59P - Efficacy of derazantinib in intrahepatic cholangiocarcinoma (iCCA) patients with FGFR2 fusions, mutations or amplifications

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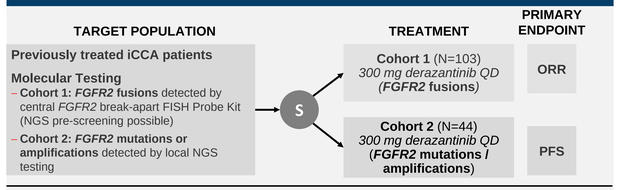
BACKGROUND

- Deregulation of the Fibroblast Growth Factor Receptor (FGFR) signaling pathway is implicated in various human cancers, including intrahepatic cholangiocarcinoma (iCCA), urothelial, gastric, breast, and lung cancers.(1) This makes activated FGFRs a promising potential therapeutic target.(2)
- FGF-FGFR signaling pathway deregulation is 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) and that of *FGFR2* mutations and amplifications together is estimated at 4%,(9) or 8-13% in smaller series.(6,10)
- Derazantinib is a potent oral inhibitor of FGFR1, FGFR2, and FGFR3.(11)
- In a previous study, derazantinib was well tolerated with a manageable side effect profile in patient populations unselected and selected for *FGFR* genetic aberrations,(12) and demonstrated clinically meaningful efficacy in patients with iCCA selected for *FGFR2* fusions, mutations and amplifications.(13-15)
- Derazantinib is developed under the FIDES program with studies in patients with iCCA, urothelial and gastric cancer harboring various FGFR genetic aberrations.
- Here, we present the data from 147 patients from the FIDES-01 study (NCT03230318), evaluating the safety and anti-tumor activity of derazantinib in previously treated patients with locally advanced or metastatic iCCA harboring *FGFR2* fusions (Cohort 1, n=103), or harboring *FGFR2* mutations or amplifications (FGFR2$^{F/M/A}$) (Cohort 2, n=44). The study has completed enrolment (**Figure 1**).

FIGURE 1



FIDES-01 study design

METHODS

Patients

- Adults aged 18 years or older
- Locally advanced or metastatic iCCA or mixed histology tumors (combined hepatocellular-cholangiocarcinoma).
- FGFR2 positive tumor molecular status for fusions, mutations or amplifications
- 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 ARUP Laboratories (Salt Lake City, UT, USA) using the FISH ZytoLight® SPEC FGFR2 Dual Color Break Apart Probe kit (ZytoVision GmbH, Bremerhaven, Germany).
- NGS testing performed or commissioned by study sites using approved institutional standard protocols, or, as applicable, US FDA-approved and/or fully CE-marked industrial scale assays, or assays exempt by the In Vitro Diagnostics Directive (*Directive 98/79/EC*).
- Patients self-administered 300 mg derazantinib QD (28-day cycle) until disease progression, unacceptable toxicity, withdrawal of consent, or investigator choice.

Outcomes and Assessments

- Primary endpoint Cohort 1: 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.
- Primary endpoint Cohort 2: Progression-free survival at 3 months (PFS3) based on survival status or central radiology review (per RECIST 1.1).
- Safety assessments based on NCI CTCAE version 5.0.

Statistical Assumptions

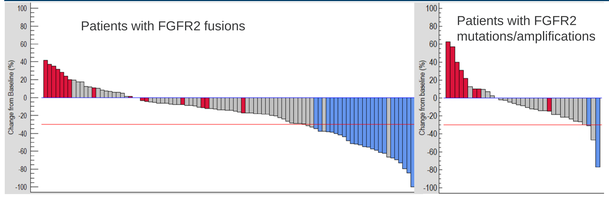
- Cohort 1: With an assumed ORR of 23%, a sample size of 100 patients would provide ~90% power to reject the null hypothesis at one-sided significance level 0.025, or equivalently to have the lower bound of confidence interval of ORR > 10%.
- Cohort 2: For PFS3 $p_0 \leq 0.45$ (H_0) is assumed and tested against a one-sided alternative, using a Simon's two-stage design. H_0 will be rejected if a PFS3 is observed in 25 or more out of 43 patients (type I error 0.0481, power ~0.80 if the true PFS3 rate is $p_1 = 0.65$).

