First-in-human study of the highly selective FGFR2 inhibitor, RLY-4008, in patients with intrahepatic cholangiocarcinoma and other advanced solid tumors

Alison M. Schram[1], Suneel Kamath[2], Anthony El-Khoueiry[3], Mitesh J. Borad[4], Kabir Mody[5], Amit Mahipal[6], Lipika Goyal[7], Vaibhav Sahai[8], Oleg Schmidt[9], Jinshan Shen[9], Kai Yu Jen[9], Alicia Deary[9], Cori Ann Sherwin[9], Mahesh Padval[9], Beni Wolf [9], Vivek Subbiah[10]

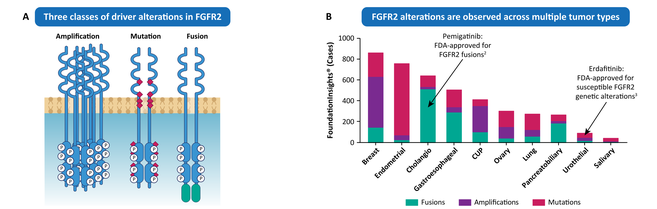
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH, USA; [3]USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [4]Mayo Clinic, Phoenix, AZ, USA; [5]Mayo Clinic, Jacksonville, FL, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]University of Michigan; Ann Arbor, MI, USA; [9]Relay Therapeutics, Inc., Cambridge, MA, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Poster TPS4165

BACKGROUND

- Fibroblast growth factor receptor 2 *(FGFR2)* is a bona fide solid tumor oncogene when activated via genomic rearrangement, gene amplification, or point mutation; however, no approved therapies target FGFR2 potently and selectively.[1]
- Several non-selective, pan-FGFR inhibitors (pan-FGFRi) are under development, including pemigatinib, erdafitinib, futibatinib, infigratinib, and derazantinib, but off-isoform toxicity (FGFR1-hyperphosphatemia; FGFR4-diarrhea) and on-target acquired resistance limit their utility.[2-6]
  - Pemigatinib is indicated for the treatment of previously treated, unresectable locally advanced, or metastatic cholangiocarcinoma with *FGFR2*-fusion or other rearrangements.[2]
  - Erdafitinib is indicated following chemotherapy for the treatment of locally advanced or metastatic urothelial cancer with susceptible *FGFR3* or *FGFR2* genetic alterations.[3]
- RLY-4008 is a novel, oral FGFR2 inhibitor designed to overcome the limitations of pan-FGFRi by potently and selectively targeting primary oncogenic FGFR2 alterations and acquired resistance mutations.
  - RLY-4008 demonstrates potent and selective efficacy against multiple primary and resistant tumor models, suggesting its potential for enhanced tolerability and broader efficacy than pan-FGFRi.
- Herein, we describe a first-in-human precision oncology study of RLY-4008 in solid tumor patients with FGFR2 alterations (NCT04526106).

Figure 1. Oncogenic FGFR2 alterations drive multiple cancers.



- Oncogenic activation of *FGFR2* occurs via genomic amplification, activating mutation, or chromosomal rearrangement/fusion, resulting in aberrant signaling that drives tumorigenesis (**Figure 1A**).[7]
- *FGFR2* driver alterations are observed across multiple tumor types, suggesting that FGFR2 inhibition has broad therapeutic potential (**Figure 1B**).[8,9]

Figure 2. Common toxicities and on-target resistance mutation limit pan-FGFRi dosing and efficacy.

