

Targeting *FGFR3* alterations with adjuvant infigratinib in invasive urothelial carcinoma: the phase III PROOF 302 trial

Sumanta K Pal^{*1}, Diederik M Somford², Petros Grivas³, Srikala S Sridhar⁴, Shilpa Gupta⁵, Joaquim Bellmunt^{6,7}, Guru Sonpavde⁸, Mark T Fleming⁹, Seth P Lerner¹⁰, Yohann Loriot¹¹, Jean Hoffman-Censits¹², Begoña P Valderrama¹³, Corina Andresen¹⁴, Marco J Schnabel¹⁵, Suzanne Cole¹⁶ & Siamak Daneshmand¹⁷

¹City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA

²Canisius Wilhelmina Hospital, 6532 SZ Nijmegen, The Netherlands

³Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, University of Washington, Seattle, WA 98195, USA

⁴Princess Margaret Hospital, Toronto, ON M5G 2C1, Canada

⁵Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH 44106, USA

⁶Beth Israel Deaconess Medical Center, Boston, MA 02215, USA

⁷PSMAR-IMIM Laboratory, Boston, MA 02215, USA

⁸Dana-Farber Cancer Institute, Boston, MA 02215, USA

⁹Virginia Oncology Associates, Norfolk, VA 23502, USA

¹⁰Baylor College of Medicine, Houston, TX 77030, USA

¹¹Gustave Roussy, Villejuif, 94805, France

¹²Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21287, USA

¹³Hospital Universitario Virgen del Rocío, 41013 Seville, Spain

¹⁴QED Therapeutics Inc., San Francisco, CA 94107, USA

¹⁵University of Regensburg, 93053 Regensburg, Germany

¹⁶UT Southwestern Simmons Comprehensive Cancer Center, University of Texas, Dallas, TX 75390, USA

¹⁷Keck School of Medicine of the University of Southern California, Los Angeles, CA 90033, USA

*Author for correspondence: Tel.: +1 626 256 4673; spal@coh.org

PROOF 302 is an ongoing randomized, double-blind, placebo-controlled, adjuvant phase III trial (NCT04197986) in approximately 218 patients from 120 centers worldwide. Eligibility criteria include post-surgical high-risk muscle-invasive upper tract urothelial cancer (85% of patients) or urothelial bladder cancer (15%), susceptible *FGFR3* alterations (activating mutations, gene fusions or rearrangements), ≤ 120 days following radical surgery and ineligible for/or refusing cisplatin-based (neo)adjuvant chemotherapy. Patients receive either oral infigratinib 125 mg or placebo daily on days 1–21 of a 28-day cycle for up to 52 weeks or until recurrence, unacceptable toxicity or death. Primary end point: centrally determined disease-free survival (DFS); secondary end points: investigator-assessed DFS, metastasis-free survival, overall survival and safety/tolerability; exploratory end points: correlative biomarker analysis, quality-of-life and infigratinib pharmacokinetics.

Plain language summary: Cancers of the bladder and other parts in the urinary system, especially those that are invasive and grow into the muscle layer, may need extra treatment after surgical removal of the tumor, particularly if there is a high risk of the cancer coming back. Chemotherapy regimens that include cisplatin are often used postoperatively, although some patients are unable to tolerate this treatment or refuse it. *FGFR3*, a protein that is encoded by the *FGFR3* gene, is often changed in these cancers. This helps the tumor grow. Infigratinib is an investigational drug that targets *FGFR3* and inhibits the abnormal growth of the tumor. In the PROOF 302 study, patients are randomly assigned to treatment with infigratinib or a placebo pill for 1 year after surgery to see if the drug is effective. The aim is to see if patients who take infigratinib have a longer time free from the disease than those who receive a placebo. The study will also look at how long patients remain free from cancer spread and how long they live overall. The study will also investigate how safe the treatment is and how easy it is to live with it. PROOF 302 is an important study as it will define the role of infigratinib in patients with cancers of the bladder and urinary system who also have *FGFR3* changes, for whom more treatment choices are needed.

Clinical Trial Registration: [NCT04197986](https://clinicaltrials.gov/ct2/show/study/NCT04197986) (ClinicalTrials.gov)

First draft submitted: 22 December 2021; Accepted for publication: 16 March 2022; Published online: 24 May 2022

Keywords: adjuvant cisplatin-based chemotherapy • adjuvant therapy • cisplatin-therapy refusal • *FGFR3* • FGFR inhibitor • fusions or rearrangements • infigratinib • muscle-invasive urothelial carcinoma • mutations • neoadjuvant cisplatin-based chemotherapy • phase III • PROOF 302 • upper tract urothelial carcinoma • urothelial bladder carcinoma • urothelial carcinoma

The mainstay of treatment for patients with nonmetastatic muscle-invasive upper tract urothelial carcinoma (UTUC) or muscle-invasive urothelial bladder cancer (UBC) is radical nephroureterectomy, distal ureterectomy or radical cystectomy with bilateral pelvic lymphadenectomy, with or without cisplatin-based (neo)adjuvant therapy [1,2]. Despite treatment with curative intent, recurrence rates are high and approximately 70% of patients with node-positive disease will have systemic recurrence [3]. For patients with high-risk disease, including residual disease after radical surgery, adjuvant therapy may improve outcomes, but consensus as to the optimal approach in this setting is lacking. In patients with UTUC, the POUT trial showed adjuvant platinum-based chemotherapy significantly improved disease-free survival (DFS) but not overall survival (OS) versus radical nephroureterectomy alone [4,5]. A 2020 meta-analysis of 14 studies in patients with UTUC concluded that adjuvant chemotherapy conferred OS and DFS benefits versus radical nephroureterectomy alone [6]. Up to 60% of patients are, however, unable to receive cisplatin-based (neo)adjuvant therapy because of cisplatin ineligibility [7–9]. Comorbidities, such as renal insufficiency, grade ≥ 2 neuropathy or hearing loss, diminished cardiac function and Eastern Cooperative Oncology Group (ECOG) performance status > 2 , may prevent a sizable proportion of patients from receiving cisplatin-based chemotherapy, which is associated with potential nephro-, neuro- and oto-toxicity, among other adverse events (AEs) [9]. As patients may express reluctance to or cannot receive (neo)adjuvant chemotherapy because of toxicity concerns and/or frailty, alternative options are needed, including clinical trials. Adjuvant nivolumab was recently shown to provide significant DFS benefit versus placebo in patients with high-risk muscle-invasive urothelial carcinoma (UC) after radical surgery, with or without previous neoadjuvant cisplatin-based combination chemotherapy, up to 20% of whom had UTUC (CheckMate274 trial) [10]. The UTUC subgroup in that trial was small and underpowered, with few events and wide CIs in DFS, and no data were presented on the impact of the presence or absence of *FGFR* alterations; consequently, the role of adjuvant therapy in UTUC remains unclear. The National Comprehensive Cancer Network guidelines (October 2021) state that adjuvant nivolumab may be considered for patients with stage II or IIIA muscle-invasive UBC who received no prior cisplatin-based chemotherapy (pT3, pT4a or pN+ tumors) or for those who received neoadjuvant cisplatin chemotherapy (ypT2–ypT4a or ypN+ tumors). For patients with UTUC, adjuvant nivolumab may be considered for those with no neoadjuvant platinum and pT3, pT4 or pN+ tumors, and those with neoadjuvant platinum and ypT2–4 or ypTN+ tumors [11]. The European Society for Medical Oncology guidelines (November 2021) do not currently recommend adjuvant nivolumab for patients with UTUC or UBC [12].

In summary, therefore, neither the POUT nor CheckMate274 trials have, as of yet, shown a significant OS benefit with adjuvant therapy. A DFS advantage was shown in unselected patients with UTUC who were treated with adjuvant platinum/gemcitabine, although the small sample size and number of events do not allow firm conclusions to be drawn regarding the benefit of adjuvant nivolumab in patients with resected UTUC. The impact of *FGFR* alterations was not examined in either study. Therefore, for selected patients with tumors harboring *FGFR3* mutation, fusion or rearrangement, participation in a randomized clinical trial comparing FGFR3-targeted therapy with placebo seems a reasonable alternative with acceptable equipoise following a thoroughly conducted discussion and informed, shared decision-making with the patient that addresses the options of platinum-based chemotherapy, nivolumab and clinical trial participation.

