Circulating-free DNA (cfDNA) and tissue next-generation sequencing analysis in a phase II study of infigratinib (BGJ398) for cholangiocarcinoma with *FGFR2* fusions

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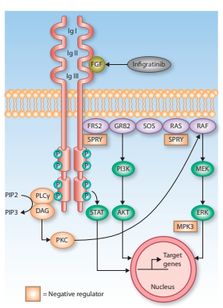
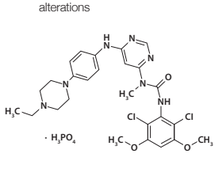
Background

- 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* fusions (i.e. translocations) represent genomic drivers of cholangiocarcinoma. They are present in 13–17% of intrahepatic cholangiocarcinomas (iCCA) and may predict tumor sensitivity to FGFR inhibitors.[1–3]
- Infigratinib (BGJ398), an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, 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.
- Here, we report a detailed analysis of tissue and cell-free DNA (cfDNA) biomarkers from NCT02150967.

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 iCCA with *FGFR2* fusions identified by molecular testing at a local/institutional laboratory or central laboratory (Foundation Medicine USA).
- 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.

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.

Biomarker studies

- Comprehensive genomic profiling (CGP) was performed by the central laboratory on tumor tissue collected prior to therapy (at screening) to confirm the *FGFR2* fusion for patient eligibility.
- cfDNA collected at screening was analyzed by a next generation sequencing using a 600-gene panel (Novartis labs).
- Genomic alterations with known or likely impacts on protein function and variants of unknown functional significance are reported.

Figure 2. Open-label, phase II study design

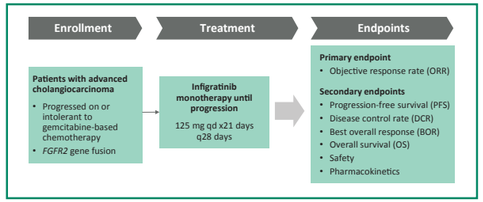


Table 1. Baseline patient demographics and clinical characteristics

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**	
Fusion positive	71 (100.0)

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
Objective 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)

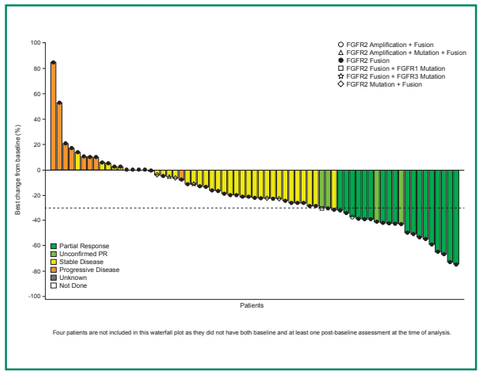
Efficacy outcome in patients with potential for confirmation*	
cORR, % (95% CI)	26.9 (16.8–39.1)
cORR in patients receiving prior lines of treatment, %	
≤1 (n=28)	39.3
≥2 (n=39)	17.9
Disease control rate (DCR), % (95% CI)	83.6 (72.5–91.5)
Median duration of response, months (95% CI)	5.4 (3.7–7.4)
Median 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.

Table 4. Infigratinib safety profile: any grade AEs ≥25%

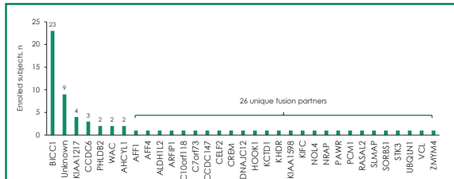
Number of patients (%)	Any grade	Grade 3/4
Hyperphosphatemia	52 (73.2)	9 (12.7)
Fatigue	35 (49.3)	3 (4.2)
Stomatitis	32 (45.1)	7 (9.9)
Alopecia	27 (38.0)	0
Constipation	25 (35.2)	1 (1.4)
Dry eye	23 (32.4)	0
Dysgeusia	23 (32.4)	0
Arthralgia	21 (29.6)	1 (1.4)
Palmar-plantar erythrodysesthesia syndrome	19 (26.8)	4 (5.6)
Dry mouth	18 (25.4)	0
Dry skin	18 (25.4)	0

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

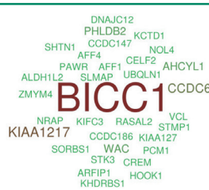


Four patients are not included in this waterfall plot as they did not have both baseline and at least one post-baseline assessment at the time of analysis.

