group 2020, section 4.3). Sponsor's note: it is recommended that women should have been using the same hormonal contraception stably for a minimum of 3 months before starting study treatment.

2 Contraception methods that in the context of this guidance are considered to have low user dependency.

3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

17.4 Appendix 4: Recommended Standards for Lymph Node Dissection (LND) at the Time of Selected Definitive Surgeries for Urothelial Carcinoma

The following is from FDA Guidance for Industry 2020 (Bladder Cancer: Developing Drugs and Biologics for Adjuvant Treatment Guidance for Industry).

Radical Cystectomy/Cystoprostatectomy:

- Perform bilateral pelvic lymphadenectomy and include common, internal iliac, external iliac, and obturator nodes.

Nephroureterectomy with Cuff of Bladder or Distal Ureterectomy

- Regional lymphadenectomy is recommended for patients with high-grade upper genitourinary (GU) tract tumors.
    - Left-sided renal pelvic, upper ureteral, and midureteral tumors:
        - Perform regional lymphadenectomy including the paraaortic lymph nodes from the renal hilum to the aortic bifurcation.
        - Most midureteral tumors will also include the common iliac, external iliac, obturator, and hypogastric lymph nodes.
- Right sided renal pelvic, upper ureteral, and midureteral tumors:
    - Perform regional lymphadenectomy including the paracaval lymph nodes from the renal hilum to the inferior vena cava (IVC) bifurcation.
    - Most midureteral tumors will also include the common iliac, external iliac, obturator, and hypogastric lymph nodes.
- Distal ureteral tumors:
    - Perform regional lymphadenectomy including the common iliac, external iliac, obturator, and hypogastric lymph nodes.

17.5 Appendix 5: Instructions for Optimal Tumor Specimens for FGFR3 testing

Instructions for Archival Tumor Tissue

The archival tumor tissue from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy) is the preferred specimen as this provides the most current readout of fibroblast growth factor receptor 3 (FGFR3) status.

If the surgical specimen is not available, an archival biopsy sample can be used when:

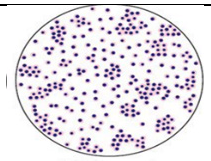
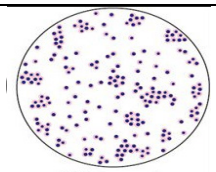
- Biopsy sample is also confirmed invasive urothelial carcinoma (≥pT2).
- Subject did not receive systemic anticancer therapy after the biopsy was obtained.
- The biopsy is collected ≤4 months before the definitive surgery.
- The most recent biopsy is submitted (if >1 biopsy procedure was performed).

Sites must consult with QED if the biopsy sample is the only sample available to submit to the central laboratory for molecular prescreening to ensure adherence with the above criteria.

Choosing the Best Tumor Block

1. The selected formalin fixed paraffin-embedded (FFPE) block should be chosen by a pathologist to contain the most amount of viable tumor. The specimen may contain non-tumor tissue; however, the specimen should be free of excessive necrosis, fibrosis, and lymphoid aggregates that can interfere with molecular testing.
2. Based on the H&E slide, estimate the tumor nuclei percentage (%TN), which is the total # of tumor cells divided by the total # of cells with nuclei. Tumor purity (based on %TN) is most important for detecting FGFR3 genetic alterations. (See Table 13: Recommendations for Tumor Nuclei Percentage).
3. The more viable tumor the better, however samples with ≥30% TN is optimum for most specimens.
4. 20% TN is the minimum tumor content allowed but this lower tumor purity may lead to a greater risk of test failures.
5. Tissue surface area (SA) should be ≥25 mm^2 to meet the tissue volume requirements of 1 mm^3 (10 slides x 4-5 µm thickness per slide x 25 mm^2 SA=1 mm^3 tissue volume).
6. Smaller specimens may qualify by sending more than 10 slides or the FFPE block to meet tissue volume requirements. Additional unstained slides may be needed to extract sufficient DNA for testing.
7. For specimens of adequate tissue size (≥25 mm^2), the central lab may perform macro-enrichment to eliminate normal tissue to meet the tumor purity requirements.

Table 13: Recommendations for Tumor Nuclei Percentage

Tumor nuclei percentage (% TN)	%TN illustration [a]	Comments
≥30% TN Optimum		More likely to pass Pathology Quality Control. Significantly higher pass rate because of higher tumor purity.
20% TN Minimum		Submit >10 slides if possible. The laboratory may attempt macro-enrichment to increase tumor purity. More likely to fail testing due to lower tumor purity.

[a] Cellularity Guide (www.mdanderson.org/documents/for-physicians/clinical-calculators/calculators-cellularity-guide.pdf)

Additional details on tumor specimen preparation are provided in the Laboratory Manual.