Herein, the authors describe the rationale for and design of the multicenter, global, double-blind, randomized, placebo-controlled phase III PROOF 302 trial (ClinicalTrials.gov: NCT04197986), which is being conducted to evaluate the efficacy and safety of adjuvant infigratinib versus placebo after nephroureterectomy, distal ureterectomy or cystectomy in patients with high-risk muscle-invasive UC. The trial is designed to enroll patients with UC harboring susceptible *FGFR3* alterations (mutation, fusion or rearrangement), predominantly those with UTUC (85%) versus UBC (15%).

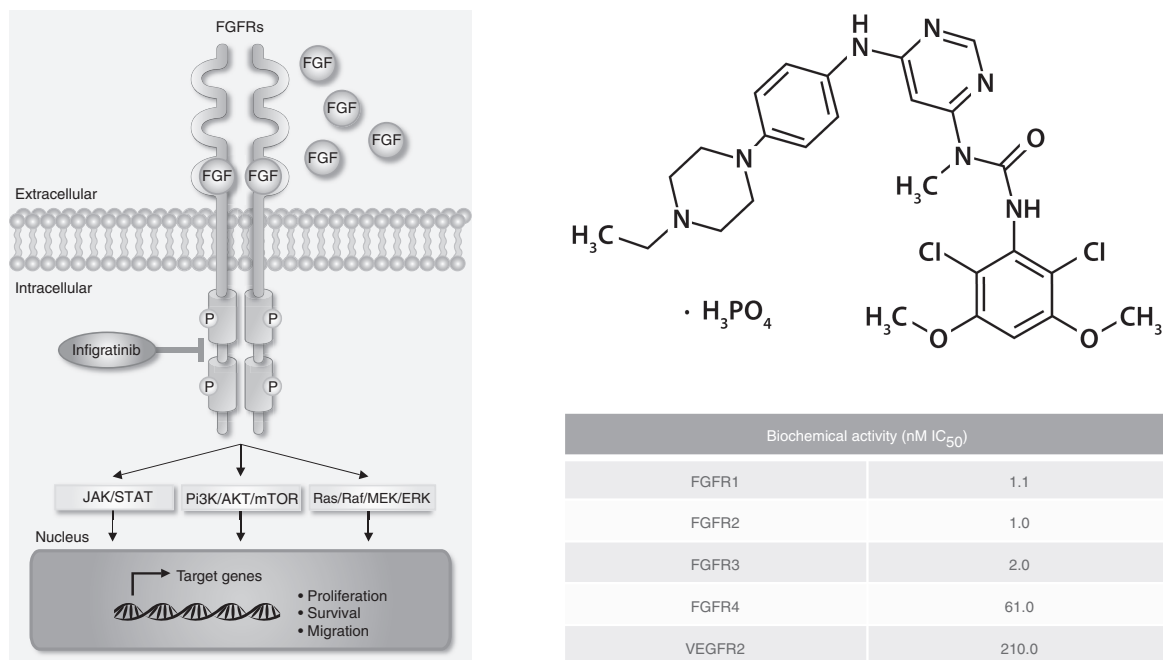


Figure 1. Infigratinib mode of action. FGFR1–4 are transmembrane receptor tyrosine kinases that dimerize upon FGF binding, becoming activated and triggering a downstream cascade of signaling pathways. This leads to the regulation of genes playing critical roles in key cellular processes such as proliferation, survival and migration. Oncogenic alterations such as gene mutations, rearrangements/fusions or amplifications may also activate FGFRs. Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Infigratinib, an orally administered, ATP-competitive, selective tyrosine kinase inhibitor, inhibits FGFRs (with greater affinity for FGFR1–3). The selective inhibitory effect of infigratinib on FGFRs results in antitumor activity. IC₅₀: Half maximal inhibitory concentration; mTOR: Mammalian target of rapamycin; P: Phosphate.

Background & rationale

The FGF/FGFR signaling pathway plays an important role in many physiological functions, including wound repair, vascular development, inflammation and normal metabolism [13]. Alterations in *FGFRs* have been implicated in oncogenesis and resistance to cancer therapies in multiple cancer types, including bladder cancer [14], cholangiocarcinoma [15], lung cancer [16] and glioblastoma [17]. *FGFR3* alterations have been identified in 49% of patients with nonmuscle invasive bladder cancer [18], up to 74% of patients with all stages of UTUC [19–22], 21–38% of patients with invasive UTUC [19–21,23,24] and 15–25% of patients with \geq T2 UBC [25,26]. Based on those findings, *FGFR* alterations represent potentially actionable genomic abnormalities of interest and adequate frequency to be studied in this setting.

Infigratinib (BGJ398) is an orally administered, ATP-competitive, selective tyrosine kinase inhibitor of FGFR1–3 (Figure 1). In May 2021, the results of an open-label phase II study of infigratinib in adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an *FGFR2* fusion or other rearrangement led to the accelerated US FDA approval of infigratinib in this indication [27]. Data from an earlier, multitumor, phase I study of infigratinib [28] demonstrated promising clinical activity and tolerability in patients with a range of solid tumors, including responses in patients with UC. This led to the recruitment of an expansion cohort of 67 patients with *FGFR3*-altered advanced or metastatic UC who were treated with a starting dose of infigratinib 125 mg/day orally on days 1–21 of a 28-day cycle (3 weeks on, 1 week off) until unacceptable toxicity or progression [29]. In this study, one patient was treatment-naïve, 19 patients had received one prior antineoplastic therapy and 47 patients had received two or more prior antineoplastic regimens; overall, 59 patients had received a platinum-based regimen. In this heavily pretreated population, confirmed responses were observed in 17 patients yielding a response rate of 25% and disease control rate of 64%. The median progression-free survival was 3.8 months (95% CI: 3.1–5.4) and the median OS was 7.8 months (95% CI: 5.7–11.6). The most common all-grade AEs were hyperphosphatemia (46%), elevated creatinine (48%), constipation (37%) and fatigue (37%). The most frequent grade 3/4 AEs were hyperlipasemia (10%), anemia (8%), fatigue (8%), hypophosphatemia (8%) and palmar–plantar erythrodysesthesia

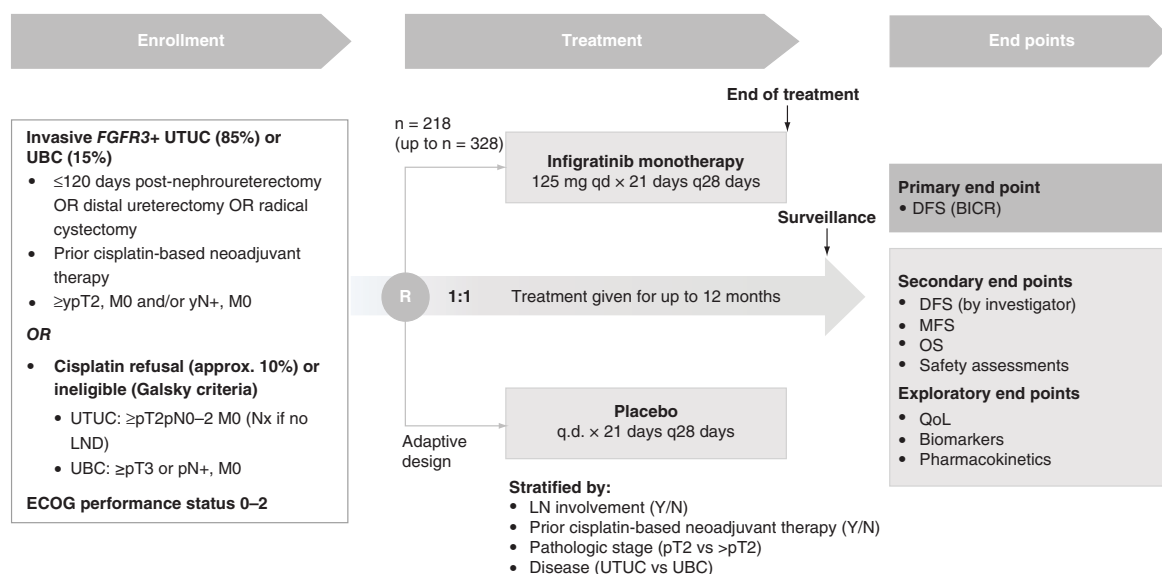


Figure 2. Study design.

