ReFocus: A Phase 1/2 study of the highly selective FGFR2 inhibitor RLY-4008 in patients with advanced solid tumors, including breast cancer

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RATIONALE FOR TARGETING *FGFR2* IN BREAST CANCER

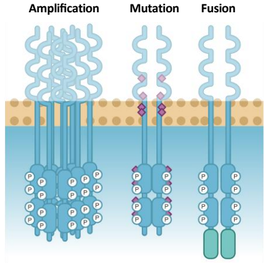
FGFR2 driver alterations in breast cancer

- Aberrant activation of FGFRs may occur through single-nucleotide variants, gene fusions, and copy number amplifications and occur across solid tumors (**Figure 1**)[1,2]
- In public datasets, *FGFR2* alterations are reported in 6–7% of breast cancer patients overall, with frequencies appearing to vary by disease subtype*[3]
  - Amplification of *FGFR2* is the most common *FGFR2* alteration seen in breast cancer[3]
  - *FGFR2* alterations vary by breast cancer subtype, with most seen in the ER+, luminal subtype[3]
- In previously published data from the ongoing ReFocus study (NCT04526106), RLY-4008, a highly selective, potent, irreversible FGFR2 inhibitor has shown promising efficacy in patients with *FGFR2*-driven cholangiocarcinoma.[4] In the non-cholangiocarcinoma cohort there were four patients with breast cancer
  - One patient with breast cancer, whose tumor had the oncogenic *FGFR2* N550K mutation, achieved a confirmed PR per RECIST 1.1 with 70 mg QD RLY-4008[5]
  - Two other patients with breast cancer, whose tumors had an *FGFR2* amplification and the *FGFR2* K660E oncogenic mutation, respectively, had a reduction in tumor size with RLY-4008[5]

*Includes *FGFR2* overexpression

Figure 1. Oncogenic *FGFR2* alterations drive multiple types of cancer

Three types of driver alterations in *FGFR2*[1]



Adapted from Babina et al.[1]

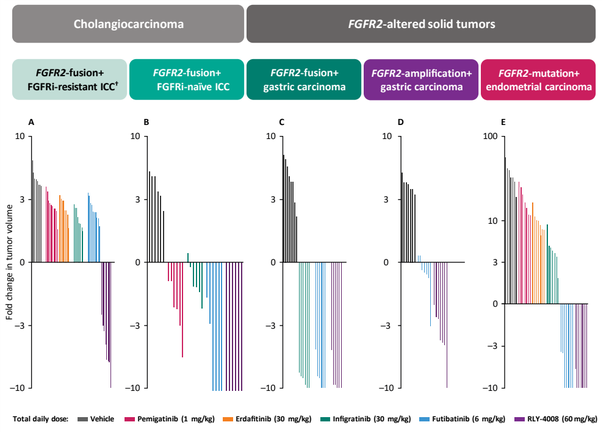
FGFR2 alterations may result as a bypass mechanism of resistance to endocrine and CDK4/6 inhibition

- Growing clinical evidence suggests enrichment of *FGFR2* alterations in hormone receptor-positive tumors resistant to CDK4/6 inhibitors (with or without endocrine therapy):
  - Recent data identified *FGFR2* amplification in 3/60 (5%) of biopsy samples from patients who were resistant to endocrine therapy[6]
  - In another study, ctDNA analysis was performed on 34 patients who progressed on endocrine therapy and CDK4/6 inhibitors. *FGFR2* alterations were detected in four patients: two had *FGFR2* amplification, and two had mutations[7]
- These findings suggest potential roles for *FGFR2*-targeted therapy in overcoming resistance to combination endocrine and CDK4/6 therapy
- There are no *FGFR2*-targeted therapies approved for breast cancer, highlighting an unmet medical need in these treatment-refractory patients

