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Derazantinib for patients with intrahepatic cholangiocarcinoma harboring *FGFR2* fusions/rearrangements: primary results from the Phase 2 study FIDES-01

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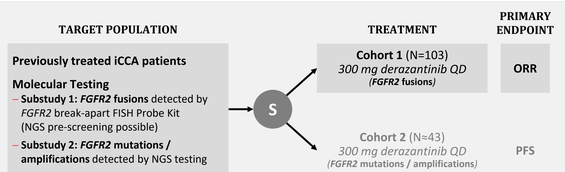
BACKGROUND

- Deregulation of the FGFR signaling pathway is implicated in various human cancers, including intrahepatic cholangiocarcinoma, urothelial, gastric, breast, and lung cancers.[(1)] This makes activated FGFRs a promising potential therapeutic target.[(2)]
- FGF-FGFR signaling pathway deregulation are associated with *FGF(R)* genetic aberrations, including aberrant gene expression, amplifications, mutations, translocations, and fusions. In iCCA, the estimated prevalence of *FGFR2* fusions is 10-16%.[(3-8)]
- Derazantinib is a potent oral inhibitor of FGFR1, FGFR2, and FGFR3.[(9)]
- In previous studies, derazantinib was well tolerated with a manageable side effect profile in patient populations both unselected and selected for *FGFR* genetic aberrations,[(10)] and demonstrated clinically meaningful efficacy in patients with intrahepatic cholangiocarcinoma selected for *FGFR2* fusions, mutations and amplifications.[(11,12)]
- Derazantinib is developed under the FIDES program with ongoing studies in patients with intrahepatic cholangiocarcinoma, urothelial and gastric cancer harboring various *FGFR* genetic aberrations.
- Here, we report the latest results from Cohort 1 of the FIDES-01 study (NCT03230318), evaluating the safety and anti-tumor activity of derazantinib in previously treated patients with locally advanced or metastatic intrahepatic cholangiocarcinoma harboring *FGFR2* fusions (**Figure 1**); the study (incl. Cohort 2) is ongoing.

FIGURE 1



FIDES-01 study design

METHODS

Patients

- Adults aged 18 years or older.
- Histological or cytological diagnosis of locally advanced or metastatic intrahepatic cholangiocarcinoma or mixed histology tumors (combined hepatocellular-cholangiocarcinoma).
- Documented disease progression following at least one previous systemic cancer therapy (previous treatment with selective FGFR inhibitors was not permitted).
- Radiologically measurable disease per RECIST 1.1.
- ECOG performance status 0–1.
- Adequate hematological laboratory values, and adequate hepatic and renal function.

Procedures and Treatment

- Central molecular prescreening for *FGFR2* fusion/rearrangement status at CLIA-certified ARUP Laboratories (Salt Lake City, UT, USA) using the FISH ZytoLight® SPEC FGFR2 Dual Color Break Apart Probe kit (ZytoVision GmbH, Bremerhaven, Germany).
- Patients self-administered 300 mg derazantinib QD (28-day cycle, continuous dosing) until disease progression, unacceptable toxicity, withdrawal of consent, or investigator choice.

Outcomes and Assessments

- Primary endpoint: Confirmed objective response rate (ORR) as measured by tumor assessments by CT (or MRI) every 8 weeks for the first 6 months, and every 12 weeks thereafter, and evaluated per independent central radiology review.
- Safety was assessed based on NCI CTCAE version 5.0.

Statistical Analysis

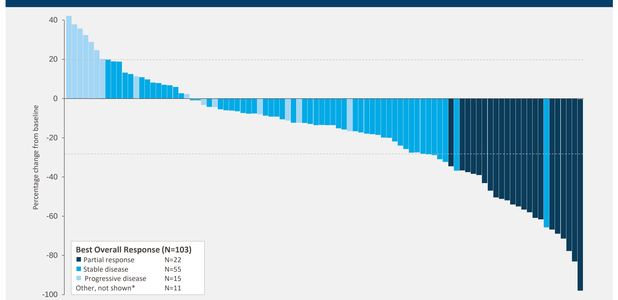
- With an assumed ORR of 23%, a sample size of 100 patients was estimated to provide approximately 90% power to reject the null hypothesis at one-sided significance level 0.025, or equivalently to have the lower bound of confidence interval of ORR > 10%.
- The primary analysis set was ITT population (data cutoff for all analyses, 06 August 2021).