BICR: Blinded independent central review; DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; LN: Lymph node; LND: Lymph node detected; MFS: Metastasis-free survival; N: No; OS: Overall survival; pT: Pathological stage; q.d.: Once daily; q28: Every 28 days; QoL: Quality-of-life; R: Randomization; UBC: Urothelial bladder cancer; UTUC: Upper tract urothelial cancer; Y: Yes.

(8%). Dose reductions were reported in 31 patients (46%). In the small subgroup of eight patients with UTUC, one complete response and three partial responses were observed, and four patients had stable disease, giving a response rate of 50% and a disease control rate of 100% [30]. In addition, Lyou and colleagues described the role of infigratinib in the early-line and salvage treatment of patients with metastatic UC and an activating *FGFR3* mutation/fusion, demonstrating safety and efficacy regardless of the line of therapy, supporting further evaluation of infigratinib across different settings in UC [31].

The FDA recently approved nivolumab for the adjuvant treatment of patients with muscle-invasive UC who are at high risk for recurrence after radical resection based on the CheckMate274 study [10]. Currently, there are no approved targeted therapies for use in the (neo)adjuvant setting for UC, although several trials have shown the activity of FGFR inhibitors in locally advanced or metastatic UC [29,32,33]. Erdaftinib received accelerated FDA approval in April 2019 as the first targeted therapy for patients with locally advanced or metastatic UC harboring *FGFR2* or *FGFR3* activating mutation or fusion after progression on platinum-containing chemotherapy [32].

PROOF 302 study design & participants

The multicenter, randomized, placebo-controlled, phase III PROOF 302 trial includes postsurgical adult patients with muscle-invasive UC, predominantly those with UTUC (85%) as well as patients with UBC (15%), with susceptible *FGFR3* genetic alterations (mutation, gene fusion or rearrangement; hereafter collectively referred to as *FGFR3* alterations). Patients are randomized within 120 days following radical nephroureterectomy, distal ureterectomy or radical cystectomy, have residual disease after neoadjuvant chemotherapy or are ineligible for or refuse cisplatin-based adjuvant chemotherapy (Figure 2). For patients with intermediate- or high-risk nonmuscle-invasive UBC, intravesical therapy with bacillus Calmette-Guérin (BCG) may be given after surgery to reduce recurrence and progression within the bladder [11,12]. Prior BCG treatment is not an exclusion criterion, however, provided an adequate washout procedure is followed. For patients who are post neoadjuvant chemotherapy, the tumor pathologic stage at surgical resection must be ≥ypT2 and/or yN+ and M0. Patients who refuse or are ineligible for cisplatin-based chemotherapy must also meet the following criteria: UTUC disease should be stage ≥pT2 pN0–2 (post-lymphadenectomy or no lymphadenectomy [pNx]) or pN+, M0; and UBC should be stage ≥pT3 or pN+, M0. Variant histology is allowed provided UC is predominant (>50%). Neuroendocrine (including small and large cell), sarcomatoid and plasmacytoid variants are excluded (any component).

Table 1. Key eligibility criteria.

Key inclusion criteria:	
Aged ≥ 18 years (≥ 20 years in Taiwan)	
Randomized within 120 days after nephroureterectomy, distal ureterectomy or cystectomy	
Histologically or cytologically confirmed invasive UC with susceptible <i>FGFR3</i> alterations. Variant histology is allowed provided UC is predominant ($>50\%$)	
Must demonstrate <i>FGFR3</i> mutation, fusion or rearrangement by the FoundationOne [®] CDx test (Foundation Medicine, MA, USA)	
Eastern Cooperative Oncology Group performance status of ≤ 2	
If post neoadjuvant chemotherapy (≥ 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m ² /cycle), pathologic stage at surgical resection must be \geq pT2 and/or yN+ and M0	
Patients who refuse cisplatin-based chemotherapy or are ineligible for cisplatin-based chemotherapy must have UTUC of stage \geq pT2 and/or pN+, M0; UBC should be stage \geq pT3 and/or pN+, M0	
Must have a centrally reviewed negative postoperative CT or negative biopsy within 28 days before randomization to confirm absence of disease at baseline	
Any AEs associated with prior surgery or neoadjuvant chemotherapy are stabilized or resolved to grade ≤ 2 before randomization	
Key exclusion criteria:	
Presence of positive invasive surgical margins following nephroureterectomy, distal ureterectomy or cystectomy. In patients ineligible for further surgery, radiotherapy or other efficacious treatment, microscopic positive noninvasive margins (e.g., carcinoma <i>in situ</i>) without gross residual disease are allowed	
Received bacillus Calmette-Guérin or other intravesical therapy for NMIBC within the previous 30 days	
Neuroendocrine (including small and large cell), sarcomatoid and plasmacytoid variants (any component)	
Previously or currently receiving treatment with a MEK or selective FGFR inhibitor	
History of primary malignancy within the past 3 years (with several protocol-defined exceptions)	
Impaired GI function or GI disease that may significantly alter the absorption of oral infigratinib (e.g., active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)	
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	
History and/or current evidence of extensive tissue calcification	
Abnormal serum calcium or phosphorus	
Current evidence of endocrine alterations of calcium/phosphate homeostasis (e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis), unless well controlled	
Currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or are strong inducers or inhibitors of CYP3A4 and medications that increase serum phosphorus and/or calcium concentration	
Clinically significant cardiac disease	
Recent (≤ 3 months before first dose of study drug) transient ischemic attack or stroke	
AE: Adverse event; CT: Computed tomography; CYP: Cytochrome P450; GI: Gastrointestinal; NMIBC: Nonmuscle invasive bladder cancer; pT: Pathological stage; UBC: Urothelial bladder cancer; UC: Urothelial carcinoma; UTUC: Upper tract urothelial cancer.	

Testing for *FGFR3* alterations occurs either after the informed consent form is signed during study prescreening (with the patient's written consent) or it may have been conducted as part of the clinical care independent of the study. For entry into the study, the presence of eligible *FGFR3* alterations must be tested for or confirmed using the FoundationOne CDx test (Foundation Medicine, MA, USA). *FGFR3* status is collected for all patients included in the prescreening process, regardless of the test result, enabling prospective assessment of *FGFR3* alteration incidence in patients with invasive UTUC and UBC. Patients with eligible *FGFR3* alteration in tumor tissue obtained from definitive/radical surgery biospecimens or, if not available, from qualifying biopsies, are offered the opportunity to participate in the study, and screening for eligibility starts after written consent for the main study has been obtained. In addition, all patients enrolled have tumor tissue baseline PD-L1 status determined, although PD-L1 expression status has no impact on eligibility. Although the presence of grossly positive invasive surgical margins following definitive surgery excludes patients from participation, those with microscopic positive noninvasive margins (e.g., carcinoma *in situ*) without gross residual disease are eligible. Other key eligibility criteria are shown in Table 1.

In the current treatment paradigm, neoadjuvant or adjuvant treatment options for patients who refuse platinum-based perioperative chemotherapy are limited to active surveillance, participation in clinical trials and more recently, treatment with adjuvant nivolumab (FDA approved on 19 August 2021). For these patients who are eligible for cisplatin-based chemotherapy but refuse it, enrollment is allowed after a detailed informed discussion with their care provider about treatment options.

Patients are randomly assigned in a 1:1 ratio to infigratinib monotherapy or placebo using interactive response technology. Patients are also stratified according to four criteria: lymph node involvement (yes vs no); prior neoadjuvant cisplatin-based chemotherapy (yes vs no); pathologic stage (pT2 vs \geq pT3); and primary tumor site (UTUC vs UBC).

Patients, investigators, the study sponsor and reviewers (imaging, ophthalmologists, etc.) are blinded to treatment assignment and administration (infigratinib or placebo), allowing unbiased assessment during the trial.

Planned study period

The study was first posted on ClinicalTrials.gov on 13 December 2019, and the first patient was enrolled in March 2020. The study is currently active and enrolling patients as of March 2022 (last update posted on ClinicalTrials.gov 26 April 2022). The last patient is expected to complete treatment in 2024.

