Tumor-agnostic efficacy and safety of lirafugratinib, a highly selective FGFR2 inhibitor, in patients with advanced solid tumors with *FGFR2* fusions or rearrangements: the ReFocus study

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KEY RESULTS

- Lirafugratinib demonstrated durable clinical activity and radiographic response across 14 solid tumor types harboring an *FGFR2* fusion or rearrangement (f/r; n=46; cORR: 37% [95% CI, 23.2–52.5]; mDoR: 7.3 months [95% CI, 3.7–12.9])
- The encouraging response rates and durability across refractory solid tumors are consistent with the robust efficacy previously demonstrated in patients with intrahepatic cholangiocarcinoma (CCA) with *FGFR2* f/r (cORR: 58–82%)[1,2]
- The differentiated safety profile (minimal off-isoform toxicity) was similar to what has been reported previously for lirafugratinib[1–3]
- These data validate *FGFR2* f/r as a tumor-agnostic target sensitive to selective *FGFR2* inhibition
- Pivotal development in solid tumors continues in the ongoing ReFocus study[4]

INTRODUCTION

- *FGFR2* f/r are oncogenic drivers in various solid tumors, and they are frequently found in intrahepatic CCA with an incidence of 10–20%[3,5–7]
- Lirafugratinib (RLY-4008), the first highly selective FGFR2i, is being evaluated in patients with advanced solid tumors with *FGFR2* alterations, including f/r, in the ongoing Phase 1/2 ReFocus trial (NCT04526106)[1–3,8]
- ReFocus previously showed promising preliminary efficacy in:
  - Pan FGFRi-naïve patients with CCA with *FGFR2* f/r (cORR at RP2D: 82.4% [95% CI, 56.6–96.2]; ORR across all doses: 57.9% [95% CI, 40.8–73.7])[8]
  - Patients with solid tumors other than CCA with *FGFR2* f/r (ORR: 35% [95% CI, 17–56]), amplifications (ORR: 24% [95% CI, 11–41]), or activating mutations (ORR: 13% [95% CI, 3–32])[1]
- Previous data have also shown selective FGFR2i and minimal off-isoform toxicity of lirafugratinib[2,3,8]
- Here, we report efficacy in patients with *FGFR2* f/r solid tumors other than CCA treated at the RP2D (70 mg QD) of lirafugratinib (data cutoff: June 26, 2024)

METHODS

- Eligible patients had advanced solid tumors with measurable disease per RECIST 1.1, *FGFR2* alteration per local assessment of tumor and/or blood, ECOG PS 0–2, and were refractory or intolerant to standard therapy
- The efficacy analysis focused on 46 FGFRi-naive patients with non-CCA solid tumors with *FGFR2* f/r who had ≥1 postbaseline tumor assessment or discontinued before having any postbaseline tumor assessment
- Tumor response was evaluated using RECIST 1.1 (investigator assessment)
- Safety was assessed in all patients in the trial (N=385) per NCI CTCAE v5.0
- All patients received lirafugratinib at RP2D (70 mg QD)

Figure 1. ReFocus: A Phase 1/2 open-label study (NCT04526106)