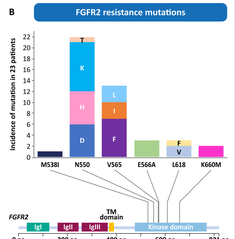
A

Clinical profile of current, non-selective inhibitors

Pan-FGFRi	Dosing	Notable Adverse Events*	Dose Modifications	Efficacy
Pemigatinib[2,11]	Discontinuous 2 weeks on/ 1 week off	Hyperphosphatemia 60% Diarrhea 47%/ Stomatitis 35% Nail toxicity 43% Dry skin 20%/PPE 15% Dry eye 35%/Retinal AE 4%	Dose interruption 43% Dose reduction 14% Discontinuation 9%	ORR: 36%, mDOR: 9.1 months Cholangiocarcinoma
Infigratinib[5]	Discontinuous 3 weeks on/ 1 week off	Hyperphosphatemia 77% Stomatitis 55% Eye disorders 68%/Retinal AE 17%	Not reported	ORR: 23%, mDOR: 5.0 months Cholangiocarcinoma
Futibatinib[4]	Continuous daily	Hyperphosphatemia 91% Diarrhea 28%/Stomatitis 20% Nail disorders 14% Dry skin 27%/PPE 21% Dry eye 15%/Retinal disorders 8%	Dose interruption 50% Dose reduction 54% Discontinuation 2%	ORR 43%, mDOR: 9.7 months Intrahepatic cholangiocarcinoma
Erdafitinib[3]	Continuous Daily based on phosphate levels	Hyperphosphatemia 76% Diarrhea 47% Onycholysis 41% Dry skin 34%/PPE 26% Dry eye 28%/Retinal AE 25%	Dose interruption 68% Dose reduction 53%	ORR 32%, mDOR: 5.4 months Urothelial carcinoma

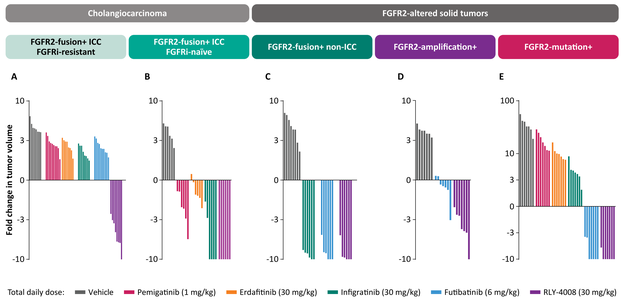
mDOR, median duration of response; ORR, objective response rate; pan-FGFRi, pan-FGFR inhibitors; PPE, palmar-plantar erythrodysesthesia.

B



On- and off-target toxicity, frequent dose modifications and on-target resistance mutations limit the clinical utility of pan-FGFRi. Hyperphosphatemia, diarrhea, skin, and ocular toxicity are common AE associated with pan-FGFRi treatment. Hyperphosphatemia and diarrhea likely represent off-isoform FGFR1/FGFR4-related toxicity (**Figure 2A**).[2-5,10,11] Acquired resistance mutations are commonly found at progression in patients with FGFR2 fusion-positive ICC treated with pan-FGFRi. The graph indicates the number of times the indicated mutant allele was detected in tissue or ctDNA in 23 patients who developed FGFR2 kinase domain mutations at progression on pan-FGFRi. N550 is a component of the "molecular brake" and V565 is the "gatekeeper" residue. Toxicity, dose modification, and acquired resistance mutations likely limit the efficacy of pan-FGFRi (**Figure 2B**).[7,10,12]

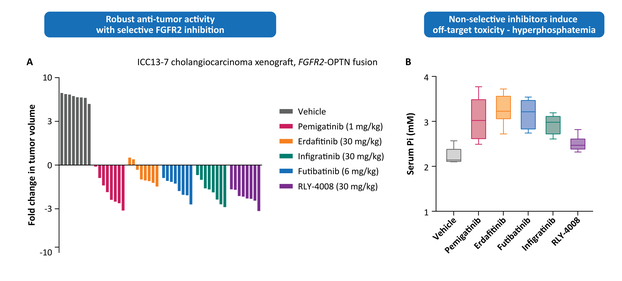
Figure 3. RLY-4008 has broad, tumor agnostic therapeutic potential across FGFR2 alterations and acquired resistance mutations.



CN, copy number; FGFRi, FGFR inhibitor; ICC, intrahepatic cholangiocarcinoma.

Preclinical tumor models validate the broad therapeutic potential of RLY-4008 across solid tumors with FGFR2 driver alterations, including those resistant to pan-FGFRi. ICC13-7 cholangiocarcinoma xenograft harboring *FGFR2*-OPTN fusion with V564F gatekeeper resistance mutation (**Figure 3A**); CC6702 cholangiocarcinoma xenograft with *FGFR2*-TTC28 fusion (**Figure 3B**); Gastric adenocarcinoma PDX, *FGFR2*-WDR11 fusion (**Figure 3C**); SNU-16 gastric carcinoma xenograft with FGFR2 amplification (FGFR2 copy number=39) (**Figure 3D**); and AN3 CA endometrial adenocarcinoma xenograft, with $FGFR2^{N549K}$ resistance mutation (**Figure 3E**). The graphs show end-of-treatment waterfall plots (change in tumor volume) for tumor models treated with 30 mg/kg RLY-4008 or the indicated pan-FGFRi used at doses equivalent to their recommended human doses.[14] RLY-4008 induces marked tumor regressions in all models regardless of indication or driver alteration, including models resistant to pan-FGFRi.