TABLE 1

Patient demographics (ITT population)

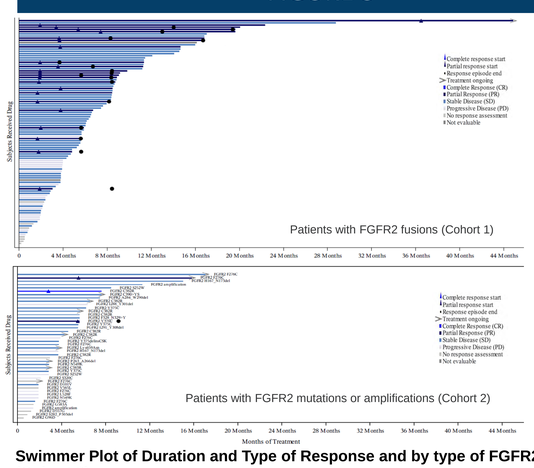
Variables	Category	Cohort 1 (FGFR2 fusions) (N=103)	Cohort 2 (FGFR2 mut/amp) (N=44)
Age	Median (range), years	56 (28-84)	63.5 (28-80)
	>65 years, n (%)	23 (22)	17 (39)
Gender, n (%)	Female	67 (65)	25 (57)
	Male	36 (35)	19 (43)
Baseline ECOG, n (%)	0	56 (54)	14 (32)
	≥1	47 (46)	30 (68)
Region, n (%)	North America	58 (56)	19 (43)
	Europe	45 (44)	25 (57)
Prior lines of treatment, n (%)	1	54 (52)	17 (39)
	2	31 (30)	17 (39)
	≥3	18 (17)	9 (20)
***FGFR2* genetic aberration, n (%)**	Fusion	103 (100)	
	Mutation	-	42 (95)
	Amplification	-	2 (5)
Ongoing study treatment		1 (1)	11 (25)

FIGURE 2



Waterfall Plot of Percent Change from Baseline in the Sum of Longest Diameters for Target Lesions based on central radiology review (patients with RECIST 1.1 baseline and post-baseline assessments)

FIGURE 3



Swimmer Plot of Duration and Type of Response and by type of FGFR2 mutation (Cohort 2)

RESULTS

Patients and treatment

- The safety and ITT population comprises 147 patients: 103 with FGFR2 fusions and 44 with FGFR2 mutations or amplifications.
- Patient demographics are shown in **Table 1**.
- Patients with FGFR2 fusions received a median number of 28-day treatment cycles of 7.0 compared to 5.0 treatment cycles in patients with FGFR2 mutations or amplifications with a dose intensity of ~95% in both cohorts.

Efficacy

- The objective response rate and disease control rate was 22.3% / 75.7% in patients with FGFR2 fusions and 6.8% / 63.6% in patients with FGFR2 mutations or amplifications.
- Median PFS and OS (months) were 7.8 / 17.2 in patients with FGFR2 fusions and 8.3 / 15.9 in patients with FGFR2 mutations or amplifications.

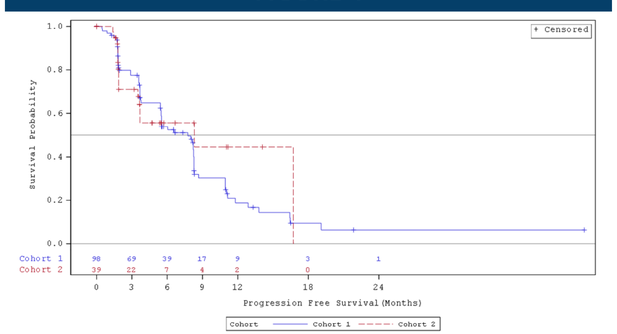
	Patients with FGFR2 fusions (Cohort 1) N=103, n (%)	Patients with FGFR2 mut/amp (Cohort 2) N=44, n (%)
Objective response rate	**23 (22.3)**	**3 (6.8)**
95% CI	14.7, 31.6	1.4, 18.7
Median duration of response (mo)†	6.4	5.6
Complete response	0	1* (2.3)
Partial reponse	23 (22.3)	2 (4.5)
Stable disease	55 (53.4)	25 (56.8)
Progressive disease	16 (15.5)	9 (20.5)
Not evaluable	1 (1.0)	0
No postbaseline assessment	8 (7.8)	7 (15.9)
Disease control rate	**78 (75.7)**	**28 (63.6)**
95% CI	66.3, 83.6	47.8, 77.6

*Complete response was observed in a patient with non-measurable disease only, per RECIST 1.1
†Kaplan-Meier estimate for Cohort 1, arithmetic median for Cohort 2

Safety

- Drug-related AEs are shown in **Table 2**. 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 (DILI) were assessed.
- Other FGFR-inhibitor-class effects reported as drug-related AEs were infrequent, mild to moderate and reversible:
  - Nail toxicities: 7.5%
  - Stomatitis: 2.0%
  - Retinal events 1.4%
  - Palmar-plantar erythrodysesthesia: 1.4%

FIGURE 4



Kaplan-Meier Plot of Progression-free Survival in Months (central review)

- Cohort 1: median PFS (95%CI): 7.8 mo (5.5, 8.3)
  PFS (95%CI) at: 6 mo: 53.9% (42.8, 63.7), 12 mo: 18.8% (10.1, 29.5)
- Cohort 2: median PFS (95%CI): 8.3 mo (3.5, 16.7)
  PFS (95%CI) at: 6 mo: 55.6% (36.0, 71.3), 12 mo: 44.5% (20.4, 66.1)