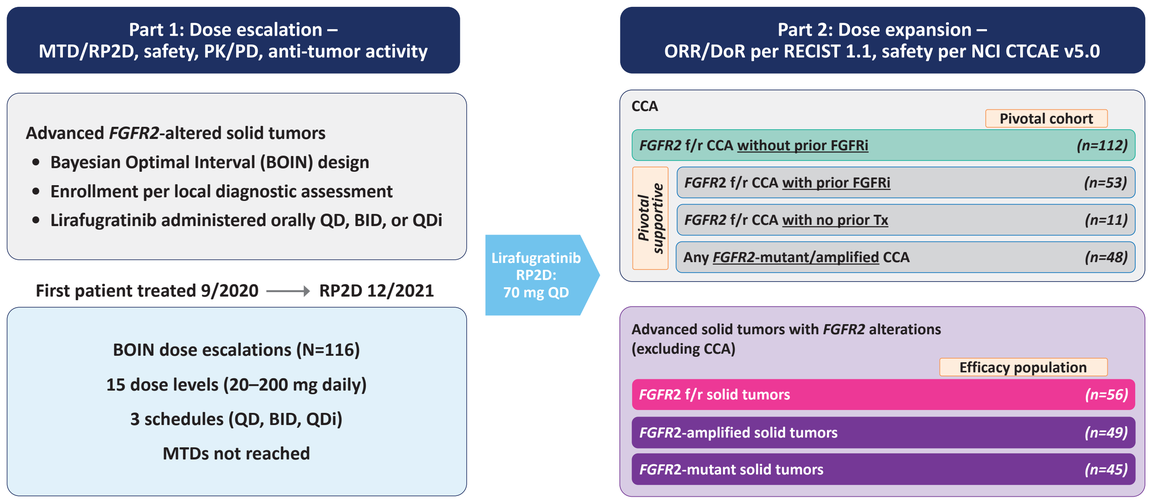


Table 1. Patient demographics and baseline characteristics

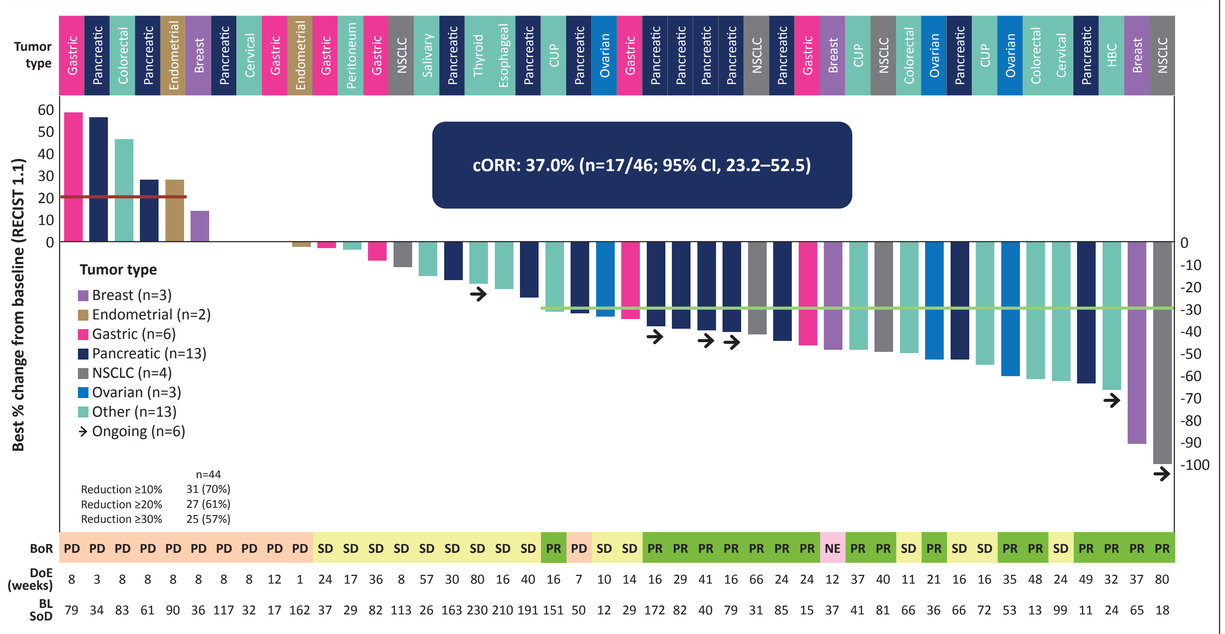
Parameter	Efficacy population (n=46)	Safety population (N=385)
Sex, n (%)		
Female	20 (43)	230 (60)
Age (years), median (range)	58 (33–82)	60 (20–84)
Race, n (%)		
White	20 (43)	215 (56)
Asian	7 (15)	64 (17)
Other/Unknown	19 (41)	106 (28)
ECOG PS, n (%)		
0	20 (43)	181 (47)
1	25 (54)	201 (52)
2	1 (2)	3 (1)
Number of prior lines of systemic therapy, median (range)	2 (1–14)	2 (0–14)
Number of prior lines of systemic therapy, n (%)		
0	0	7 (2)
1	12 (26)	129 (34)
2	17 (37)	109 (28)
≥3	17 (37)	140 (36)
Prior systemic therapy, n (%)		
Chemotherapy + ICI	16 (35)	122 (32)

Table 2. Efficacy by *FGFR2* f/r solid tumor type, excluding CCA (n=46)