Treatment assignment

Eligible patients receive oral infigratinib at a starting dose of 125 mg or placebo administered orally q.d. on days 1 to 21 of a 28-day cycle for a maximum of 52 weeks (13 cycles), or until blinded independent central review (BICR) confirms investigator-assessed recurrence (local/regional or contralateral invasive disease or metastatic recurrence, whichever occurs first), or other criteria for permanent treatment discontinuation. If locally diagnosed recurrence is not confirmed by BICR, treatment continues until recurrence is confirmed by BICR, if considered by the investigator to be in the patient's best interest and no other permanent treatment discontinuation criteria are met.

Patients who do not tolerate the protocol-specified dosing are managed by dose adjustments (dose holds and dose reductions). Treatment-related toxicity is managed as described in the study protocol and following institutional guidelines. Each patient is allowed up to three dose reductions according to protocol-specified dose modifications for toxicities considered related to study treatment, with the minimum daily infigratinib dose being 50 mg. Following resolution of toxicity to baseline or grade \leq 1, study drug treatment is resumed either at the same or a lower dose. The study drug must be permanently discontinued in the event of a treatment delay of \geq 14 days due to treatment-related toxicity, as well as for protocol-prespecified toxicity-specific discontinuation criteria. The protocol was amended to allow for situations where, with prospective approval from the sponsor's medical monitor, the maximum delay of 14 days' interruption for treatment-related toxicity may be extended to a maximum of 28 days before permanent treatment discontinuation is required. In addition to treatment-related toxicity, per the investigator's medical judgment, dose holds can be initiated by the study investigator for the patient's safety (e.g., perioperatively). Patients who permanently discontinue the study drug for treatment-related toxicity before having reached the efficacy end point requiring treatment discontinuation continue in the study and are followed up for study-specified assessments (efficacy, safety, quality-of-life [QoL], pharmacokinetics [PK] and biomarkers).

Outcome measures & end points

The primary objective of the PROOF 302 study is to determine if treatment with infigratinib as adjuvant therapy improves DFS confirmed by BICR compared with placebo in patients with invasive UC and susceptible *FGFR3* alterations after radical nephroureterectomy, distal ureterectomy or radical cystectomy (Table 2). The primary end point is independent, blinded, centrally reviewed DFS, defined as the interval between the date of randomization and the date of local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier.

Secondary objectives are investigator-determined DFS including intraluminal low-risk (noninvasive, low-grade or high-grade) recurrence in patients treated with infigratinib versus placebo; investigator-determined metastasis-free survival of patients treated with infigratinib versus placebo; OS in patients treated with infigratinib versus placebo; and safety and tolerability of infigratinib when administered in the adjuvant setting. Exploratory objectives include: comparison of QoL and patient-reported outcomes in patients treated with infigratinib versus placebo; evaluation of PK parameters for infigratinib; evaluation of the overall tumor genomic landscape in patients with invasive UC; and evaluation of biomarkers and their potential associations with efficacy, recurrence, survival and resistance to study medication.

Study assessments

Efficacy is assessed by recurrence via CT/MRI scans, cystoscopy (for patients with a urinary bladder), biopsies if feasible and safe for the patient and urine cytology, as well as by OS. Response to treatment is assessed in

Table 2. PROOF 302 objectives and end points.

Objectives	End points
Primary	
To determine if treatment with infigratinib improves centrally reviewed DFS compared with placebo in patients with invasive UC with susceptible <i>FGFR3</i> 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 patients treated with infigratinib vs placebo	Investigator-reviewed DFS, including intraluminal low-risk recurrence, from date of randomization to any recurrence or death due to any cause, whichever occurs earlier
To compare MFS in patients 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 patients treated with infigratinib vs placebo	OS (from date of randomization to death)
To compare investigator-reviewed DFS in patients 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 AEs and serious AEs, laboratory abnormalities and other safety findings
Exploratory	
To compare QoL in patients treated with infigratinib vs placebo	QoL measured using 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 patients with invasive UC	Prevalence of genomic alterations and their correlations with available clinicopathologic and demographic features in patients with invasive UC
To evaluate biomarkers related to the biology of UC and their potential association with efficacy, disease recurrence and resistance to study medication	Genomic and proteomic assessments of tumor tissue and urine and blood plasma cfDNA samples from baseline to disease recurrence and the determination of the prognostic and/or predictive value of biomarkers
AE: Adverse event; DFS: Disease-free survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; EQ-5D-5L: EuroQOL 5-dimensions, 5-levels questionnaire; MFS: Metastasis-free survival; OS: Overall survival; PK: Pharmacokinetics; QoL: Quality-of-life; UBC: Urothelial carcinoma of the bladder; UC: Urothelial carcinoma; UTUC: Upper tract urothelial carcinoma.	

accordance with the protocol-specified criteria for recurrence that are used by both the BICR (primary end point) and by the investigator (secondary efficacy end points). CT/MRI scans are performed at baseline within 28 days before randomization and require BICR confirmation of lack of recurrence/metastasis for enrollment. Thereafter, the schedule repeats every 3 months up to 24 months after starting treatment and annually thereafter or until metastatic recurrence is confirmed by BICR or metastatic recurrence is confirmed by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. Cystoscopy (for patients with a urinary bladder) and urine cytology are performed at screening, at 3, 6, 9 and 12 months on study, at the end of therapy and every 6 months thereafter until 24 months after the start of treatment, and then annually or until metastatic recurrence as previously described. All postbaseline radiological assessments, including imaging obtained at unscheduled timepoints to assess for disease recurrence, are read locally and submitted for BICR together with any supporting reports, including pathology and cytology reports if a biopsy was conducted in conjunction with a suspected recurrence.

All patients will be followed up for survival status and use of new anticancer therapy after discontinuation from study treatment every 6 months for the first year and annually thereafter until 1 year after the final DFS event goal for the study is reached. Patients who do not receive the planned treatment course for reasons other than recurrence will continue to have efficacy assessments, including survival follow-up, until 1 year after the final DFS event goal is reached. All patients are followed for long-term survival for approximately 14 years after the final DFS event goal is reached. Patients who discontinue study treatment without having reached recurrence as described, and start new anticancer therapy, will continue to be assessed by imaging until metastatic recurrence is confirmed by BICR.

Patient QoL is evaluated at baseline and at every visit until the first 6-month follow-up visit after discontinuation of study treatment using the European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire core module (C30) and the EuroQoL 5-dimensions, 5-levels (EQ-5D-5L) questionnaire.

Blood samples are collected for safety monitoring (hematology and chemistry), biomarkers (cfDNA) and PK analysis, as presented in Table 3. Plasma concentrations of infigratinib and its active metabolites are measured and trough and maximum plasma concentrations are calculated. Blood and urine samples for assessment of cfDNA are collected for analysis of DNA to explore whether genomic alterations or other biomarkers in tumor samples

Table 3. Schedule of assessments: pharmacokinetic and blood and urine cfDNA sample collection, laboratory parameters and adverse events and concomitant medication assessments.

Cycle	Day	PK [†]		cfDNA [†]	Clinical chemistry [‡]	Hematology [‡]
		Predose (h before dose)	Postdose (h ± 30 min)	Blood and urine (predose)		
1	1	0	4	X	X	X
1	4				X	
1	7				X	
1	14				X	
1	21 [§]	0	4	X	X	
2	21 [§]	0	4		X	X
3	21 [§]	0	4	X	X	
4	21 [§]	0	4		X	X
5	21 [§]	0	4	X	X	
6	21 [§]	0	4		X	
7	21 [§]	0	4	X	X	X
8	21 [§]	0	4		X	
9	21 [§]	0	4	X	X	
10	21 [§]	0	4		X	X
11	21 [§]	0	4	X	X	
12	21 [§]	0	4		X	
13	21 [§]	0	4	X	X	X
13	28 (or EOT) [¶]	If within 24 h of last dose	NA	If not done within 28 days prior	X	X

[†]On the days of PK and cfDNA sampling, patients should not take their study drug dose at home; patients should take their study drug with them to the study center where dosing is supervised and the administration time recorded. If a patient is not on study drug, then no PK or cfDNA sample is collected. PK and cfDNA sampling will resume once the patient is back on study drug. On PK sampling days after C1D1, the time of the last study drug dose (i.e., time of infiratinib/placebo administration on the previous day) before the predose PK sample is recorded in the electronic case report form. For any patient who permanently discontinues study drug, attempts should be made to collect PK and blood (two tubes, 16–20 ml) and urine cfDNA samples from the patient at the time of discontinuation, if the samples can be collected within 24 hours of the last dose.

