PROOF 302: A randomized, double-blind, placebo-controlled, phase III trial of infigratinib as adjuvant therapy in patients with invasive urothelial carcinoma harboring susceptible *FGFR3* alterations

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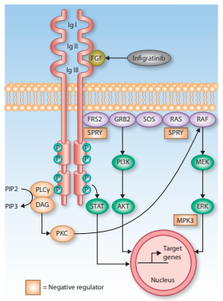
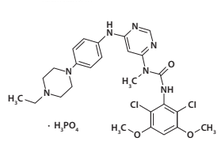
Background

- Radical surgery ± cisplatin-based (neo)adjuvant therapy is the mainstay of treatment for invasive upper tract urothelial cancer (UTUC) or urothelial bladder cancer (UBC), but recurrence rates are high.
- Furthermore, many patients are unable to receive cisplatin-based (neo) adjuvant therapy because of cisplatin ineligibility.
- Fibroblast growth factor receptor 3 (FGFR3) genetic alterations occur in up to 70% of UTUC and up to 20% of UBC and may represent a potential candidate for targeted therapy.[1–4]
- Infigratinib (BGJ398), a selective FGFR1–3 inhibitor, has shown promising clinical activity and tolerability in patients with advanced urothelial carcinoma having susceptible *FGFR3* alterations.[5]
- The PROOF 302 study is evaluating the efficacy and safety of infigratinib as adjuvant therapy in patients with high-risk invasive urothelial carcinoma and susceptible *FGFR3* alterations.

Figure 1. Infigratinib: an oral FGFR1–3 selective kinase inhibitor



- Infigratinib is an orally-available, selective, ATP-competitive FGFR inhibitor
  - FGFR1–3 >4
- Infigratinib has proven activity in tumor models with *FGFR* alterations

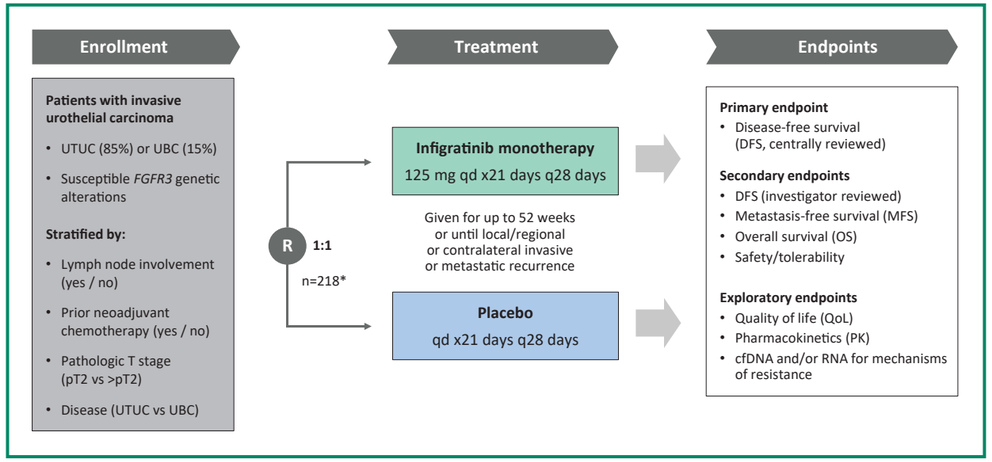


Biochemical activity (nM IC_{50})	
FGFR1	1.1
FGFR2	1.0
FGFR3	2.0
FGFR4	61.0
VEGFR2	210.0

PROOF 302 study design

- Multicenter, double-blind, randomized, placebo-controlled phase 3 study to evaluate efficacy of infigratinib as adjuvant treatment for patients with invasive urothelial carcinoma with susceptible *FGFR3* genetic alterations.
- Adults with high-risk invasive UTUC or UBC with susceptible *FGFR3* genetic alterations who are ≤120 days following surgical resection and ineligible for cisplatin-based (neo)adjuvant chemotherapy or with residual disease after cisplatin-based neoadjuvant therapy are eligible. If neoadjuvant treatment did not include cisplatin, the patient may enroll if they have residual disease and are ineligible for adjuvant cisplatin.
- PROOF 302 is an international study involving approximately 120 centers and a target enrollment of over 200 patients.
- Trial registration: clinicaltrials.gov NCT04197986.

