Infigratinib versus gemcitabine plus cisplatin multicenter, open-label, randomized, phase 3 study in patients with advanced cholangiocarcinoma with *FGFR2* gene fusions/translocations: the PROOF trial

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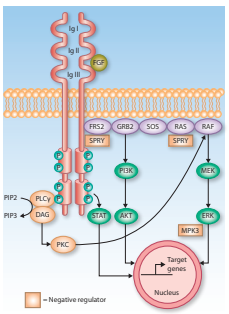
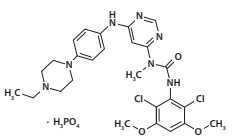
Background

- Cholangiocarcinoma is the most common biliary tract malignancy with an estimated incidence in Europe of 0.4–1.8/100,000 patients, and approximately 5,000–10,000 new cases annually in the USA.
- The fibroblast growth factor receptor (FGFR) family plays an important role in cholangiocarcinoma.
- *FGFR* translocations (i.e. fusion events) represent driver mutations in cholangiocarcinoma. They are present in 13–17% of intrahepatic cholangiocarcinomas and may predict tumor sensitivity to FGFR inhibitors.[1–3]
- Infigratinib (BGJ398), an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor (Figure 1), has shown clinical activity against tumors with *FGFR* alterations.[4]
- Based on earlier response data of infigratinib in relapsed/refractory cholangiocarcinoma with *FGFR2* fusions/translocations (phase 2 study CBJG398X2204),[5,6] the PROOF trial is evaluating infigratinib versus gemcitabine + cisplatin in front-line patients with advanced cholangiocarcinoma with *FGFR2* gene fusions/translocations.

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



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

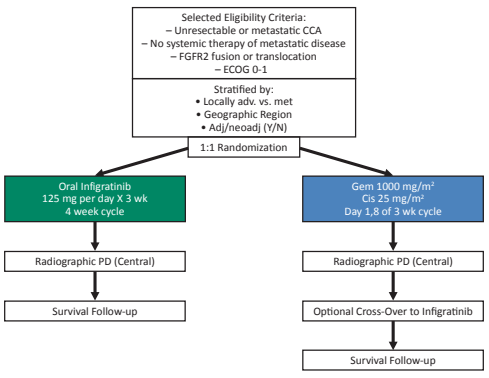


Biochemical activity (nM IC_{50})	
FGFR1	1.1
FGFR2	1.0
FGFR3	2.0
FGFR4	61.0
VEGFR2	210.0

PROOF study design

- PROOF is a multicenter, open-label, randomized, controlled phase 3 study to evaluate the efficacy of infigratinib vs gemcitabine + cisplatin in patients with advanced/metastatic or inoperable cholangiocarcinoma with *FGFR2* fusions/translocations.
- Clinicaltrials.gov identifier: NCT03773302
- PROOF is a multicenter study involving approximately 145 sites worldwide.

Figure 2. PROOF study design



Study objectives

- **Primary objective:** determine if infigratinib improves centrally assessed PFS vs gemcitabine + cisplatin in patients with advanced/metastatic or inoperable cholangiocarcinoma with *FGFR2* gene fusions/translocations.
- **Secondary objectives:**
  - Evaluate efficacy of infigratinib vs gemcitabine + cisplatin in terms of overall survival (OS).
  - Evaluate efficacy of infigratinib vs gemcitabine + cisplatin in terms of investigator-assessed PFS and overall response rate (ORR) based on central and investigator assessments.
  - Further evaluate efficacy in patients treated with these regimens in terms of best overall response (BOR), duration of response and disease control rate determined centrally and by the investigator.
  - Characterize the safety and tolerability of single-agent infigratinib.
- **Exploratory objectives:**
  - Compare quality of life (QOL) in patients treated with these regimens.
  - Calculate selected pharmacokinetic parameters for infigratinib.
  - Evaluate correlation between co-existing mutations, including molecular testing, and response rate of clinical endpoints.

Key inclusion criteria

- Histologically or cytologically confirmed non-resectable, recurrent, or metastatic cholangiocarcinoma. Patients with gallbladder cancer or ampullary carcinoma are not eligible.
- Written documentation of local or central laboratory determination of FGFR2 gene fusions/translocations.
- A representative tumor sample available for central FGFR2 fusion/translocation molecular testing.
- Full recovery from prior surgery, adjuvant radiotherapy or chemotherapy, and photodynamic treatment.
- Age ≥18 years.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
- Life expectancy >3 months.
- Recovery from adverse events (AEs) associated with previous systemic anti-cancer therapies to baseline or Grade 1, except for alopecia.

