Clinical activity of lirafugratinib (RLY-4008), a highly selective FGFR2 inhibitor, in patients with advanced *FGFR2*-altered solid tumors: the ReFocus study

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Poster No. B033
Presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. October 11-15, 2023, Boston, MA, USA

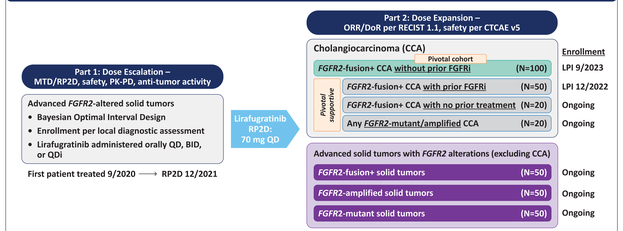
KEY RESULTS

- ReFocus data validate lirafugratinib as the first highly selective FGFR2 inhibitor active across oncogenic driver alterations
- Encouraging response rates and initial durability across refractory solid tumors augment robust efficacy previously demonstrated in cholangiocarcinoma (ORR 58%–82%)
- Solid tumors other than CCA:
  - *FGFR2* Fusion/Rearrangement: 35% ORR; duration of response range 1.9+–11.5 mo
  - *FGFR2* Amplification: 24% ORR; duration of response range 2.7+–12.8+ mo
  - *FGFR2* Mutation: 13% ORR; duration of response range 9.2–14.9+ mo in a subset of tumors across a heterogeneous mutation spectrum
  - Durable responses observed across 9 tumor types beyond CCA, with promising initial signal across *FGFR2* alterations in refractory HR+HER2- breast cancer (40% ORR; 70% DCR; N=10)
- Efficacy in *FGFR2*-altered solid tumors together with lirafugratinib's differentiated safety profile (minimal off-isoform toxicity) suggest broad therapeutic potential
- Pivotal development in cholangiocarcinoma and across solid tumors continues in the ongoing ReFocus study

INTRODUCTION

- *FGFR2* alterations, including fusions/rearrangements (f/r), amplifications and activating mutations, are oncogenic drivers in solid tumors including intrahepatic cholangiocarcinoma (CCA; fusions/rearrangements in 10–20%), gastric cancer (9%), gastroesophageal cancer (~4–8%), and breast cancer (~2–3%)[1–4]
- Lirafugratinib (RLY-4008), the first highly selective FGFR2 inhibitor, is being evaluated in patients with advanced solid tumors with *FGFR2* alterations in the ongoing Phase 1/2 ReFocus trial (NCT04526106)[5,6–8]
- ReFocus has so far shown promising preliminary efficacy in pan-FGFRi-naive patients with CCA with *FGFR2* f/r:[6–8]
  - Selective FGFR2 inhibition
  - Minimal off-isoform toxicity
- Confirmed ORR at RP2D: 82.4% (95% CI, 56.6, 96.2); ORR across all doses: 57.9% (95% CI, 40.8, 73.7)[7]
- We report preliminary data from patients in the ReFocus trial who have solid tumors other than CCA with *FGFR2* fusions and/or amplifications (data cut-off: August 23, 2023)

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



METHODS

- This efficacy analysis focused on 84 patients with *FGFR2* fusions, amplifications, or mutations by local testing who had measurable disease and ≥1 post-baseline tumor assessment or discontinued before having any post-baseline tumor assessment. Tumor response was evaluated using RECIST 1.1 (investigator assessment)
- The safety population included all patients with solid tumors that were not CCA (N=124, including FGFRi-pretreated and naive) who received ≥1 dose of lirafugratinib administered at the recommended phase 2 dose
- All patients received lirafugratinib at 70 mg QD

Table 1: Baseline demographics and tumor characteristics (patients with solid tumors)

Parameter	Efficacy population (N=84)	Safety population (N=124)
Sex, n (%)		
Female	51 (61)	74 (60)
Age (years), median (range)	**62 (33, 84)**	**62 (20, 84)**
Race, n (%)		
White	46 (55)	65 (52)
Asian	12 (14)	19 (15)
Other/Unknown	26 (31)	40 (32)
ECOG PS, n (%)		
0	31 (37)	49 (40)
1	52 (62)	70 (56)
2	1 (1)	2 (2)
Median (range) prior lines of systemic therapy, n (%)	**2.5 (0, 11)**	**3 (0, 14)**
0	2 (2)	2 (2)
1	14 (17)	23 (19)
2	26 (31)	35 (28)
≥3	42 (50)	64 (52)
Prior systemic therapy, n (%)		
Chemotherapy	79 (94)	118 (95)
FGFR inhibitor	0	21 (17)

Parameter	Efficacy population (N=84)
Tumor types, n (%)	
Gastric	26 (31)
Breast	14 (17)
Pancreatic	7 (8)
Ovarian	5 (6)
Colorectal	4 (5)
NSCLC	4 (5)
Endometrial	4 (5)
CUP	3 (4)
Salivary gland	2 (2)
Others*	15 (18)
FGFR2 oncogenic alteration, n (%) by local testing	
FGFR2 fusion or rearrangement	26 (31)
FGFR2 amplification**	34 (40)
FGFR2 mutation	24 (29)

*Includes ameloblastic, ampullary, cervical, duodenal, esophageal, fallopian, melanoma, orbital, thyroid cancers. Three patients in the safety population were missing ECOG at time of data cut.
**Amplification defined as *FGFR2* locus with copy number ≥8 in tumor tissue, or validated by next-generation sequencing. No amplification cutoff is defined for circulating tumor DNA.