Figure 2. PROOF 302 study design



UTUC: upper tract urothelial cancer
UBC: urothelial bladder cancer

Study objectives/endpoints

Table 1. PROOF 302 objectives and endpoints

Objectives	Endpoints
Primary	
Determine if treatment with infigratinib improves centrally reviewed disease-free survival (DFS) compared with placebo treatment in patients 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	
Compare DFS including intraluminal low-risk 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.
Compare metastasis-free survival (MFS) of 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.
Compare OS in patients treated with infigratinib vs placebo.	OS (from date of randomization to death).
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.
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	
Compare QoL in patients treated with infigratinib vs placebo.	QoL as measured by the EQ-5D-5L and EORTC QLQ C30 scales.
Evaluate the PK of infigratinib.	PK parameters (trough and maximum plasma concentration).
Evaluate cfDNA and/or RNA for mechanisms of resistance.	*FGFR3* alterations detected by cfDNA and/or RNA sequencing as biomarkers of disease recurrence.

cfDNA=cell-free DNA; 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; RNA=ribonucleic acid.

Table 2. Key inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria
1. Have histologically or cytologically confirmed, invasive urothelial carcinoma with susceptible *FGFR3* alterations within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy.	1. Presence of positive surgical margins following nephroureterectomy, distal ureterectomy, or cystectomy.
2. If the patient received neoadjuvant chemotherapy, pathologic stage at surgical resection must be AJCC Stage ≥ypT2 and/or yN+.	2. Have received Bacillus Calmette-Guerin (BCG) or other intravesical therapy for Non-Muscle Invasive Bladder Cancer (NMIBC) within the previous 30 days.
3. If the patient did not receive neoadjuvant chemotherapy: – Must be ineligible to receive cisplatin-based adjuvant chemotherapy per the Galsky criteria. – UTUC: pathologic stage must be AJCC Stage ≥pT2 pN0–2 M0 (post-lymphadenectomy or no lymphadenectomy [pNx]). – UBC: pathologic stage should be AJCC Stage ≥pT3 or pN+.	3. Have previously or currently is receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor. 4. Have impaired gastrointestinal (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). 5. Have current evidence of corneal or retinal disorder/keratopathy. 6. Have a history and/or current evidence of extensive tissue calcification. 7. Have current evidence of endocrine alterations of calcium/phosphate homeostasis (e.g. parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis), unless well controlled. 8. Are currently receiving or are planning to receive treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications that increase serum phosphorus and/or calcium concentration. 9. Clinically significant cardiac disease. 10. Recent (<3 months prior to first dose of study drug) transient ischemic attack or stroke.
4. Have Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.	
5. Have no evidence of metastatic disease based on screening CT or MRI.	

Treatment

- Patients are randomized 1:1 to oral infigratinib 125 mg or placebo once daily on days 1–21 of a 28-day cycle.
- Treatment continues for up to 52 weeks or until disease recurrence, unacceptable toxicity or death.

Dose modifications/treatment delays

- Patients who do not tolerate the protocol-specified dosing are managed by dose adjustments.
- Each patient is allowed up to three dose reductions according to investigator decision and protocol-specified dose modifications for AEs.
- Following resolution of toxicity to baseline or grade ≤1, treatment is resumed at either the same or lower dose of study drug.

Planned patient population and current status

Planned sample size/statistics

- Initially, 218 patients are planned to be enrolled at over 120 sites in 9 countries.
- The study will start with a group sequential design with one interim analysis after approximately 35 centrally reviewed DFS events (50% of the initial event goal).
- No more than 15% of the population will be enrolled with UBC and ≤25% of UTUC patients will have AJCC Stage pT2 UTUC (limit based on stratification).
- Assuming disease recurrence in 46% of patients (first 2 years) and a 5% yearly recurrence rate in the third year and beyond for the placebo group, the required initial sample size is designed to assess 70 centrally reviewed DFS events, assuming 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.

Current status

- The study is active with the first patient dosed in early 2020.
- The last patient is expected to complete treatment in 2024.

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