[‡]Samples for clinical laboratory tests (including hematology, clinical chemistry and pregnancy) are collected and analyzed on the scheduled day even if the 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 -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 4 hours after study drug administration.

[§]A window of -2 days is allowed before D21 (specifically on D19, D20 or D21).

[¶]Blood (two tubes, 16–20 ml) and urine cfDNA samples are 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 (two tubes, 16–20 ml) and urine samples are collected for analysis of cfDNA. Sample for PK is collected if within 24 h of last dose of study drug.

AE: Adverse event; C: Cycle; D: Day; EOT: End of treatment; h: Hour; NA: Not applicable; PK: Pharmacokinetic.

may also be observed in blood or urine and if any biomarkers are prognostic and/or predictive of efficacy, disease recurrence and/or associated with resistance to infiratinib.

With the patient's consent, tumor samples collected upon local/regional or contralateral invasive or metastatic recurrence as part of the standard of care may be provided to the sponsor for exploratory objectives related to biomarkers of UC biology and potential associations of biomarkers with efficacy, disease recurrence and resistance to study medications.

Safety assessments performed at screening and at visits throughout the treatment period include AEs and serious AEs (SAEs), clinical laboratory tests (blood and urine), physical examinations, vital signs, ECGs (at screening, cycle 1 day 1, cycle 2 day 1 and cycle 13 day 28 or end of treatment), ECOG performance status and ophthalmic assessments. Retinal optical coherence tomography scan images are read locally and the scans are sent for storage to an ophthalmic imaging vendor to be read if necessary. AEs and SAEs are assessed until 30 days after the end of treatment.

An independent Data Monitoring Committee (DMC) periodically monitors patient data at regularly scheduled meetings, according to a prespecified DMC charter, and at the interim analysis. The DMC reviews formal interim trial results when 35 DFS events confirmed by BICR (independent of investigator assessment) have occurred, considers the overall risk and benefit to trial participants and makes recommendations as to whether the trial should continue in accordance with the protocol or if the sample size needs to be increased according to prespecified rules and advises regarding steps to ensure patient safety and the ethics and integrity of the trial.

Supportive care guidelines

Strategies for the management of potential infigratinib-related toxicities are summarized in Table 4. These include hyperphosphatemia, skin and subcutaneous toxicities and ocular disorders, among others [34–36].

Hyperphosphatemia is a recognized on-target effect of potent and selective FGFR pathway inhibitors [36]. Patients are advised to avoid foods high in phosphate and restrict dietary phosphate to 600–800 mg/day. Unless otherwise specified by the local prescribing information or institutional practice, hyperphosphatemia should be managed as shown in Table 4. Patients who experience hyperphosphatemia should remain on a low-phosphate diet if possible and take a phosphate binder on the days the study drug is taken even if serum phosphorus is normalized. Patients do not need to be on a low-phosphate diet or take a phosphate binder during their 1-week off-study treatment period unless serum phosphate is not normalized. Recommendations for the management of stomatitis, palmar–plantar erythrodysesthesia syndrome, paronychia and alopecia are shown in Table 4. As a general guideline, if toxicity is treated and tolerable, study treatment may be continued for grade 1 and 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 tolerable grade 2 toxicity.

COVID-19 vaccinations

The effect of COVID-19 vaccines has not been studied in combination with infigratinib, hence the safety and efficacy 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. In general, COVID-19 vaccines are allowed and can be administered any time before, during and after study participation, as determined to be safe in the clinical judgment of the treating physician/study investigator, who should assess the risk for each patient in the context of the study. Whenever feasible, vaccinations may be administered at least 30 days before randomization. All applicable guidelines should be followed and vaccinations should be given in adherence to the manufacturer's guidelines for eligibility and contraindications. Patients vaccinated for COVID-19 should be closely monitored and any observed AEs and/or SAEs should be reported.

Statistical considerations

Approximately 218 patients with invasive UTUC (85%) or UBC (15%) are initially planned for study participation at over 120 sites in at least nine countries. Enrollment of patients refusing cisplatin-based perioperative therapy will be capped at approximately 10% of the total population (~22 patients). Also, no more than 25% of patients with UTUC will have stage pT2 disease, the limit being based on stratification.

The study starts with a group sequential design, with one formal interim analysis after approximately 35 BICR-confirmed DFS events (i.e., 50% of the initial event goal). Assuming disease recurrence in 46% of patients in the first 2 years and a 5% annual recurrence rate in the third year and beyond for the placebo group, the required initial sample size is designed to assess 70 BICR-confirmed DFS events, assuming 3-year uniform enrollment, 1-year follow-up, 10% yearly dropout rate and a hazard ratio (HR) of 0.5. The sample size provides 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 a one-sided alpha of 0.025.

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 because of futility at the interim DFS analysis if the futility boundary for testing DFS is crossed. The futility stopping boundary is nonbinding to allow for additional considerations. 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% to a maximum sample size of 328 patients (164 per group) to reach 105 BICR-confirmed DFS events (independent of investigator assessment) at the final DFS analysis.

Sensitivity analyses may be conducted to evaluate the potential effect on efficacy outcomes of enrolling patients refusing cisplatin-based chemotherapy (yes vs no) and the reason for not receiving cisplatin-based chemotherapy (ineligible vs refusal) in the two treatment arms using a Cox regression model with this factor as a covariate. If an adequate number of patients with a component of variant histology or with microscopic positive noninvasive margins (e.g., carcinoma *in situ*) without gross residual disease are enrolled, sensitivity analysis will be conducted to account for variations in response.

Table 4. Management of infigratinib-related toxicity.

Hyperphosphatemia	
Recommendations: 1) Dietary restrictions: patients should avoid foods high in phosphate and restrict dietary phosphate to 600–800 mg/day <ul style="list-style-type: none"> • High-phosphate foods include dairy products, meats, nuts and other high-protein foods, processed foods and dark cola drinks 2) Monitoring: serum phosphorus is checked at screening and starting on day 4 on study <ul style="list-style-type: none"> • If patient develops hyperphosphatemia, initiate treatment with phosphate binders (e.g., sevelamer, sucroferriic oxyhydroxide, lanthanum carbonate, ferric citrate, etc.); phosphate binders are taken within 30 min of a meal on the day when taking study drug • Patients who develop hyperphosphatemia should keep to a low-phosphate diet if possible and take a phosphate binder on the days study drug is taken even if their serum phosphorus is normalized • Patients do not need to be on a low-phosphate diet or take a phosphate binder during their 1-week off period unless serum phosphorus is not normalized 3) Management: <ul style="list-style-type: none"> • For serum phosphorus >5.5–≤7.5 mg/dl: <ul style="list-style-type: none"> ◦ Start sevelamer 800 mg t.i.d. with meals ◦ Increase the dose of sevelamer up to 1200 mg every 8 h • For serum phosphorus >7.5 mg/dl: <ul style="list-style-type: none"> ◦ Increase the dose of sevelamer up to 1600 mg (2 tablets per meal) every 8 h ◦ Consider adding acetazolamide 2–3 tablets (250 mg) per day 	
General recommendation	Phosphate-lowering therapy: optimize dose and schedule in accordance with package insert or Follow local or institutional guidelines
Other recommendations	Phosphate-binder dosing continues during study drug dose interruptions for hyperphosphatemia and serum phosphate values are monitored frequently (e.g., every 2–3 days) Phosphate-binder dosing should be held: <ul style="list-style-type: none"> • During the week off of the cycle (days 22–28) unless serum phosphate is not normalized and • During study drug dose interruptions for nonhyperphosphatemia AEs
Serum phosphate >5.5–≤7.5 mg/dl	Maintain dose level of study drug and optimize phosphate-lowering therapy as clinically indicated
Serum phosphate >7.5 mg/dl for >7 days despite maximal phosphate-lowering therapy	Hold dose of study drug until resolved to serum phosphate ≤5.5 mg/dl or Restart study drug at the same dose level with maximal phosphate-binder dosing if the patient did not receive maximal phosphate-binder dosing for serum phosphate >7.5 mg/dl for >7 days
A single serum phosphate >9.0 mg/dl regardless of duration or dose of phosphate-lowering therapy	Reduce study drug by one dose level if patient had maximal phosphate-lowering therapy for serum phosphate >7.5 mg/dl for >7 days or a one-time serum phosphate of >9.0 mg/dl and Restart study drug with maximal phosphate-binder dosing
Grade 4 (serum phosphate with life-threatening consequences; urgent intervention indicated, e.g., 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: <ul style="list-style-type: none"> • If resolved within ≤7 days after suspending study drug, maintain dose level • If resolved between >7 days and 14 days, reduce study drug by one 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
Eye disorders	
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 <ul style="list-style-type: none"> • If resolved within ≤14 days, reduce study drug by one 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 <ul style="list-style-type: none"> • If resolved within ≤14 days, reduce one dose level • If not resolved within ≤14 days, discontinue study drug
ADL: Activities of daily living; AE: Adverse event; b.i.d.: Two times daily; i.v.: Intravenous; OTC: Over the counter; q.d.: Once daily; q.i.d.: Four times daily; t.i.d.: Three times daily; TMP/SMX DS: Sulfamethoxazole and trimethoprim.	