RLY-4008: A NOVEL, HIGHLY SELECTIVE FGFR2 INHIBITOR

- RLY-4008 is a highly selective, potent, irreversible FGFR2 inhibitor designed based on insights into the differences in conformational dynamics between FGFR2 and other FGFRs. This approach has delivered a degree of selectivity not previously achieved for FGFR2, with the potential to overcome the limitations of pan-FGFR inhibitors. RLY-4008 is the first known highly selective FGFR2 small-molecule inhibitor to reach the clinic
- Tumor models demonstrate the broad therapeutic potential of RLY-4008 across *FGFR2*-driven solid tumors. Marked reductions in tumor volume were seen with RLY-4008 in:[8]
  - ICC13-7-FGFR2^{V565F} cholangiocarcinoma xenograft with *FGFR2-OPTN* fusion with V565F gatekeeper resistance mutation (**Figure 2A**)
  - CC6702 cholangiocarcinoma xenograft with *FGFR2-TTC28* fusion (**Figure 2B**)
  - Gastric adenocarcinoma xenograft with *FGFR2-WDR11* fusion (**Figure 2C**)
  - SNU-16 gastric carcinoma xenograft with *FGFR2* amplification (*FGFR2* copy number=39) (**Figure 2D**)
  - AN3 CA endometrial adenocarcinoma xenograft, with *FGFR2*^{N549K} resistance mutation (**Figure 2E**)

Figure 2. Preclinically, RLY-4008 has broad, tumor-agnostic therapeutic potential across *FGFR2* alterations and acquired resistance mutations[8]



†RLY-4008 was dosed at 30 mg/kg QD in this tumor model.
BID, twice daily; FGFRi, FGFR inhibitor; ICC, intrahepatic cholangiocarcinoma; QD, once daily.
RLY-4008 was dosed at 30 mg/kg BID in all tumor models except for in *FGFR2*-fusion+, FGFRi-resistant ICC, in which RLY-4008 was dosed at 30 mg/kg QD. Pan-FGFRi were used at doses equivalent to their recommended human doses.

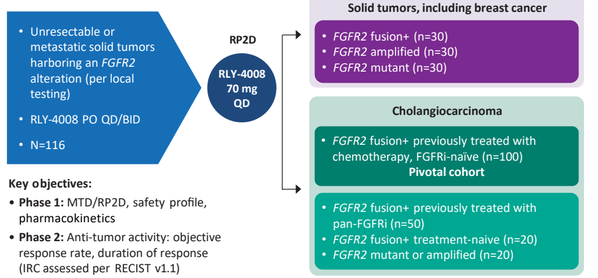
Limitations of pan-FGFR inhibitors

- Various pan-FGFRi are in clinical development; to date, four agents are approved in solid tumors, but none are indicated for the treatment of breast cancer[9–12]
- In Phase 1 studies, a reduction in tumor burden or stable disease has been observed in some patients with breast cancer, although patient numbers are very low[13–15]
- The utility of pan-FGFRi has been limited by off-isoform toxicity, such as hyperphosphatemia – caused by inhibition of FGFR1 – and acquired resistance mutations in *FGFR2*[16]

ReFocus: STUDY DESIGN

- ReFocus (NCT04526106) is an international, multicenter, open-label, first-in-human study of the highly selective FGFR2 inhibitor, RLY-4008, in adults with unresectable or metastatic solid tumors harboring an *FGFR2* alteration (**Figure 3**)

Figure 3. ReFocus: An open-label Phase 1/2 study of RLY-4008. Pivotal cohort in cholangiocarcinoma; additional cohorts in patients with advanced, *FGFR2*-driven solid tumors, including breast cancer



Key objectives:
- **Phase 1:** MTD/RP2D, safety profile, pharmacokinetics
- **Phase 2:** Anti-tumor activity: objective response rate, duration of response (IRC assessed per RECIST v1.1)

BID, twice a day; FGFRi, FGFR inhibitors; IRC, independent review committee; MTD, maximum tolerated dose; PO, by mouth; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.