Key exclusion criteria

- Treatment with any systemic anti-cancer therapy for unresectable, recurrent, or metastatic cholangiocarcinoma. Prior neoadjuvant or adjuvant therapy is permitted if completed >6 months prior to first dose of study drug.
- History of a liver transplant.
- Prior or current treatment with a MEK or selective FGFR inhibitor.
- History of another primary malignancy within 3 years except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated malignancy that is not expected to require treatment for recurrence during the course of the study.
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

Treatment

- Patients are randomized 1:1 to oral infigratinib once daily for 21 days of a 28-day treatment cycle versus IV gemcitabine (1000 mg/m2) + cisplatin (25 mg/m2) on days 1 and 8 of a 21-day cycle.
- Treatment will continue until confirmed progressive disease by central review, intolerance, withdrawal of informed consent, or death.
- After 8 cycles of gemcitabine + cisplatin, patients can continue treatment if the investigator considers that they are deriving continued benefit.
- Patients on the gemcitabine + cisplatin arm with central radiographic progression can cross-over to infigratinib.

Dose modifications/treatment delays

- Patients who do not tolerate the protocol-specified dosing schedule are permitted to have dose adjustments in order to allow continuation of study drug.
- Each patient is allowed up to two dose reductions (Table 1).
- Patients should discontinue infigratinib if toxicities persist following two dose reductions, unless discussed and approved by the QED Therapeutics' Medical Monitor.

Table 1. Dose-reduction scheme for infigratinib

Dose reduction	Starting dose level 0	Dose level –1	Dose level –2
Infigratinib	125 mg	100 mg	75 mg

Efficacy evaluation

- Tumor response will be evaluated by independent central review and by the investigator according RECIST Version 1.1.[7]
- Patient management will be based upon investigator evaluations; patients should remain on study drug until central confirmation of progressive disease.
- Survival status and use of new anticancer medications will be followed approximately every 3 months once progressive disease has been documented and centrally confirmed.
- Survival status and use of anticancer therapy will be followed up to 1 year after the time at which 251 centrally confirmed PFS events are reached (i.e. end of study).

Safety evaluation

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

Quality of life evaluation

- QOL will be evaluated using the EQ-5D, which measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, anxiety, and general health; the EORTC QLQ-C30, a reliable and valid measure of QOL in cancer patients; and the EORTC QLQ-BIL21, a disease-specific module for patients with cholangiocarcinoma and gallbladder cancer.

Pharmacokinetics (infigratinib group only)

- On the days of PK sampling, patients should bring their study drug with them to the clinic and take it immediately after the pre-dose PK sample is taken.
- The PK parameters C_{ss}, AUC_{ss}, CL/F, and R_{acc} will be calculated for infigratinib, and the concentrations of the metabolites will be evaluated. For patients in the infigratinib group who discontinue study drug, attempts should be made to collect a PK blood sample from the patient at the time of discontinuation.

Biomarkers

- Archival or newly obtained tumor samples will be collected to explore mechanisms of resistance to cancer treatment using next generation sequencing analysis.
- Blood samples will also be collected for assessment of cell-free DNA.

Planned patient population and current status

Planned sample size/statistics

- Approximately 350 patients who have tumors with confirmed *FGFR2* gene fusions/translocations by a central laboratory (175 patients per group) are planned for study participation.
- Assuming a PFS hazard ratio (HR) of 0.7 comparing infigratinib to gemcitabine with cisplatin, the study will provide approximately 80% power to demonstrate that infigratinib improves the centrally assessed PFS compared to treatment with gemcitabine and cisplatin at a 2-sided significance level of 0.05.
- The study employs a group sequential design with one interim analysis on PFS, which will be conducted when approximately 33% of the PFS events are observed. The primary analysis for PFS will be conducted after approximately 251 PFS events have been observed.

Current status

- The study was initiated in February 2019 and is projected to reach the planned number of PFS events in approximately 32 months from randomization of the first subject.

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References

1. Graham RP, et al. Hum Pathol 2014;45:1630–8.
2. Ross JS, et al. Oncologist 2014;19:235–42.
3. Farshidfar F, et al. Cell Rep 2017;18:2780–94.
4. Guagnano V, et al. Cancer Discov 2012;2:1118–33.
5. Javle M, et al. Proc APCCA 2019 (poster P-19).
6. Javle M, et al. J Clin Oncol 2018;36:276–82.
7. Eisenhauer EA, et al. Eur J Cancer 2009;45:228–47.

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