TABLE 1

Patient demographics (ITT population)

Baseline variables	Category	All Patients (N=103)
Age	Median (range), years	56 (28-84)
	>65 years, n (%)	23 (22)
Sex, n (%)	Female	67 (65)
	Male	36 (35)
Baseline ECOG, n (%)	0	56 (54)
	≥1	47 (46)
Region, n (%)	North America	58 (56)
	Europe	45 (44)
Prior lines of treatment, n (%)	1	54 (52)
	2	31 (30)
	≥3	18 (17)
***FGFR2* genetic aberration, n (%)**	FISH	42 (41)
	NGS	61 (59)

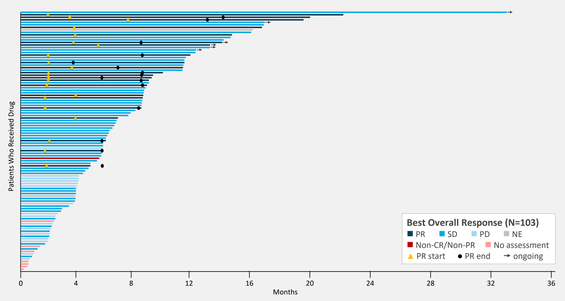
FIGURE 2



Best percent change in target lesion size (primary endpoint, ITT population).

* Radiographic evaluation by blinded independent central review; results from 92 patients with measurable disease and at least one post-baseline assessment are shown. Of the 11 patients not shown, seven patients had no post-baseline assessment, three were RECIST non-evaluable, and one patient without centrally-confirmed measurable disease at baseline had a best response of non-CR/non-PD (patient data are shown in **Figure 3**).

FIGURE 3



Treatment duration and best overall response (ITT population).

Radiographic evaluation by blinded independent central review.

RESULTS

Patients and treatment

- The ITT population includes 103 patients assigned to derazantinib treatment with eligible *FGFR* status.
- Patient demographics are shown in **Table 1**.
- Patients received a median of 6 cycles (range, 1–36) with a duration of 28 days, and the mean dose intensity was 93% (SD, 11%).

Efficacy

- Median follow-up was 12.6 months (95% CI, 6.7–18.9).
- A BOR of PR was assessed in 22 patients (no CRs assessed), and 56 patients had SD (**Figure 2**). ORR was 21.4% (95% CI, 13.9–30.5) and DCR was 75.7% (95% CI, 66.3–83.6).
- Median DOR among responders was 6.4 months (95% CI, 4.6–9.2), as shown in **Figure 3**.
- Median PFS was 8.0 months (95% CI, 5.5–8.3; **Figure 4A**).
- Median OS was 15.9 months (95% CI, 12.5–22.6; **Figure 4B**), with data being immature at the data cutoff (61 [59%] of 103 patients had died).
- ORR (**Figure 5A**) and PFS (**Figure 5B**) were consistent across predefined patient subgroups.
- Time to progression (TTP) was 8.1 months (95% CI, 5.5–8.3); patients had a markedly longer TTP with derazantinib as compared to treatment received immediately prior to the study (4.5 months [95% CI, 3.4–6.6]; descriptive p-value 0.002).