KEY ELIGIBILITY CRITERIA

Inclusion criteria

- ≥18 years of age
- Histologically or cytologically confirmed diagnosis of unresectable intrahepatic cholangiocarcinoma or other advanced solid tumors, **including breast cancer**
- Measurable disease by RECIST v1.1
- ECOG performance status 0 or 1
- Refractory, intolerant to, or declined standard therapy, including pan-FGFRi
- Documented *FGFR2* fusion, copy number amplification, or mutation in blood and/or tumor per local assessment

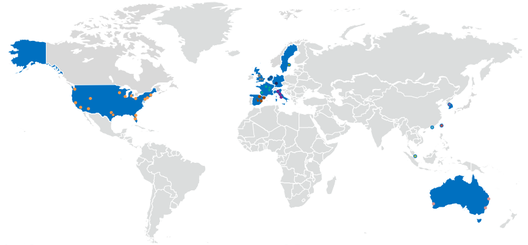
Exclusion criteria

- 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 anticancer therapy within 14 days or five half-lives (whichever is shorter) prior to the first dose of the study drug. Adjuvant hormonal therapy (e.g. previously treated breast cancer) is not exclusionary

STUDY ENROLLMENT AND CURRENT STATUS

- The target enrollment for ReFocus is 400 patients across all cohorts, including patients with breast cancer
- Recruitment is ongoing at sites in the United States, Europe, Asia, and Australia (**Figure 4**).

Figure 4. Open study sites for the ReFocus study



- **United States**
  - Mayo Clinic, Scottsdale, AZ
  - UCSF Helen Diller Family Comprehensive Cancer Center, CA
  - USC Norris Cancer Center, CA
  - Mayo Clinic Jacksonville, FL
  - H. Lee Moffitt Cancer Center and Research Institute, FL
  - University of Chicago Medical Center, IL
  - Massachusetts General Hospital, MA
  - University of Michigan, MI
  - Mayo Comprehensive Cancer Center, MN
  - Memorial Sloan Kettering Cancer Center, NY
  - Cleveland Clinic Foundation, OH
  - Fox Chase Cancer Center, PA
  - University of Texas MD Anderson Cancer Center, TX
  - Texas Oncology-Baylor Charles A. Sammons Cancer Center, TX
  - University of Utah Huntsman Cancer Institute, UT
  - Virginia Mason Medical Center, WA
- **Hong Kong**
  - Queen Mary Hospital
- **Republic of Korea**
  - Samsung Medical Center – PPDS, Seoul Teugbyeolsi
  - Asan Medical Center – PPDS, Seoul Teugbyeolsi
  - Seoul National University Hospital, Seoul Teugbyeolsi
- **Singapore**
  - National Cancer Center
- **Taiwan**
  - China Medical University Hospital
- **France**
  - Centre Georges François Leclerc, Côte-d'Or
  - EDOG – Institut Bergonie – PPDS, Gironde
  - Centre Léon Bérard, Rhône
  - Institut Gustave Roussy, Val-de-Marne
- **Germany**
  - University of Heidelberg, Heidelberg
- **Italy**
  - Istituto Nazionale Tumori Regina Elena, Lazio
  - Istituto Europeo Di Oncologia, Lombardia
  - Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" – IRST S.r.l – PPDS, Emilia-Romagna
- **Netherlands**
  - Nederlands Kanker Instituut Antoni Van Leeuwenhoek Ziekenhuis, Noord-Holland
  - Erasmus Medical Center, Rotterdam
- **Spain**
  - Hospital Universitario Vall d'Hebron – PPDS, Barcelona
  - START MADRID_Hospital Universitario Fundacion Jimenez Diaz, Madrid
  - START MADRID_Hospital Universitario HM Sanchinarro – CIOCC, Madrid
  - Clinica Universidad Navarra, Navarra
  - Hospital Clinico Universitario de Valencia, Valencia
- **Sweden**
  - Karolinska Universitetssjukhuset, Solna
- **UK**
  - The Christie NHS Foundation Trust, Lancashire
  - Sarah Cannon Research Institute, London
  - University College London Hospitals, London
- **Australia**
  - St. Vincent's Hospital Sydney, New South Wales
  - Icon Cancer Care South Brisbane, Queensland
  - Linear Clinical Research Ltd, Western Australia

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Abbreviations

BID, twice daily; CDK, cyclin-dependent kinase; CNS, central nervous system; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor; ICC, intrahepatic cholangiocarcinoma; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.