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

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Background
- 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 inoperable cholangiocarcinomas and may predict tumor sensitivity to FGFR inhibitors.1–3

Studies show that FGFR2 gene fusions/translocations are present in 13–17% of intrahepatic cholangiocarcinomas and may predict tumor sensitivity to FGFR inhibitors.1–3 Infigratinib inhibits FGFR1–3 with a Ki of 6.1 nM and 2.0 nM against FGFR2 and FGFR3, respectively.

Infigratinib: an oral FGFR1–3 selective tyrosine kinase inhibitor

The PROOF trial is evaluating infigratinib versus gemcitabine plus cisplatin in advanced cholangiocarcinomas (Figure 1), which 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 plus cisplatin in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations.

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

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 overall response rate (ORR), duration of response and disease control rate determined centrally and by the investigator.

Figure 2. PROOF study design

Efficacy evaluation
- Tumor response will be evaluated by independent central review and by the investigator according RECIST Version 1.1.
- Patient management will be based on investigational evaluations; patients should remain on study drug until central confirmation of progressive disease.
- Survival status and use of additional therapy 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 evaluations, vital signs, physical exam, lab values, and cardiac imaging.
- 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-BL2, a disease-specific module for patients with cholangiocarcinoma and gallbladder cancer.

Planned patient population and current status
- 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 plus cisplatin, the study will provide approximately 90% 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 study will be stopped if 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 34 months from randomization of the first subject.

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References

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