Tumor type	Patients n	cORR %	cORR 95% CI	DoR Range (months)
***FGFR2* f/r solid tumor type (excl. CCA)**	46	37.0	(23.2–52.5)	1.6+ –16.6+
Pancreatic	13	46.2	(19.2–74.9)	1.6+ –11.5
Gastric	7	14.3	(0.4–57.9)	3.7
NSCLC	4	75.0	(19.4–99.4)	7.4+ –16.6
Colorectal	4	25.0	(0.6–80.6)	7.3
Ovarian	3	66.7	(9.4–99.2)	2.1+ –5.1
CUP	3	66.7	(9.4–99.2)	3.0–7.2
Breast	3	33.3	(0.8–90.6)	5.5
Endometrial	2	PD, PD	-	-
Cervical	2	SD, PD	-	-
HBC	1	PR	-	5.5+
Esophageal	1	SD	-	-
Peritoneum	1	SD	-	-
Salivary	1	SD	-	-
Thyroid	1	SD	-	-

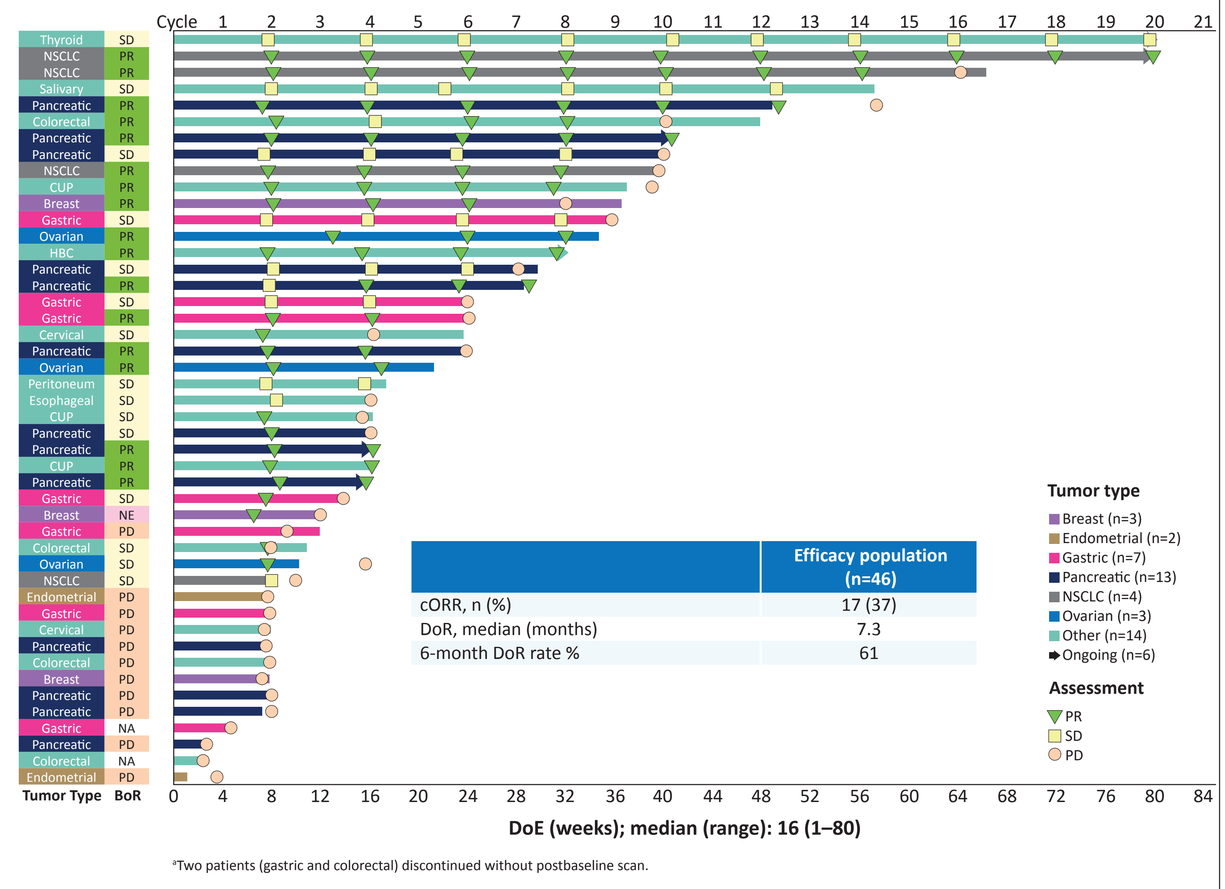
+: Denotes censored time.