Table 4. Management of infigitinib-related toxicity (cont.).

Eye disorders	
Dry eye and blurred vision:	
The following supportive measures can be implemented individually or in combination and as advised in consultation with an ophthalmologist	
<ul style="list-style-type: none"> • Artificial tears, q.i.d. • Artificial tears without preservative, six times per day • Ointments (any OTC agents or petroleum jelly such as Vaseline®) • Steroid drops (prescription; may help with corneal haze) • Punctal plugs (requires ophthalmologist management) 	
Diarrhea	
<ul style="list-style-type: none"> • Patients 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 anti-diarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management • Some patients may require concomitant treatment with >1 anti-diarrheal agent • If the anti-diarrheal agents do not control diarrhea to tolerable levels, study treatment should be temporarily interrupted, or dose reduced (125 → 100 → 75 [→ 50] mg × 1 q.d.) 	
Grade 1 (increase of <4 stools/day over baseline; mild increase in ostomy output compared with baseline)	Maintain dose level of study drug, initiate anti-diarrheal treatment
Grade 2 (increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared with baseline; limiting instrumental ADL)	<ul style="list-style-type: none"> • Hold dose of study drug until resolved to grade ≤1 • Optimize anti-diarrheal treatment • For recurrence of grade 2 diarrhea, hold dose of study drug until resolved to grade ≤1, then reduce study drug by one dose level
Grade 3 (increase of ≥7 stools/day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL)	<ul style="list-style-type: none"> • Hold dose of study drug until resolved to grade ≤1 • Optimize anti-diarrheal treatment • Reduce study drug by one dose level • For reoccurrence of grade 3 diarrhea despite optimal anti-diarrheal treatment, discontinue study drug
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue study drug
Skin and subcutaneous tissue disorders	
Alopecia:	
Grade 1 (hair loss of <50% of normal for that individual; wig/hairpiece to camouflage not needed)	Continue study drug <ul style="list-style-type: none"> • Minoxidil 5% (OTC) solution or foam q.d. to scalp
Grade 2 (hair loss of ≥50% of normal for that individual; wig/hairpiece to camouflage is needed; associated with psychosocial impact)	Continue study drug <ul style="list-style-type: none"> • Minoxidil 5% (OTC) solution or foam b.i.d. to scalp • Fluocinonide 0.05% solution daily to scalp
Additional guidelines	Hair camouflaging methods (e.g., TOPPIK™) may be considered. Alopecia typically reverses when treatment is discontinued
Palmar–plantar erythrodysesthesia syndrome:	
Grade 0/1 (minimal skin changes or dermatitis, e.g., erythema, edema or hyperkeratosis, without pain)	Continue study drug <ul style="list-style-type: none"> • Urea 20% or ammonium lactate 12% lotions b.i.d. to hands and feet
Grade 2 (skin changes, e.g., peeling, blisters, bleeding, fissures, edema or hyperkeratosis, with pain; limiting instrumental ADL)	Continue study drug <ul style="list-style-type: none"> • Urea 20% or ammonium lactate 12% b.i.d. to hands and feet • Fluocinonide 0.05% cream b.i.d. to hands and feet
Grade 3 (severe skin changes, e.g., peeling, blisters, bleeding, fissures, edema or hyperkeratosis, with pain; limiting self-care ADL)	Hold study drug until resolved to grade ≤1 <ul style="list-style-type: none"> • Urea 20% or ammonium lactate 12% b.i.d. to hands and feet • Fluocinonide 0.05% cream b.i.d. to hands and feet
Additional guidelines	Prevention strategies 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 (e.g., saunas, sun exposure)
Paronychia:	
Grade 1 (nail fold edema or erythema; disruption of the cuticle)	Continue study drug <ul style="list-style-type: none"> • Clindamycin 1% solution around and under nails t.i.d. • Soak for 15 min daily in white vinegar in tap water (1:1) • Topical povidone-iodine 2–10% applied b.i.d.
Grade 2 (local intervention indicated; oral intervention indicated [e.g., antibiotic, antifungal, antiviral therapy; nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL])	Continue study drug <ul style="list-style-type: none"> • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg b.i.d. or TMP/SMX DS b.i.d. for 14 days • Soak for 15 min daily in white vinegar in tap water (1:1) • Topical povidone-iodine 2–10% applied b.i.d. • Dermatology consultation
ADL: Activities of daily living; AE: Adverse event; b.i.d.: Two times daily; i.v.: Intravenous; OTC: Over the counter; q.d.: Once daily; q.i.d.: Four times daily; t.i.d.: Three times daily; TMP/SMX DS: Sulfamethoxazole and trimethoprim.	

Table 4. Management of infigratinib-related toxicity (cont.).

Skin and subcutaneous tissue disorders	
Grade 3 (operative intervention indicated; i.v. antibiotics indicated; limiting self-care ADL)	Hold study drug until resolved to grade ≤ 1 <ul style="list-style-type: none"> • Obtain bacterial cultures to confirm sensitivity to antimicrobial therapy • Cefadroxil 500 mg b.i.d. or TMP/SMX DS b.i.d. for 14 days • Dermatology consultation
Stomatitis:	
Grade 1/2 (erythema of the mucosa [grade 1]; patchy ulcerations or pseudomembranes [grade 2])	Continue study drug <ul style="list-style-type: none"> • Dexamethasone elixir 0.5 mg/ml swish and spit 1 teaspoon (5 ml) t.i.d.
Grade 3 (confluent ulcerations or pseudomembranes; bleeding with minor trauma)	Hold study drug until resolved to grade ≤ 1 <ul style="list-style-type: none"> • Dexamethasone elixir 0.5 mg/ml swish and spit 1 teaspoon (5 ml) t.i.d. • Clotrimazole 10 mg lozenges 3–5 times/daily
Additional guidelines	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:	
Patients 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 (e.g., 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 (e.g., cevimeline and pilocarpine, and intraoral topical agents, e.g., chewing gums and saliva stimulants and substitutes)	
ADL: Activities of daily living; AE: Adverse event; b.i.d.: Two times daily; i.v.: Intravenous; OTC: Over the counter; q.d.: Once daily; q.i.d.: Four times daily; t.i.d.: Three times daily; TMP/SMX DS: Sulfamethoxazole and trimethoprim.	

Conclusion

FGF/FGFR pathway activation is frequent and biologically relevant in UC and has been associated with possible resistance to chemotherapy and anti-PD(L)1 therapy. The FGFR inhibitor erdafitinib received accelerated FDA approval in patients with locally advanced or metastatic UCs harboring *FGFR2* or *FGFR3* activating mutation or fusion after progression on platinum-containing chemotherapy. Infigratinib demonstrated significant antitumor activity with a manageable toxicity profile in patients with UTUC or UBC in an expansion cohort of a phase I study in patients with advanced or metastatic UC with *FGFR3* alteration. This provided a strong rationale for the investigation of single-agent infigratinib in the adjuvant UC setting in a predominantly UTUC population. As no FGFR-targeted therapies are currently approved for adjuvant treatment of UC, the ongoing randomized phase III PROOF 302 study, the rationale, design, eligibility and methodology of which are described in this publication, will assess the efficacy and tolerability of adjuvant infigratinib monotherapy compared with placebo in patients with high-risk muscle-invasive UTUC or UBC and susceptible *FGFR3* alteration.

