A phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor (TKI), in patients with previously-treated advanced cholangiocarcinoma containing *FGFR2* fusions

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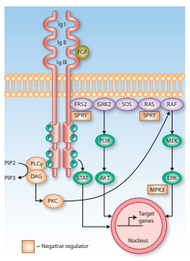
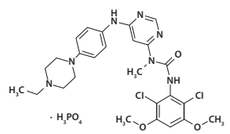
Background

- Cholangiocarcinomas are often diagnosed at an advanced unresectable stage, with few treatment options available after disease progression while receiving gemcitabine and cisplatin first-line chemotherapy, resulting in poor patient prognosis.
- Numerous cancers have fibroblast growth factor receptor (FGFR) genomic alterations. *FGFR* translocations (i.e. fusion events) represent driver mutations in cholangiocarcinoma. They are present in 13–17% of intrahepatic cholangiocarcinomas (IHC) 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 preliminary clinical activity against tumors with *FGFR* alterations.[4]
- In early-phase clinical evaluation, infigratinib showed a manageable safety profile and single-agent activity.[5,6]
- A multicenter, open-label, phase II study (NCT02150967) evaluated the antitumor activity of infigratinib in patients with previously-treated advanced IHC containing *FGFR2* fusions.

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



Study methods

Patients

- Histologically or cytologically confirmed advanced/metastatic IHC with *FGFR2* fusions or other *FGFR* genetic alterations identified by local Clinical Laboratory Improvement Amendments – certified testing or at a central facility.
- The protocol was modified to limit enrollment to only tumors with *FGFR2* fusions.
- Measurable or evaluable disease according to RECIST (version 1.1), an ECOG performance status of 0 or 1, and evidence of disease progression after one or more prior regimens of gemcitabine-based combination therapy or gemcitabine monotherapy.

Treatment

- Patients received infigratinib 125 mg once daily for 21 days followed by 7 days off in 28-day cycles.
- To manage hyperphosphatemia, prophylactic use of sevelamer, a phosphate-binding agent, was recommended on days of infigratinib administration per the product packaging information and institutional guidelines. Patients were also instructed to adhere to a low-phosphate diet.
- Patients continued infigratinib treatment until unacceptable toxicity, disease progression, and/or investigator discretion, or consent withdrawal.
- Dose modifications were based on the worst preceding toxicity. Treatment was resumed after resolution or reduction to grade 1 toxicity, with each patient allowed two dose reductions (100 mg, 75 mg) before infigratinib discontinuation.

Outcomes

- Tumor response was assessed per RECIST version 1.1, using CT or MRI.
- Primary and secondary efficacy endpoints – see Figure 2.
- Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events, version 4.03, during treatment and until 30 days after the last dose was administered.
- *FGFR* genetic alteration was required to confirm patient eligibility. These and other concurrent genetic alterations were correlated with clinical outcome.

Statistics

- Data were combined from all participating study sites for the analyses.
- Efficacy and safety analyses included all patients whose tumors had *FGFR2* fusions and received at least one infigratinib dose.

Table 1. Baseline patient demographics and clinical characteristics

Characteristic	N=71
Median age, years (range)	53 (28–74)
Male / female	27 (38.0) / 44 (62.0)
Race	
White	55 (77.5)
Black	3 (4.2)
Asian	4 (5.6)
Other / unknown	3 (4.2) / 6 (8.5)
ECOG performance status	
0 / 1	29 (40.8) / 42 (59.2)
Prior lines of therapy	
≤1	32 (45.1)
≥2	39 (54.9)
FGFR2 status	
Translocation positive	71 (100.0)
Mutated	5 (7.0)

Figure 2. Open-label, phase II study design

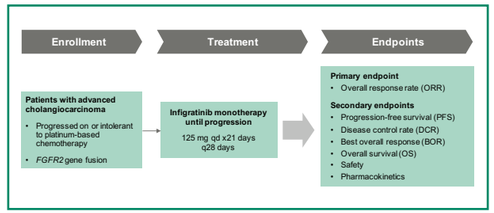


Table 2. Patient disposition

	Number %
Total receiving treatment	71 (100.0)
Treatment ongoing	9 (12.7)
Ended treatment	62 (87.3)
Missing	1 (1.4)
Adverse event	6 (8.5)
Death	1 (1.4)
Lost to follow-up	1 (1.4)
Physician decision	5 (7.0)
Progressive disease	44 (62.0)
Subject/guardian decision	4 (5.6)

Table 3. Clinical activity of infigratinib in advanced cholangiocarcinoma

Efficacy outcome in all fusion patients	N=71
Overall response rate (ORR; confirmed & unconfirmed), % (95% CI)	31.0 (20.5–43.1)
Complete response, n (%)	0
Partial response – confirmed, n (%)	18 (25.4)
Stable disease, n (%)	41 (57.7)
Progressive disease, n (%)	8 (11.3)
Unknown, n (%)	4 (5.6)
Efficacy outcome in patients with potential for confirmation*	
cORR, % (95% CI)	26.9 (16.8–39.1)
cORR in patients receiving prior lines of treatment, %	
≤1 (n=28)	39.3
≥2 (n=39)	17.9
Disease control rate (DCR), % (95% CI)	83.6 (72.5–91.5)
Median duration of response, months (95% CI)	5.4 (3.7–7.4)
Median PFS, months (95% CI)	6.8 (5.3–7.6)
Median OS, months (95% CI)	12.5 (9.9–16.6)

*Patients completed (or discontinued prior to) 6 cycles. Investigator-assessed.