Figure 4. Selective FGFR2 inhibition with RLY-4008 is efficacious and precludes off-target toxicity.



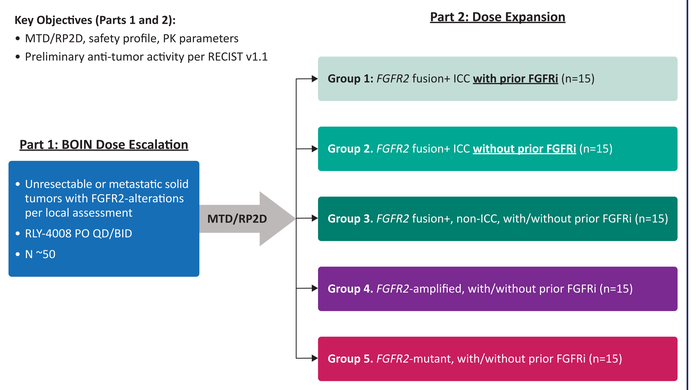
Pi, phosphate levels.

Anti-tumor activity (**Figure 4A**) and serum phosphate levels (**Figure 4B**) in a cholangiocarcinoma FGFR2-fusion xenograft model (ICC13-7 with *FGFR2*-OPTN fusion) treated with RLY-4008 or the indicated pan-FGFRi used at doses equivalent to their recommended human doses.[14] Note that only RLY-4008 induces tumor regression without altering serum phosphate levels ($P > 0.01$, one-way ANOVA). In contrast, all pan-FGFR inhibitors cause hyperphosphatemia (32%-47% increase in serum phosphate over vehicle) due to their inhibition of FGFR1 as observed in clinical studies.

STUDY DESIGN

RLY-4008-101 is an international, multi-center, open-label, first-in-human study of highly selective FGFR2-inhibitor, RLY-4008, in adult patients who have unresectable or metastatic solid tumors with FGFR2 alteration.

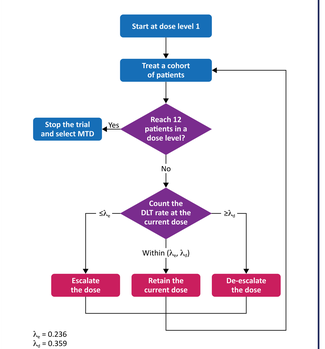
Figure 5. RLY-4008-101 study design (NCT04526106).



BID, twice a day; BOIN, Bayesian Optimal Interval; ICC, intrahepatic cholangiocarcinoma; MTD, maximum tolerated dose; pan-FGFRi, pan-FGFR inhibitors; PO, by mouth; PK, pharmacokinetics; RP2D, recommended phase 2 dose; QD, once a day.

DESIGN FEATURES OF THE RLY-4008-101 DOSE ESCALATION/DOSE EXPANSION

Figure 6. BOIN Decision Schema.



★ **Bayesian Optimal INterval (BOIN)[15] Dose Escalation**

- ★ Flexible cohort size with capacity for accelerated dose titration and additional accrual to tolerable dose levels
  - Enables rigorous assessment of safety, pharmacokinetics (PK), and anti-tumor activity to define optimal dose and schedule
- ★ Superior operating characteristics relative to traditional 3+3 design and continual reassessment designs
  - Minimizes treatment at subtherapeutic and overly toxic dose levels
  - More accurately determines maximum tolerated dose (MTD) via isotonic regression of observed dose-limiting toxicities (DLT) rate across all cohorts
  - Permits re-escalation to dose levels prematurely deemed too toxic (eg, 2 of 3 patients with DLT) based on subsequent cohort expansion data and prespecified toxicity rate and boundaries (escalation, λ_e; de-escalation, λ_d)

★ **MTD/RP2D Dose Expansion**

- ★ Defines preliminary efficacy in 5 groups defined by genotype and indication (**Figure 5**).