In the era of growing aspiration toward precision medicine and personalized oncology practice, and specifically for high-risk muscle-invasive UC where there remains a great unmet need, this important study will contribute to a better understanding of the potential role of adjuvant infigratinib as targeted therapy following definitive surgery for muscle-invasive UC in patients with susceptible *FGFR3* alterations. This phase III trial will also provide updated knowledge of the incidence of *FGFR3* alterations, specifically in this disease stage, where current data seem limited. PROOF 302 will also explore the potential for further evaluation of the therapeutic benefit of FGFR inhibitors in relation to higher or lower PD-L1 expression levels in patients with *FGFR3* alterations in UBC and in UTUC.

Executive summary

Introduction

- For patients with high-risk upper tract urothelial carcinoma (UTUC) or muscle-invasive urothelial bladder cancer (UBC), including those with residual disease after surgery, adjuvant platinum-based chemotherapy may improve clinical outcomes.
- Many patients are unable or unwilling to receive platinum-based (neo)adjuvant chemotherapy because of cisplatin ineligibility and/or toxicity concerns.
- Alternative options are needed for these patients, including participation in clinical trials. Selected patients with tumors with susceptible *FGFR3* alterations (mutation, gene fusion or rearrangement) may be eligible to participate in a randomized trial comparing infigratinib, an *FGFR3*-targeted therapy, with placebo.

Background & rationale

- Infigratinib (BGJ398) is a potent, orally administered, selective, ATP-competitive, small-molecule kinase inhibitor of *FGFRs*, with the highest affinity for *FGFR1–3*. Infigratinib is approved by the FDA for use in adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with an *FGFR2* fusion or other rearrangement.
- Infigratinib demonstrated efficacy in the early-line and salvage treatment of patients with urothelial carcinoma (UC) and activating *FGFR3* mutation/fusion, supporting its further development across different settings in UC.
- Currently, there are no selective *FGFR* inhibitors approved in the adjuvant setting for patients with invasive UC.

PROOF 302 trial study design & eligibility

- PROOF 302 is a phase III, multicenter, open-label, randomized, placebo-controlled study designed to evaluate the efficacy of infigratinib as adjuvant treatment following definitive surgery in adult patients with invasive UC (UTUC [85% of patients] and UBC [15%]) and susceptible *FGFR3* alterations.
- Patients are randomized within 120 days following radical nephroureterectomy, distal ureterectomy or radical cystectomy, have residual disease after neoadjuvant therapy or are ineligible for or refuse cisplatin-based (neo)adjuvant chemotherapy.
- For entry into the study, the presence of eligible *FGFR3* alterations must be tested for or confirmed using the FoundationOne CDx test (Foundation Medicine). Testing for *FGFR3* alterations occurs either during prescreening for the study or may have been conducted independently of the study.
- Approximately 218 patients will be enrolled initially. Patients are randomized 1:1 to receive oral infigratinib at a starting dose of 125 mg or placebo, administered orally once daily on days 1–21 of a 28-day cycle for a maximum of 52 weeks or until recurrence, unacceptable toxicity or death.

Outcome measures & end points

- The primary end point is independent, blinded, centrally reviewed disease-free survival (DFS). Secondary end points include investigator-determined DFS, investigator-determined metastasis-free survival, overall survival, safety and tolerability.
- Exploratory end points are correlative biomarker analysis, quality-of-life and infigratinib pharmacokinetics.

Conclusion

- The ongoing randomized phase III PROOF 302 study has been designed to assess the efficacy and tolerability of adjuvant infigratinib monotherapy compared with placebo in patients with high-risk, invasive UC and susceptible *FGFR3* alterations.
- Ultimately, this study will define the potential role of infigratinib as an *FGFR3*-targeted, adjuvant therapy for patients with UC and susceptible *FGFR3* alterations, for whom there still is a high unmet need.

Author contributions

All authors made a substantial contribution to the concept of the work and data interpretation. C Anderson designed and drafted the work. All authors critically revised the work, approved the final version for submission, and agree to be accountable for all aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

The authors thank all patients participating in this study, the patients' families, the clinical investigators, clinical research nurses, clinical research monitors, data management team and all other members of the PROOF 302 clinical study team. They also thank D Savastano and G Pedrioli at Helsinn Group, and F Avogadri at QED Therapeutics for helping with editorial review, and L Miller and D Carman at Miller Medical Communications for their medical editing and writing assistance.

Financial & competing interests disclosure

SK Pal: support for the present manuscript: QED Therapeutics Inc; research support: QED Therapeutics Inc. DM Somford: advisory/consultancy: Astellas, Janssen, Bayer, MSD; research grant/funding (institution): Astellas, Besins, Dutch Cancer Society; contracted research (institution): Janssen, Eli Lilly, Astellas, Blue Earth Diagnostics, Bayer, SPL Medical, QED Therapeutics. P Grivas:

Support for the present manuscript: QED Therapeutics Inc.; In the last three years (unrelated to this manuscript) has provided consultancy to AstraZeneca, Astellas Pharma, Bristol Myers Squibb, Clovis Oncology, Dyania Health, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Immunomedics/Gilead, Infinity Pharmaceuticals, Janssen, Merck & Co., Mirati Therapeutics, Pfizer, Regeneron Pharmaceuticals, QED Therapeutics, Seattle Genetics, 4D Pharma PLC, UroGen; his institution has received research funding from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, GlaxoSmithKline, Immunomedics/Gilead, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics; G1 Therapeutics. SS Sridhar: consulting: Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, EMD Serono, Hoffmann-La Roche, Immunomedics, Ipsen, Janssen, Merck, Pfizer, Seagen. Research funding (Institution): Bayer, Janssen. S Gupta: honoraria (institution): BMS, Pfizer; consultant/advisor: BMS, Merck, Pfizer, EMD Sorono, Eli Lilly, Aveo, AstraZeneca, Guardant Health, Gilead Biosciences; speaker: BMS, Seattle Genetics, Gilead Biosciences. J Bellmunt: honoraria (self): Pfizer, Merck, BMS, AstraZeneca, Pierre Fabre; honoraria (institution): Takeda, MSD; advisory/consultancy fees: Pfizer, Merck, BMS, AstraZeneca, Roche/Genentech, Pierre Fabre; research grant/funding (institution): Takeda, Pfizer; travel/accommodations/expenses: Pfizer; licensing/royalties: UpToDate. SP Lerner: consulting fees: Aura Bioscience, BMS, C2i Genomics, FerGene, Genentech, Merck, Pfizer/EMD Serono, QED Therapeutics, Stimit, UroGen, Vaxiion, Verity; contracted research: Endo, FKD, JBL (SWOG), QED Therapeutics, UroGen, Vaxiion, Viventia; intellectual property rights: TCGA classifier; fees for CME/CE services: Annenberg Center for Health Sciences, Clinical Care Options, Grand Rounds Urology, Ology, UroToday. Y Lorient: grants/contracts (institution): Janssen, Celsius, MSD; payment/honoraria (self) BMS, MSD, AstraZeneca, Roche, Janssen, Astellas, Seattle Genetics, Immunomedics, Pfizer, Merck KGaA; payments/honoraria (institution): BMS, Janssen, Pfizer, Merck KGaA; support for attending meetings/travel: BMS, Roche, AstraZeneca, MSD. J Hoffman-Censits: support for the present manuscript: QED Therapeutics Inc.; consulting fees: Seattle Genetics (advisory board) and AstraZeneca (consultant); medical writing services: Genentech. BP Valderrama: has received speaking honoraria from Pierre Fabre, Novartis, Bristol Myers Squibb, Ipsen, Roche, Astellas Pharma, Bayer, EUSA Pharma; consultant or advisory role: Astellas Pharma, Roche, Novartis, Pfizer, Bristol Myers Squibb, Ipsen, Pierre Fabre, Sanofi, MSD, EUSA Pharma; travel/accommodations: Bristol Myers Squibb, Pfizer, Roche, Ipsen, Astellas. C Andresen: employment: QED Therapeutics Inc.; stock ownership: QED Therapeutics Inc. MJ Schnabel: advisory board member: Bayer, Bristol Myers Squibb, Ipsen, Merck & Co, Pfizer; honoraria: Bayer, Bristol Myers Squibb, GlaxoSmithKline, Ipsen, Medac, Merck, MSD, Pfizer; travel/accommodation/expenses: Apogepha, Janssen, Ipsen, Pfizer; stock ownership: Biontec; institutional grants/contracts: Ipsen, Janssen, AstraZeneca, QED Therapeutics Inc. S Cole: research funding (institution): Exelixis, Merck Sharpe & Dohme. S Daneshmand: advisory board member: Janssen, Ferring, Photocure, Taris, Spectrum, Pacific Edge, QED, AbbVie, Johnson & Johnson, Seattle Genetics, Nucleix, Aduro, BMS; consulting fees: Janssen, Ferring, Photocure, Taris, Spectrum, Pacific Edge, QED, AbbVie, Johnson & Johnson, Seattle Genetics, Nucleix, Aduro, BMS; institutional grants or contracts: Photocure, Janssen, Ferring, Taris, Pacific Edge, Johnson and Johnson, BMS; investments: Taris. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The PROOF 302 study is funded by Helsinn Healthcare S.A. Prior to March 2022, the study was co-funded by Helsinn Healthcare S.A. and QED Therapeutics, an affiliate of BridgeBio. S.A. Medical writing assistance was provided by Miller Medical Communications; this assistance was co-funded by Helsinn Healthcare S.A. and QED Therapeutics, an affiliate of BridgeBio.