Safety population includes 124 FGFR inhibitor (FGFRi)-naive and pretreated patients with tumors other than CCA, with *FGFR2* fusions, amplifications, or mutations by local testing, and who received ≥1 dose of lirafugratinib administered at the recommended phase 2 dose. Efficacy population includes 84 patients in the safety population who were FGFRi-naive, had measurable disease, and ≥1 post-baseline tumor assessment.

Figure 2: Lirafugratinib shows a consistent efficacy signal across a range of solid tumors with *FGFR2* f/r or amplification

Figure 3: Responses are durable across solid tumors with *FGFR2* f/r or amplification

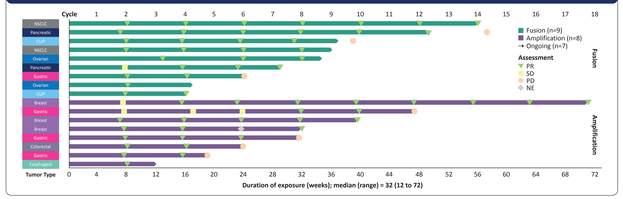
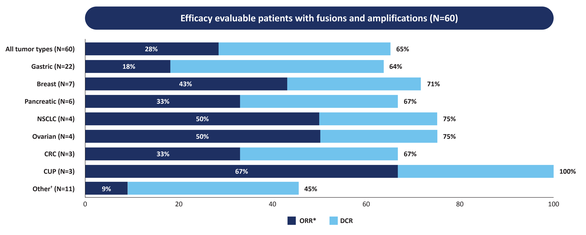


Table 2: Efficacy by *FGFR2* oncogenic alteration

Parameter	Fusion N=26	Amplification N=34	Mutation N=24
Best Overall Response, n (%)			
Partial response, n (%)*	**9 (35)**	**8 (24)**	**3 (13)**
Stable disease, n (%)	9 (35)	13 (38)	7 (29)
Progressive disease, n (%)	6 (23)	9 (26)	12 (50)
Not evaluable, n (%)**	2 (8)	4 (12)	2 (8)
ORR n (%); 95% CI	**9 (35); 17, 56**	**8 (24); 11, 41**	**3 (13); 3, 32**
DoR, months, min, max	**1.9+, 11.5**	**2.7+, 12.8+**	**9.2, 14.9+**
Disease control rate, n (%); 95% CI	**18 (69); 48, 86**	**21 (62); 44, 78**	**10 (42); 22, 63**

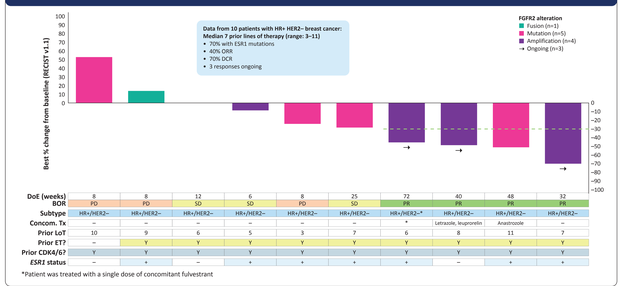
*Including 1 ongoing uPR in a patient with ovarian cancer with an *FGFR2* fusion, confirmed after data extraction; 1 ongoing uPR in a patient with esophageal cancer with *FGFR2* amplification; and 1 ongoing uPR in a patient with gastric cancer with *FGFR2* mutation.
**Including n=2 fusion: 1 patient who discontinued due to death before first post-baseline scan and 1 patient with 1 post-baseline scan who did not meet the minimum duration of >8 weeks from baseline for SD; n=4 amplification: 3 patients who discontinued before first post-baseline scan and 1 patient with 1 post-baseline scan who did not meet the minimum duration of >8 weeks from baseline for SD; n=2 mutation: 2 patients who discontinued before first post-baseline scan.
+: Response ongoing at time of data cut-off.

Figure 4: Responses across tumor types with *FGFR2* fusion or amplification



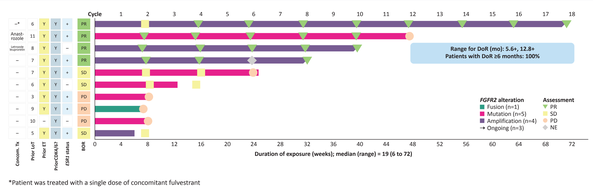
*ORR includes PRs and one ongoing uPR in a patient with ovarian cancer with *FGFR2* fusion confirmed after data extraction, and one ongoing uPR in a patient with esophageal cancer with *FGFR2* amplification.
†Other tumor types include: ampullary, cervical, endometrial, esophageal, fallopian, melanoma, salivary, thyroid.

