Infigratinib versus gemcitabine plus cisplatin as first-line therapy in patients with advanced cholangiocarcinoma with *FGFR2* gene fusions/rearrangements: phase 3 PROOF trial

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Background

- The fibroblast growth factor receptor (FGFR) family plays an important role in cholangiocarcinoma.
- *FGFR* rearrangements (i.e. fusion events) represent driver mutations in cholangiocarcinoma. They are present in 13–17% of intrahepatic cholangiocarcinomas (CCA) and may predict tumor sensitivity to FGFR inhibitors.[1–3]
- Infigratinib (BGJ398), an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, has shown clinical activity against tumors with *FGFR* alterations.[4]
- A multicenter, open-label, phase 2 study (CBJG398X2204) evaluated the antitumor activity of infigratinib in patients with previously-treated CCA containing *FGFR2* fusions:
  - Previously presented results showed that infigratinib led to a confirmed objective response rate of 26.9% and a duration of response of 5.4 months.[5,6] Infigratinib-associated adverse events were manageable with phosphate binders, routine supportive care and dose reductions.
- Based on these earlier findings, the PROOF trial is evaluating infigratinib versus gemcitabine + cisplatin in front-line patients with advanced CCA with *FGFR2* gene fusions/rearrangements.

Table 1. PROOF objectives

Objectives
Primary
• Determine if infigratinib improves progression-free survival (PFS) vs gemcitabine + cisplatin in patients with advanced/metastatic or inoperable CCA with *FGFR2* gene fusions/rearrangements, assessed by blinded independent central review (BICR).
Secondary
• 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 objective response rate (ORR) based on BICR 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 by BICR and by the investigator. • Characterize the safety and tolerability of single-agent infigratinib.
Exploratory
• 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.

Treatment

Treatment

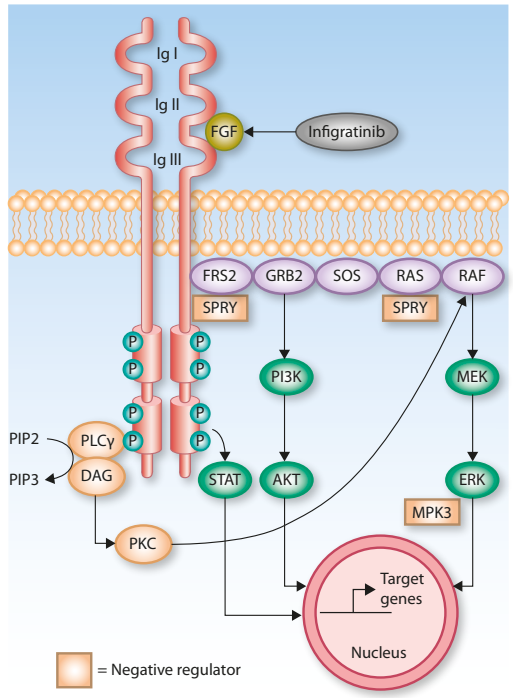
- Patients are randomized 2:1 to oral infigratinib once daily for 21 days of a 28-day treatment cycle versus IV gemcitabine (1000 mg/m^2) + cisplatin (25 mg/m^2) on days 1&8 of a 21-day cycle.
- Treatment will continue until progressive disease confirmed by central review, intolerance, withdrawal of informed consent, or death.
- Patients on the gemcitabine + cisplatin arm with central radiographic progression can cross-over to infigratinib.

Dose modifications

- 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.
- Patients should discontinue infigratinib if toxicities persist following two dose reductions, unless discussed and approved by the QED Therapeutics' Medical Monitor.