Abbreviations: AE: Adverse Event; ALT: Alanine Aminotransferase; amp : amplification ; AST: Aspartate Aminotransferase; CE: Conformité Européenne; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Events; DILI: Drug-Induced Liver Injury; ECOG: Eastern Cooperative Oncology Group; FDA: US Food and Drug Administration; FGFR: Fibroblast Growth Factor Receptor; iCCA: intrahepatic Cholangiocarcinoma; ITT: intent-to-treat ; mo: months; mut: mutation; NCI: National Cancer Institute; ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-free Survival; PFS3: PFS at 3 months; QD: once daily; RECIST: Response Evaluation Criteria In Solid Tumors; US: United States of America.

TABLE 2

Most common (≥10%) treatment-related adverse events

System Organ Class / Preferred Term	Safety Population (N=147), n (%) All Grades	Grade ≥3
Total patients with ≥ 1 adverse event	130 (88)	47 (32)
Metabolism and nutrition disorders		
Hyperphosphatemia / blood phosphorus increased†	52 (35)	6 (4)
Decreased appetite	16 (11)	1 (1)
General disorders and administration site conditions		
Fatigue / asthenia	49 (33)	6 (4)
Gastrointestinal disorders		
Nausea	47 (32)	1 (1)
Dry mouth	40 (27)	0
Diarrhea	29 (20)	2 (1)
Vomiting	25 (17)	0
Eye disorders		
Dry eye*	35 (24)	0
Vision blurred	18 (12)	1 (1)
Investigations		
AST increased†	34 (23)	15 (10)
ALT increased†	32 (22)	13 (9)
Nervous system disorders		
Dysgeusia	22 (15)	0
Skin and subcutaneous tissue disorders		
Alopecia	20 (14)	0

*Includes dry eye and xerophthalmia.
† Investigator reported adverse events of AST or ALT elevations

CONCLUSIONS

- **Derazantinib treatment results in meaningful clinical benefit for patients with FGFR2 genetic aberrations including FGFR2 fusions and FGFR2 mutations or amplifications**
- **Derazantinib has a well manageable adverse event profile, with a low incidence of nail toxicities, stomatitis, hand-foot syndrome and retinal FGFR-inhibitor class effects.**

DISCLOSURE — DISCLAIMER

Disclosures: M. Borad disclosures are listed on esmo.org. M. Dimova-Dobreva, M. Saulay, M. Engelhardt and A. Boncompagni are full-time employees of Basilea Pharmaceutica International Ltd, the Sponsor of study FIDES-01.
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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REFERENCES

1. Helsten T et al. (2016) The FGFR landscape in cancer: Analysis of 4,853 tumors by next-generation sequencing. Clin. Cancer Res. 22:259-267.
2. Babina IS, Turner NC (2017) Advances and challenges in targeting FGFR signalling in cancer. Nat. Rev. Cancer 17:318–332.
3. Cleary JM et al. (2021) FGFR2 extracellular domain in-frame deletions are therapeutically targetable genomic alterations that function as oncogenic drivers in cholangiocarcinoma. Cancer Discov. 11:2488-2505.
4. Silverman IM et al. (2021) Clinicogenomic analysis of FGFR2-rearranged cholangiocarcinoma identifies correlates of response and mechanisms of resistance to pemigatinib. Cancer Discover. 11:326-339.
5. Jain A et al. (2018) Cholangiocarcinoma with FGFR genetic aberrations: a unique clinical phenotype. JCO Precision Oncology 2:1-12.
6. Farshidfar F et al. (2017) Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-mutant molecular profiles. Cell Rep. 18: 2780–94.
7. Graham RP et al. (2014) Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Human Pathol. 45: 1630-1638.
8. Arai Y et al. (2014) Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatol. 59:1427–34.
9. Basilea, data on file (16-Apr-2020).
10. Jiao Y et al. (2013) Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. Nat. Genet. 45:1470–1473.
11. Hall TG et al. (2016) Preclinical activity of ARQ 087, a novel inhibitor targeting FGFR dysregulation. PLoS One 11:e0162594.
12. Papadopoulos KP et al. (2017) A Phase 1 study of ARQ 087, an oral pan-FGFR inhibitor in patients with advanced solid tumours. Br J Cancer 117:1592-1599.
13. Mazzaferro V et al. (2019) Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. Br. J. Cancer 120:165–171.
14. Droz Dit Busset M et al. (2020) Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: Pooled analysis of clinical trials and early access programs. Ann. Oncol. 31:S1231.
15. Droz dit Busset M et al. (2021) Derazantinib for patients with intrahepatic cholangiocarcinoma harboring FGFR2 fusions / rearrangements: Primary results from the Phase 2 study FIDES-01. Ann. Oncol. 32:S376-S381.