Figure 5: Promising anti-tumor activity in heavily pretreated HR+ HER2– breast cancer with *FGFR2* alterations



*Patient was treated with a single dose of concomitant fulvestrant

Figure 6: Durable responses in heavily pretreated HR+ HER2– breast cancer with *FGFR2* alterations



*Patient was treated with a single dose of concomitant fulvestrant

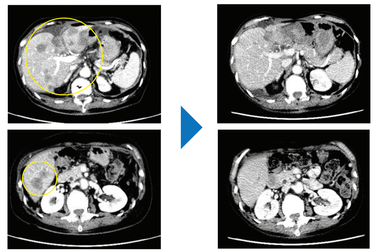
Figure 7: Marked response in a heavily pretreated patient with *FGFR2*-amplified HR+ breast cancer

Patient profile

- 66-year-old female with HR+/HER2– mBC
- *FGFR2* amplification (copy number: 10)
- 6 prior lines of therapy

Impact of lirafugratinib

- ctDNA cleared at Week 4
- Initial PR at Week 16, confirmed at Week 23
- Treatment ongoing at Week 72



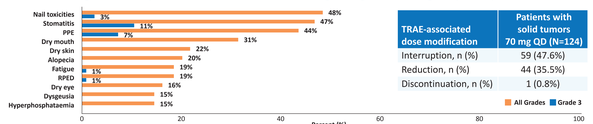
Courtesy of Dr Tai, NCC Singapore.
Preliminary data as of 23 August 2023

SAFETY PROFILE

- The TRAE profile is consistent with the known safety profile of lirafugratinib
- TRAEs reflect selective FGFR2 inhibition and were mostly low-grade, manageable with dose modification, and generally reversible on-target events
- FGFR off-isoform toxicities, such as hyperphosphatemia, were uncommon and transient

Figure 8: TRAEs are consistent with known safety profile of lirafugratinib

TRAEs occurring in ≥15% of patients with solid tumors receiving lirafugratinib 70 mg QD (N=124)



TRAE-associated dose modification	Patients with solid tumors 70 mg QD (N=124)
Interruption, n (%)	59 (47.6%)
Reduction, n (%)	44 (35.5%)
Discontinuation, n (%)	1 (0.8%)

Safety population: FGFRi-naive and FGFRi-pretreated non-CCA

Treatment ongoing: N=38 (30.6%)
Discontinued from study treatment N=86 (69.4%):
- Due to progressive disease N=73 (58.9%)
- Due to adverse event N=3 (2.4%)

No treatment-related grade 4/5 AEs

References

1. Helsten T, et al. *Clin Cancer Res*. 2016;22:259-67.
2. Gu W, et al. *Am J Cancer Res*. 2021;11:3893-3906.
3. Cho MT, et al. *Cancers (Basel)*. 2022;14:392.
4. Hierro C, et al. *Ann Oncol* 2017;28:1207-1216.
5. Subbiah V, et al. *Cancer Discov*. 2023 13 (9): 2012–2031.
6. Goyal L, et al. *Mol Cancer Ther* (2021) 20 (12_Supplement): P02-02
7. Hollebecque A, et al. *Annals of Oncology* (2022) 33 (suppl_7): S808-S869.
8. Borad MJ, et al. *J Clin Oncol*. 2023;41(suppl): 4009-4009.

Abbreviations

AE, adverse event; BID, twice daily dosing; BOR, best overall response; CCA, cholangiocarcinoma; CDK, cyclin-dependent kinase; CI, confidence interval; CRC, colorectal cancer; CTCAE: common terminology criteria for adverse events; CUP, carcinoma of unknown primary; DCR, disease control rate; DoR, duration of response; ESR1, estrogen receptor 1; FGFR, fibroblast growth factor receptor; FGFRi, fibroblast growth factor receptor inhibitor; f/r, fusion or rearrangement; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LPI, last patient in; LoT, line of treatment; mBC, metastatic breast cancer; MTD, maximum tolerated dose; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PK, pharmacokinetics; PPE, Palmar-plantar erythrodysesthesia; (u)PR, (unconfirmed) partial response; QD, once daily; QDi, once daily dosing, 3 weeks on, 1 week off; RECIST, Response Evaluation Criteria In Solid Tumors; RPED, retinal pigment epithelial detachment; RP2D, recommended Phase 2 dose; SD, stable disease; TEAE, treatment emergent adverse event; TRAE, treatment-related adverse event; Tx, treatment.

Acknowledgments

The authors would like to thank the study participants and their families, and study investigators and research staff at the ReFocus study sites.
This study was sponsored by Relay Therapeutics, Inc. Medical writing support was provided by Christine Elsner of BOLDSCIENCE Inc., funded by Relay Therapeutics.