Ethical conduct of research

This study was designed, is being implemented, and will be reported in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. The protocol will be reviewed and approved by Institutional Review Board/Independent Ethics Committee/Research Ethics Board at participating institutions. All patients provided written informed consent.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: ●● of considerable interest

1. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 25(Suppl. 3), iii40–48 (2014).
2. Chang S, Bochner B, Chou R *et al.* Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J. Urol.* 198, (2017).
3. Karakiewicz PI, Shariat SF, Palapattu GS *et al.* Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J. Urol.* 176(4 Pt 1), 1354–1361 (2006).

4. Birtle A, Johnson M, Chester J *et al.* Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet* 395(10232), 1268–1277 (2020).
5. Birtle AJ, Chester JD, Jones RJ *et al.* Updated outcomes of POUT: a phase III randomized trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC). *J. Clin. Oncol.* 39(Suppl. 6), 455–455 (2021).
6. Leow JJ, Chong YL, Chang SL, Valderrama BP, Powles T, Bellmunt J. Neoadjuvant and adjuvant chemotherapy for upper tract urothelial carcinoma: a 2020 systematic review and meta-analysis, and future perspectives on systemic therapy. *Eur. Urol.* 79(5), 635–654 (2020).
7. Dash A, Galsky MD, Vickers AJ *et al.* Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 107(3), 506–513 (2006).
8. Dreicer R. New option for cisplatin-ineligible urothelial cancer. *Lancet Oncol.* 18(11), 1428–1430 (2017).
9. Galsky MD, Hahn NM, Rosenberg J *et al.* A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol.* 12(3), 211–214 (2011).
10. Bajorin DF, Witjes JA, Gschwend JE *et al.* Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N. Engl. J. Med.* 384(22), 2102–2114 (2021).
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Bladder Cancer version 1.2022 (2022). www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
12. Powles T, Bellmunt J, Comperat E *et al.* Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* 33(3), 244–258 (2021).
13. Itoh N, Ornitz DM. Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease. *J. Biochem.* 149(2), 121–130 (2011).
14. Ross JS, Wang K, Khaira D *et al.* Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder reveals a high frequency of clinically relevant genomic alterations. *Cancer* 122(5), 702–711 (2016).
15. Borad MJ, Champion MD, Egan JB *et al.* Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma. *PLoS Genet.* 10(2), e1004135 (2014).
16. Wang R, Wang L, Li Y *et al.* FGFR1/3 tyrosine kinase fusions define a unique molecular subtype of non-small cell lung cancer. *Clin. Cancer Res.* 20(15), 4107–4114 (2014).
17. Singh D, Chan JM, Zoppoli P *et al.* Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science* 337(6099), 1231–1235 (2012).
18. Pietzak EJ, Bagrodia A, Cha EK *et al.* Next-generation sequencing of nonmuscle invasive bladder cancer reveals potential biomarkers and rational therapeutic targets. *Eur. Urol.* 72(6), 952–959 (2017).
19. Moss TJ, Qi Y, Xi L *et al.* Comprehensive genomic characterization of upper tract urothelial carcinoma. *Eur. Urol.* 72(4), 641–649 (2017).
20. Sfakianos JP, Cha EK, Iyer G *et al.* Genomic characterization of upper tract urothelial carcinoma. *Eur. Urol.* 68(6), 970–977 (2015).
21. Bagrodia A, Audenet F, Pietzak EJ *et al.* Genomic profile of urothelial carcinoma of the upper tract from ureteroscopic biopsy: feasibility and validation using matched radical nephroureterectomy specimens. *Eur. Urol. Focus* 5(3), 365–368 (2019).
22. Audenet F, Isharwal S, Cha EK *et al.* Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma. *Clin. Cancer Res.* 25(3), 967–976 (2019).
23. Bagrodia A, Cha EK, Sfakianos JP *et al.* Genomic biomarkers for the prediction of stage and prognosis of upper tract urothelial carcinoma. *J. Urol.* 195(6), 1684–1689 (2016).
24. Robertson AG, Kim J, Al-Ahmadie H *et al.* Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell* 174(4), 1033 (2018).
25. Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. *Nat. Rev. Cancer* 15(1), 25–41 (2015).
26. Rouprêt M, Babjuk M, Compérat E *et al.* European Association of Urology Guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. *Eur. Urol.* 68(5), 868–879 (2015).
27. Javle M, Roychowdhury S, Kelley RK *et al.* Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol. Hepatol.* 6(10), 803–815 (2021).
- **This is a phase II study demonstrating the efficacy of infigratinib in patients with cholangiocarcinoma.**
28. Nogova L, Sequist LV, Perez Garcia JM *et al.* Evaluation of BGJ398, a fibroblast growth factor receptor 1–3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. *J. Clin. Oncol.* 35(2), 157–165 (2017).
29. Pal SK, Bajorin D, Dizman N *et al.* Infigratinib in upper tract urothelial carcinoma versus urothelial carcinoma of the bladder and its association with comprehensive genomic profiling and/or cell-free DNA results. *Cancer* 126(11), 2597–2606 (2020).
- **This work presents an initial report of the efficacy of infigratinib in patients with urothelial carcinoma.**

30. Dizman N, Rosenberg JE, Hoffman-Censits JH *et al.* Infigratinib in upper tract urothelial carcinoma vs urothelial carcinoma of the bladder and association with comprehensive genomic profiling/cell-free DNA results. *J. Clin. Oncol.* 37(Suppl. 15), 4510–4510 (2019).
31. Lyou Y, Rosenberg JE, Hoffman-Censits J *et al.* Infigratinib in early-line and salvage therapy for FGFR3-altered metastatic urothelial carcinoma. *Clin. Genitourin. Cancer* 20(1), 35–42 (2022).
- **This study supports the further evaluation of infigratinib across different settings in urothelial carcinoma.**
32. Loriot Y, Necchi A, Park SH *et al.* Erdaftinib in locally advanced or metastatic urothelial carcinoma. *N. Engl. J. Med.* 381(4), 338–348 (2019).
33. Powles T, Carroll D, Chowdhury S *et al.* An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer. *Nat. Med.* 27(5), 793–801 (2021).
34. Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: ready for “prime time” in biliary tract cancer. *J. Hepatol.* 73(1), 170–185 (2020).
35. Magone MT, Hartley IR, Fitzgibbon E *et al.* Ocular adverse effects of infigratinib, a new fibroblast growth factor receptor tyrosine kinase inhibitor. *Ophthalmology* 128(4), 624–626 (2020).
36. Lyou Y, Grivas P, Rosenberg JE *et al.* Hyperphosphatemia secondary to the selective fibroblast growth factor receptor 1–3 inhibitor infigratinib (BGJ398) is associated with antitumor efficacy in fibroblast growth factor receptor 3-altered advanced/metastatic urothelial carcinoma. *Eur. Urol.* 78(6), 916–924 (2020).