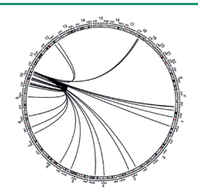
Figure 4. *FGFR2* fusion partners



- 32 different *FGFR2* fusion partners were identified in 71 enrolled subjects by NGS of tumor tissue using a 324 gene panel (Foundation Medicine, USA). The partner gene information for 9 subjects was unknown: intron 17 rearrangement (n=4) and rearrangement by FISH (n=5).

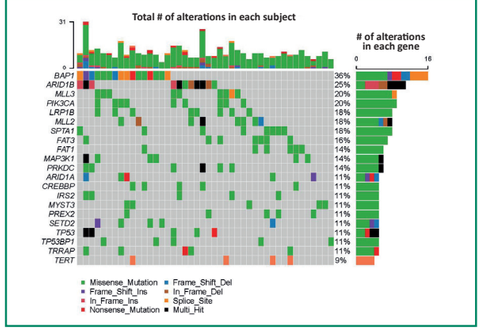


- Word cloud of *FGFR2* rearrangements scaled by frequency. *FGFR2-BICC1* is the most frequent fusion (37%).



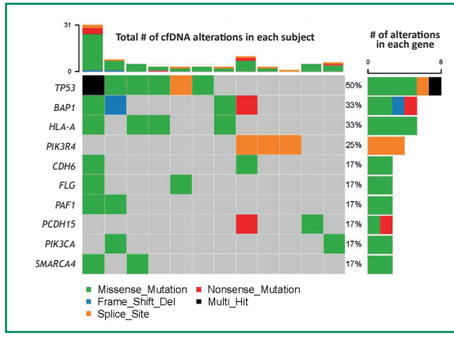
- Circos plot of *FGFR2* rearrangements. 66% of rearrangements occured in cis between *FGFR2* and other genes on chromosome 10.

Figure 5. Oncoplots of tumor genomic profiles



- 15 patients had tumor mutational burden (TMB) data available. All 15 patients were TMB low.
- *BAP1* (36%), *ARID1B* (25%), *MLL3* (20%) and *PIK3CA* (20%) were most frequently altered.
- Actionable mutations in *IDH2* and *PIK3CA* and copy number changes in *CDK4* and *MET* were identified in individual subjects.
- Coincident amplification of *FGFR2* (1) and different mutations in *FGFR2* (3) and *FGFR3* (1) were also observed in five subjects with *FGFR2* fusions.

Figure 6. Oncoplots of cfDNA genomic profiles



- Genomic alterations in cfDNA were identified by NGS using a 600-gene panel (Novarits Labs).
- *FGFR2* fusions were concordant in 8/14 (57%) of subjects with tumor tissue and cfDNA. Notably, additional *FGFR2* fusions were identified in two subjects that were not present in tumor tissue.
- *TP53* (50%), *BAP1* (33%), and *HLA-A* (33%) were most frequently altered in cfDNA. Three subjects also had known deleterious alterations in *PIK3CA* (*E454K* & *M1004I*) and *BRAF* (*BRA-ZP3* fusion).

Conclusions

- Infigratinib is an oral, FGFR1–3-selective TKI that shows meaningful clinical activity against chemotherapy-refractory cholangiocarcinoma containing *FGFR2* fusions.
- The large assortment of *FGFR2* fusion gene partners identified in this study underscores the diversity of *FGFR2* rearrangements that may drive cholangiocarcinoma.
- Other co-occurring genetic alterations with likely functional and variants of unknown significance were identified, which may alter pathways related to treatment effect and/or duration of response.
- Although cfDNA analysis was performed in a limited number of subjects, preliminary data suggest that cfDNA analysis may be valuable for the identification of *FGFR2* fusions and to study intratumoral heterogeneity.

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