A retrospective analysis of post second-line chemotherapy treatment outcomes for patients with advanced or metastatic cholangiocarcinoma and *FGFR2* fusions

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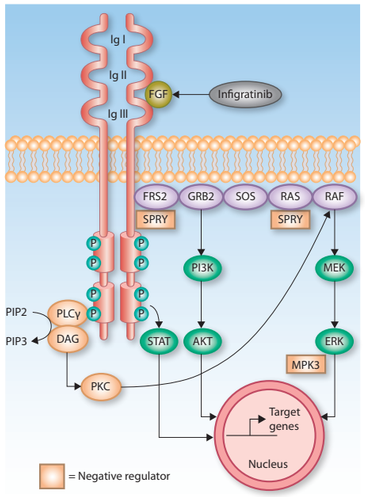
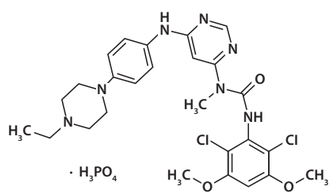
Background

- Cholangiocarcinoma (CCA) is the most common biliary tract malignancy with an estimated incidence of 8,000–10,000 patients/year in the US.
- Chemotherapy is the most common second-line treatment with reported outcomes in patients with advanced/metastatic CCA. Response rates of <10% and median progression-free survival (PFS) times of ~3–4 months have been reported with second-line chemotherapy regimens, including FOLFOX in the ABC-06 trial.[1,2]
- Numerous cancers have fibroblast growth factor receptor (FGFR) genomic alterations. *FGFR* fusions and rearrangements represent genomic drivers of CCA. They are present in 13–17% of intrahepatic cholangiocarcinomas (iCCA) and may predict tumor sensitivity to FGFR inhibitors.[3–5]
- Multiple targeted agents are in development for patients with FGFR2 fusions. To date, the outcome of patients with iCCA and FGFR2 fusions receiving standard second-line chemotherapy is unknown.

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



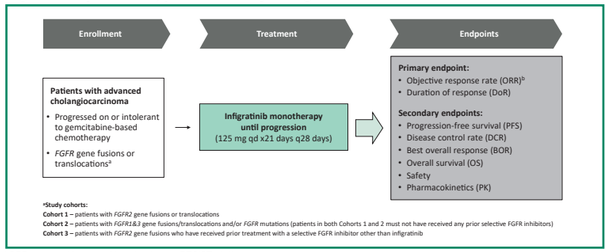


- Infigratinib (BGJ398), an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, has shown preliminary clinical activity against tumors with *FGFR* alterations.[6]
- In early-phase clinical evaluation, infigratinib showed a manageable safety profile and single-agent activity.[7,8]
- A multicenter, open-label, phase II study (NCT02150967) evaluated the antitumor activity of infigratinib in patients with previously-treated advanced CCA containing *FGFR2* fusions.
- In this poster, we examine outcomes following infigratinib administered as third- and later-line treatment in patients with CCA and FGFR2 fusions.

Methods

- Patients with advanced CCA and *FGFR2* fusions after prior treatment with gemcitabine-based chemotherapy were enrolled in a single-arm phase 2 study (NCT02150967) of infigratinib (Figure 2).
- Findings from the phase 2 study have been presented/published previously.[8,9]
- A retrospective analysis of a subset of patients from study Cohort 1 who received infigratinib as third- or later-line treatment was performed:
  - Prior anti-cancer treatment medical history collected in the clinical database (including regimens, start and stop dates for regimen and best response, reason and date for disease progression) was reviewed.
    - A prior systemic therapy (oral or intravenous) was counted as a line of treatment if given in the therapeutic or palliative setting for advanced or metastatic CCA.
    - Documentation of the same agent or regimen twice, sequentially, was counted as two separate lines of treatment if radiological progression was documented after the first line of treatment.
  - PFS is defined as the time from the initial dose to the date of progression or death, whichever came first.
    - PFS and response rate (best overall response) to the second-line prior anti-cancer systemic treatment (pre-infigratinib) was calculated based on investigator-reported medical histories. Confirmation of response was not collected in the clinical database. PFS was censored at the end date of chemotherapy if no radiological progression was reported.
    - PFS and ORR by investigator review were then calculated in the same patients following third-line or later-line therapy with infigratinib. Confirmation of objective responses was done no sooner than 4 weeks as per RECIST version 1.1. PFS is censored on the last valid tumor assessment date if radiological progression or death is not reported.