Figure 3. Efficacy of infigratinib in *FGFR2* fusion-positive cholangiocarcinoma

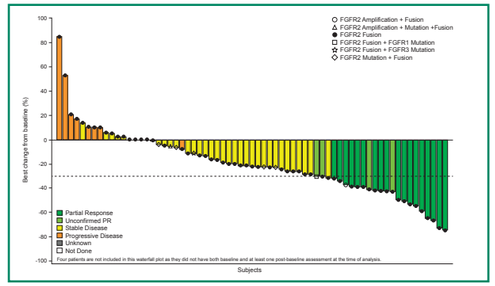
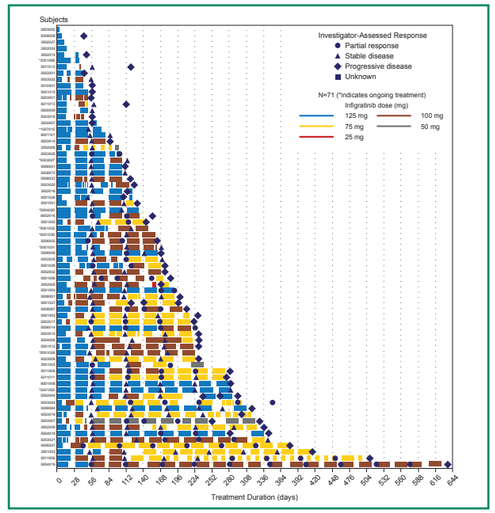


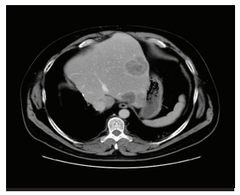
Figure 4. Tumor response with treatment exposure



Response to infigratinib in *FGFR2* fusion-positive cholangiocarcinoma

- 50-year old male with intrahepatic cholangiocarcinoma.
- s/p right hepatectomy, systemic chemotherapy with gemcitabine and cisplatin and pembrolizumab.
- Partial response on infigratinib noted at first restaging in multiple liver metastases.
- Molecular profile: *FGFR2* rearrangement, PTCH1, ARID1A, BCORL1, MAP2K4, MLL3, NUP93, SPEN, TP53. MSI high and TMB-high.

Before



After

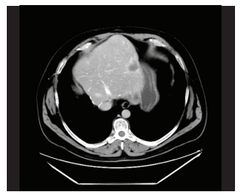


Table 4. Infigratinib safety profile: any grade AEs ≥20%

Number of patients (%)	Any grade	Grade 3/4
Hyperphosphatemia	52 (73.2)	9 (12.7)
Fatigue	35 (49.3)	3 (4.2)
Stomatitis	32 (45.1)	7 (9.9)
Alopecia	27 (38.0)	0
Constipation	25 (35.2)	1 (1.4)
Dry eye	23 (32.4)	0
Dysgeusia	23 (32.4)	0
Arthralgia	21 (29.6)	1 (1.4)
Palmar-plantar erythrodysesthesia syndrome	19 (26.8)	4 (5.6)
Dry mouth	18 (25.4)	0
Dry skin	18 (25.4)	0
Diarrhea	17 (23.9)	2 (2.8)
Hypophosphatemia	17 (23.9)	10 (14.1)
Nausea	17 (23.9)	1 (1.4)
Vomiting	17 (23.9)	1 (1.4)
Hypercalcemia	16 (22.5)	3 (4.2)
Vision blurred	16 (22.5)	0
Decreased appetite	15 (21.1)	1 (1.4)
Weight decreased	15 (21.1)	2 (2.8)

Table 5. Infigratinib safety profile: grade 3/4 AEs >3%

Number of patients (%)	Grade 3/4
Hypophosphatemia	10 (14.1)
Hyperphosphatemia	9 (12.7)
Hyponatremia	8 (11.3)
Stomatitis	7 (9.9)
Lipase increased	4 (5.6)
Palmar-plantar erythrodysesthesia syndrome	4 (5.6)
Abdominal pain	3 (4.2)
Anemia	3 (4.2)
Blood alkaline phosphatase increased	3 (4.2)
Fatigue	3 (4.2)
Hypercalcemia	3 (4.2)

Conclusions

- Infigratinib is an oral, FGFR1—3-selective TKI that shows meaningful clinical activity against chemotherapy-refractory cholangiocarcinoma containing *FGFR2* fusions.
- Infigratinib-associated toxicity is manageable with phosphate binders and routine supportive care.
- This promising antitumor activity and manageable safety profile supports continued development of infigratinib in this highly selected patient population.

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