Figure 2. Lirafugratinib showed a consistent efficacy signal across a range of non-CCA solid tumors with *FGFR2* f/r (n=44[a])



[a]Two patients (gastric and colorectal) discontinued without postbaseline scan.

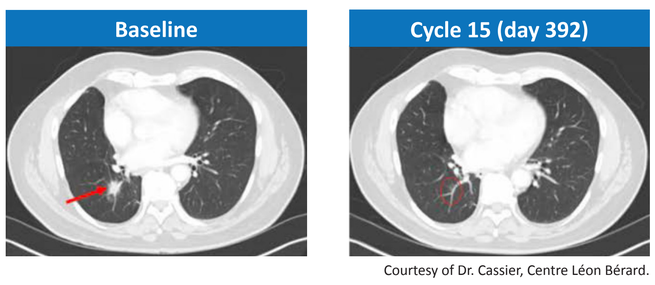
Figure 3. Responses were durable across non-CCA solid tumors with *FGFR2* f/r (n=44[a])



[a]Two patients (gastric and colorectal) discontinued without postbaseline scan.

Figure 4. Robust efficacy in *FGFR2* fusion mNSCLC

66-year-old male patient with mNSCLC (*FGFR2-POC1B* fusion) with prior surgery, PBC, and IO. On study, he had a PR at his first postbaseline assessment and further regression with continued treatment. His response is ongoing after >16 months (as of the data cutoff date; BoR=PR, including CR in the lung target lesion).



Courtesy of Dr. Cassier, Centre Léon Bérard.

SAFETY

- TRAEs were consistent with the known safety profile of lirafugratinib
- Most TRAEs were low-grade, reversible, and manageable on-target events
- Clinically significant FGFR2 off-isoform toxicities, such as hyperphosphatemia and diarrhea, were uncommon
- Overall, 258 patients (67%) had treatment-related dose interruptions, 206 (54%) had treatment-related dose reductions, and 8 (2%) had treatment-related discontinuations

Table 3. TRAEs were consistent with the known safety profile of lirafugratinib in all patients with non-CCA *FGFR2*-altered solid tumors (N=385)

	Parameter	Lirafugratinib 70 mg QD (N=385)	
	Grade	**Any, %**	**Grade ≥3, %**
Lirafugratinib TRAEs (≥15%)	Any	98	42
	Nail toxicities	71	8
	Stomatitis	66	12
	PPE	65	19
	Dry mouth	44	0
	Alopecia	38	0
	RPED	28	2
	Dry skin	25	0
	Dysgeusia	25	1
	Dry eye	24	0
	Fatigue	19	1
	Rash	19	3
	Hyperphosphatemia	18	0

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Abbreviations

BID, twice daily dosing; BL, baseline; BOIN, Bayesian Optimal Interval; BoR, best overall response; CCA, cholangiocarcinoma; CI, confidence interval; CR, complete response; CT, chemotherapy; CUP, carcinoma of unknown primary; DoE, duration of exposure; (m)DoR, median duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; f/r, fusion or rearrangement; FGFR(i/2), fibroblast growth factor receptor (inhibitor/2); HBC, hepatobiliary cancer; ICI, immune checkpoint inhibitor; IO, immunotherapy; MTD, maximum tolerated dose; NA, not applicable; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; NE, not evaluable; (m)NSCLC, (metastatic) non-small cell lung cancer; (c)ORR, (confirmed) objective response rate; PBC, platinum-based chemotherapy; PD, progressive disease; PK/PD, pharmacokinetics/pharmacodynamics; *POC1B*, POC1 centriolar protein B; PPE, palmar-plantar erythrodysesthesia syndrome; PR, partial response; QD, once daily; QDi, once daily dosing, 3 weeks on, 1 week off; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RP2D, recommended Phase 2 dose; RPED, retinal pigment epithelial detachment; SD, stable disease; SoD, sum of diameters; TRAE, treatment-related adverse event; Tx, treatment.

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