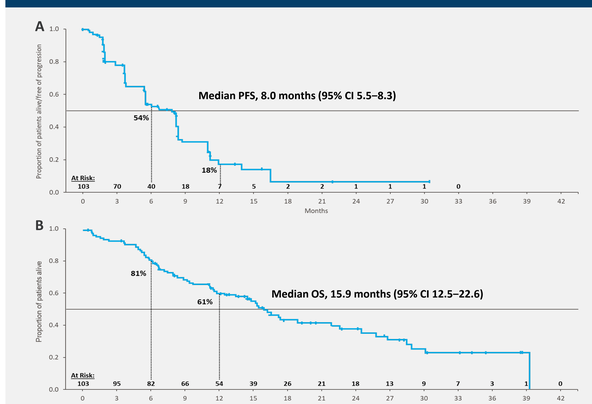
Safety

- Drug-related AEs (i.e., AEs with a reasonable relationship to derazantinib treatment per Investigator assessment) are shown in **Table 2**. For 76% of patients, hyperphosphatemia was reported as drug-related AE and/or a laboratory value worsening from baseline.
- Severe (grade ≥ 3) drug-related AEs were infrequent with the exception of AST and ALT elevations (**Table 2**); no cases of drug-induced liver injury were assessed.
- FGFR-inhibitor-class effects were infrequent, mild to moderate (grade 1–2 only), and reversible:
  - Nail toxicities (7%)
  - Palmar-plantar erythrodysesthesia (2%)
  - Stomatitis (2%)
  - Central serous retinopathy (1%).

CONCLUSIONS

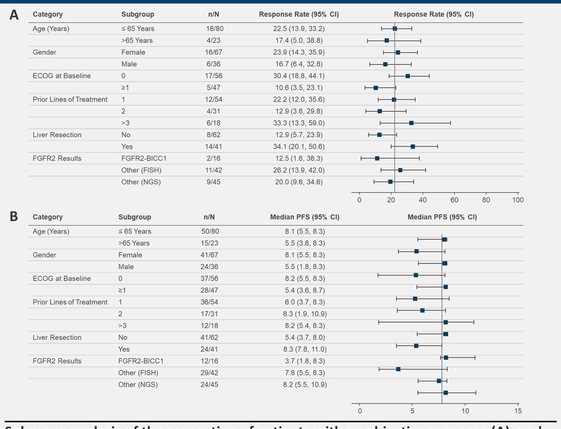
- **Patients with recurrent FGFR2^{F+} iCCA attained a clinically meaningful ORR (21%), DCR (76%), and median PFS (8.0 months).**
- **Derazantinib had a notably well manageable adverse event profile, with a low incidence of nail toxicities, stomatitis, hand-foot syndrome and retinal FGFR-inhibitor class effects.**

FIGURE 4



Kaplan-Meier analysis of progression-free (A) and overall survival (B)

FIGURE 5



Subgroup analysis of the proportion of patients with an objective response (A), and patients alive and free of progression (B)

TABLE 2

Most common (≥10%) treatment-related toxicities

System Organ Class / Preferred Term	Safety Population (N=103), n (%)	
	All Grades	Grade 3*
Total patients with ≥ 1 adverse event	**91 (88)**	**36 (35)**
Metabolism and nutrition disorders		
Hyperphosphatemia / phosphate increased†	38 (37)	4 (4)
General disorders and administration site conditions		
Fatigue / asthenia	35 (34)	5 (5)
Gastrointestinal disorders		
Nausea	30 (29)	1 (1)
Dry mouth	24 (23)	0
Diarrhea	21 (20)	1 (1)
Vomiting	15 (15)	0
Eye disorders		
Dry eye‡	31 (30)	0
Vision blurred	14 (14)	1 (1)
Investigations		
AST increased†	25 (24)	10 (10)
ALT increased†	24 (23)	10 (10)
Nervous system disorders		
Dysgeusia	16 (16)	–
Skin and subcutaneous tissue disorders		
Alopecia	14 (14)	–
Dry skin	12 (12)	0
Blood and lymphatic system disorders		
Anemia	11 (11)	1 (1)

*No grade 4/5 toxicities reported.
†Reported adverse event data only (excluding laboratory abnormalities worsening from baseline).
‡Includes dry eye, xerophthalmia, keratitis, cornea verticillata, blepharitis, foreign body sensation, corneal disorder/erosion.

DISCLOSURE — DISCLAIMER

Disclosure: M. Droz dit Busset has no disclosures. F. Cantero, M. Saulay, and S. Braun are full-time employees of Basilea Pharmaceutica International Ltd., the Sponsor of study FIDES-02.
Disclaimer: Derazantinib and its uses are investigational and have not been approved by a regulatory authority for any use. Efficacy and safety have not been established. The information presented should not be construed as a recommendation for use. The relevance of findings in nonclinical/preclinical studies to humans is currently being evaluated.
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