The BOIN escalation begins with the protocol-specified dose level 1. The decision to dose escalate, de-escalate, or maintain the current dose is made based on the observed DLT rate in relation to λ_e and λ_d. Dose escalation/de-escalation proceeds until 12 patients have been treated at a given dose level. The MTD is then determined via isotonic regression of the DLT rate across all cohorts. An RP2D ≤ MTD may be selected based on the observed safety, PK, and anti-tumor activity (**Figure 6**).

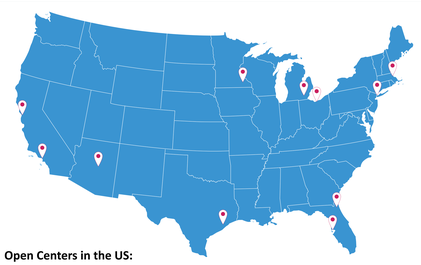
KEY ELIGIBILITY CRITERIA

- ≥ 18 years of age
- Histologically or cytologically confirmed diagnosis of unresectable ICC or other advanced solid tumors
- Measurable or evaluable disease by RECIST v1.1
- ECOG performance status 0-2
- Refractory, intolerant to, or declined standard therapy, including pan-FGFRi
- Documented FGFR2 fusion, amplification, or mutation in blood and/ or tumor per local assessment
- No history or ongoing, clinically significant corneal or retinal disorder
- No history of prolonged QT syndrome or Torsades de pointes
- No clinically significant, uncontrolled cardiovascular disease
- No uncontrolled/unstable CNS metastases or primary CNS tumor
- No known primary driver alteration other than FGFR2 that is amenable to approved targeted therapy (eg, EGFR, ALK, ROS, RET, HER2, PI3K, BRAF)
- No anticancer therapy within 14 days or 5 half-lives (whichever is shorter) prior to the first dose of study drug

STUDY ENROLLMENT AND CURRENT STATUS

The target enrollment for RLY-4008-101 is ~125 patients. Recruitment is ongoing at 11 study centers in the US. Study centers are expected to open in Europe, Asia and Australia in 2H 2021.

Figure 7. RLY-4008-101 US Study Centers.



Open Centers in the US:

- Mayo Clinic, Phoenix, AZ
- UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA
- USC/Norris Comprehensive Cancer Center, Los Angeles, CA
- Mayo Clinic, Jacksonville, FL
- Moffitt Cancer Center, Tampa, FL
- Massachusetts General Hospital, Boston, MA
- University of Michigan; Ann Arbor, MI
- Mayo Clinic, Rochester, MN
- Memorial Sloan Kettering Cancer Center, New York, NY
- Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH
- The University of Texas MD Anderson Cancer Center, Houston, TX

References

1. Katoh M. *Nat Rev Clin Oncol.* 2019;16:105-122.
2. Pemazyre (pemigatinib)[package insert]. Wilmington, DE: Incyte Corporation; 2020. Revised February 2021.
3. Balversa (erdafitinib)[package insert]. Horsham, PA: Janssen Products, LP; 2019. Revised April 2020.
4. Goyal L, et al. AACR 2021. Presentation CT010.
5. Javle MM, et al. *J Clin Oncol.* 2021;39(suppl 3):265.
6. Mazzaferro V, et al. *Br J Cancer.* 2019;120:165-171.
7. Babina IS, Turner NC. *Nat Rev Cancer.* 2017;17:318-332.
8. Porębska N, et al. *J Clin Med.* 2018;8:7.
9. Touat M, et al. *Clin Cancer Res.* 2015;21:2684-2694.
10. Goyal L, et al. *Cancer Discov.* 2017;7:252-263.
11. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21:671-684.
12. Goyal L, et al. 32nd EORTC/AACR/NCI Virtual Symposium. Abstract 49.
13. Varghese AM, et al. *JCO Precis Oncol.* 2021;5:44-50.
14. Casaletto J, et al. AACR 2021. Poster 1455.
15. Liu S, Yuan Y. *J R Stat Soc Ser C App Stat.* 2015;64:507-523.

Acknowledgments

The authors would like to thank the patients, their families, and all study team members involved in this study.

Editorial and graphics support was provided by Bio Connections (Variam Group LLC) and funded by Relay Therapeutics, Inc., Cambridge, MA.

Presented at the 2021 American Society of Clinical Oncology Annual Meeting, June 4–June 8, 2021. Virtual Format. For more information, please contact: ClinicalTrials@relaytx.com.