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

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



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

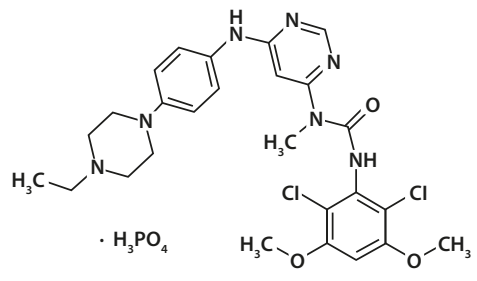


Figure 2. PROOF study design

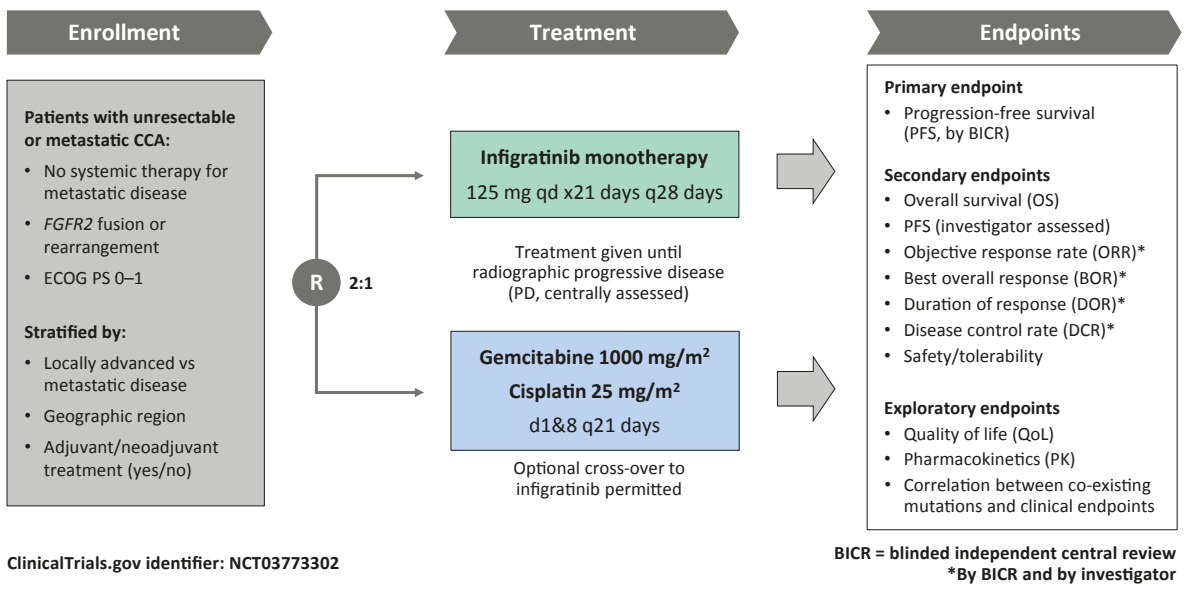


Table 2. Key inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria
1. Histologically or cytologically confirmed non-resectable, recurrent, or metastatic CCA. Patients with gallbladder cancer or ampullary carcinoma are not eligible	1. Treatment with any systemic anti-cancer therapy for unresectable, recurrent, or metastatic CCA. Prior neoadjuvant or adjuvant therapy is permitted if completed >6 months prior to first dose of study drug
2. Written documentation of local or central laboratory determination of *FGFR2* gene fusions/ rearrangements	2. History of a liver transplant
3. A representative tumor sample available for central *FGFR2* fusion/rearrangement molecular testing	3. Prior or current treatment with a MEK or selective FGFR inhibitor
4. Full recovery from prior surgery, adjuvant radiotherapy or chemotherapy, and photodynamic treatment	4. 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
5. Age ≥18 years	5. 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)
6. ECOG performance status ≤1	
7. Life expectancy >3 months	
8. Recovery from adverse events associated with previous systemic anti-cancer therapies to baseline or Grade 1, except for alopecia	

Evaluations

Efficacy evaluation

- Tumor response will be evaluated by BICR and by the investigator according RECIST Version 1.1.
- 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 until 274 OS 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 CCA and gallbladder cancer.

Pharmacokinetics (infigratinib group only)

- The PK parameters C_{max}, C_{min} 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 384 patients who have tumors with confirmed *FGFR2* gene fusions/rearrangements by a central or local laboratory are planned for study participation.
- Assuming a PFS hazard ratio (HR) of 0.65 comparing infigratinib to gemcitabine with cisplatin, the study will provide approximately 90% power to demonstrate that infigratinib improves the PFS assessed by BICR 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 50% of the PFS events are observed. The primary analysis for PFS will be conducted after approximately 255 PFS events have been observed.

Current status

- Recruitment started in December 2019.
- The study has an estimated primary completion date of September 2023.

References

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