Figure 2. Open-label, phase 2 study design



[b]ORR assessed by central imaging (as per RECIST v1.1)

Table 1. Baseline patient and disease characteristics

Characteristic	All patients (N=71)	Third-/later-line infigratinib (n=37)
Median age, years (range)	**53 (28–74)**	**54 (31–74)**
Male / female, n (%)	**27 (38) / 44 (62)**	**14 (38) / 23 (62)**
Race, n (%)		
White	55 (78)	28 (76)
Black / African American	3 (4)	2 (5)
Asian	4 (6)	2 (5)
Other / unknown	9 (13)	5 (14)
ECOG performance status, n (%)		
0 / 1	29 (41) / 42 (59)	16 (43) / 21 (57)
Prior lines of therapy, n (%)		
≤1	34 (48)	0
≥2	37 (52)	37 (100)
***FGFR2* status, n (%)**		
Fusion positive	71 (100)	37 (100)

Figure 3. Schematic of the analysis

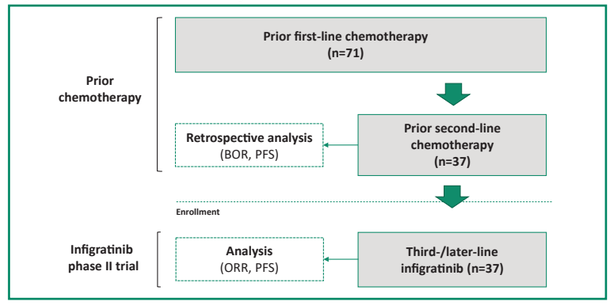
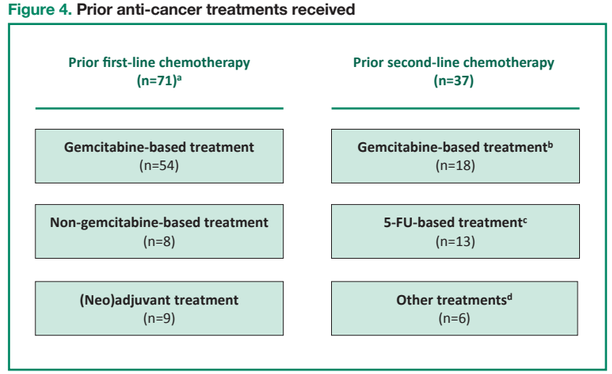


Figure 4. Prior anti-cancer treatments received



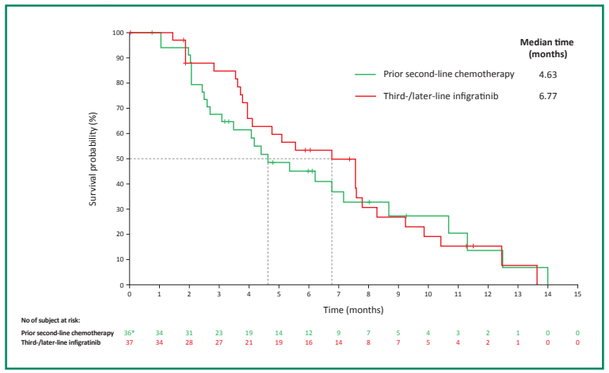
[a]all except one subject received gemcitabine-based therapy prior to infigratinib treatment
[b]11 patients who previously received gemcitabine-based treatment were retreated with gemcitabine-based treatment
[c]5-FU-based treatments: 5 FOLFOX, 7 FOLFIRI;
[d]Other treatments: capecitabine, etc

Table 2. Clinical activity of infigratinib in third/later-line vs retrospective second-line treatment

	Patients receiving prior second-line therapy (n=37)	
	Prior second-line chemotherapy[a,b]	Third-/later-line infigratinib[c]
Best overall response, n (%)		
Complete response	0	0
Partial response	2 (5.4)	8 (21.6)
Stable disease	10 (27.0)	22 (59.5)
Progressive disease	14 (37.8)	4 (10.8)
Unknown	10 (27.0)	0
Not done	1 (2.7)	3 (8.1)
Objective response rate (ORR), % (95% CI)	5.4 (0.7–18.2)	21.6 (9.8–38.2)
Median PFS, months (95% CI)	4.6 (2.7–7.2)	6.8 (3.9–7.8)

[a]Investigator response from medical history
[b]Confirmed and unconfirmed responses per investigator review
[c]Confirmed responses per investigator review

Figure 5. Progression-free survival



*One patient received only 1 day of prior second-line chemotherapy and discontinued due to reasons other than disease progression. Consequently, their PFS was censored at 1 day (0.03 months).

Conclusions

- Infigratinib is an oral, FGFR1–3-selective TKI that shows meaningful clinical activity against chemotherapy-refractory CCA containing *FGFR2* fusions, with a confirmed ORR of 26.9% (95% CI 16.8–39.1) and a DOR of 5.4 months (95% CI 3.7–7.4).[9]
- A limitation of this retrospective analysis is reliance upon investigator assessment of medical history for retroactive adjudication of response or progression on prior standard second-line chemotherapy in patients with CCA and *FGFR2* fusions.
- Nevertheless, these retrospectively analyzed outcomes from second-line chemotherapy in patients with CCA and *FGFR2* fusions were similar to those reported in the literature[10] for all patients with CCA regardless of genomic status and remain dismal.
- Infigratinib administered as third- and later-line treatment resulted in a meaningful PFS and ORR benefit in patients with CCA and *FGFR2* fusions.

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