First Results of RLY-4008, a Potent and Highly Selective FGFR2 Inhibitor in a First-in-Human Study in Patients with FGFR2-Altered Cholangiocarcinoma and Multiple Solid Tumors

Lipika Goyal1, Mitesh J. Borad2, Vivek Subbiah3, Amit Mahipal4, Suneel Kamath5, Kabir Mody6, Robin Kate Kelley7, Richard Kim8, Vaibhav Sahai9, Anthony El-Khoueiry10, Efrat Dotan11, Oleg Schmidt-Kittler12, Jinshan Shen12, Kai Yu Jen12, Alicia Deary12, Wei Guo12, Mahesh Padval12, Cori Ann Sherwin12, Charles Ferte12, Beni Wolf12 and Alison M. Schram13

1Massachusetts General Hospital, Boston, MA; 2Mayo Clinic, Phoenix, AZ; 3The University of Texas M.D. Anderson Cancer Center, Houston, TX; 4Mayo Clinic, Rochester, MN; 5Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH; 6Mayo Clinic, Jacksonville, FL; 7UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; 8Moffitt Cancer Center, Tampa, FL; 9University of Michigan; Ann Arbor, MI; 10USC/Norris Comprehensive Cancer Center, Los Angeles, CA; 11Fox Chase Cancer Center, Philadelphia, PA; 12Relay Therapeutics, Inc., Cambridge, MA; 13Memorial Sloan Kettering Cancer Center, New York, NY
Speaker Name: Dr. Lipika Goyal

I have the following financial relationships to disclose:

Consultant for: Alentis Therapeutics AG, Black Diamond, Basilea, Exelixis, H3Biomedicine, Incyte Corporation, QED Therapeutics, Servier, Sirtex Medical Ltd, Taiho Oncology Inc.

Grant/Research support from: Adaptimmune, Bayer, Eisai, Merck, Macrogenics, Genentech, Novartis, Incyte, Eli Lilly, Loxo Oncology, Relay Therapeutics, QED, Taiho Oncology, Leap Therapeutics, Bristol Meyers Squibb, Nucana, Servier.

Data Safety Monitoring Committee: AstraZeneca.

I will not discuss off label use and/or investigational use in my presentation.
FGFR2 is a clinically validated therapeutic target

3 key oncogenic FGFR2 alterations

FGFR2 mediates key cellular functions including cell survival, proliferation, differentiation, and migration

FGFR2 alterations drive multiple solid tumors*

FGFR2 alterations represent ~8K-20K patients in the US per year

FGFR2-altered cancers remain a high medical need

Current FDA Accelerated Approvals (AA) for FGFR2-Altered Cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>FGFR2 Fusion &amp; Rearrangement</th>
<th>FGFR2 Oncogenic Mutation</th>
<th>FGFR2 Amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFRi-naïve Cholangiocarcinoma</td>
<td>Pemigatinib</td>
<td>Infigratinib</td>
<td></td>
</tr>
<tr>
<td>FGFRi-naïve Urothelial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFRi-resistant Cholangiocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other FGFR2-altered solid tumors</td>
<td></td>
<td></td>
<td>No effective targeted therapy</td>
</tr>
</tbody>
</table>

*Data source: FoundationInsights® database, using 8 copies as the threshold for amplification, and including only mutations with known or likely functional significance. Cholangio, cholangiocarcinoma; CUP, carcinoma unknown primary; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor.
RLY-4008 is the first highly selective irreversible FGFR2 inhibitor

**RLY-4008 is highly selective for FGFR2 over FGFR1, FGFR3, and FGFR4**

**RLY-4008 potently and selectively inhibits FGFR2 driven cellular proliferation**

*Indicates that IC$_{50}$ > 1000 nM (cellular assay)

IC$_{50}$ half-maximal inhibitory concentration; A, amplification; F, fusion; M, mutation; D, dependent as per DepMap.

RLY-4008 was designed to selectively bind to FGFR2 to avoid off-isoform toxicities (FGFR1 – hyperphosphatemia; FGFR4 – diarrhea)
RLY-4008 has potent *in vivo* antitumor activity against primary FGFR2 alterations and common resistance mutations

A. FGFR2-fusion+ ICC
   - FGFRi-naïve

B. FGFR2-fusion+ ICC
   - FGFRi-resistant (V565F mutation)

C. FGFR2-fusion+ non-ICC

D. FGFR2 activating mutation+
   - (N550K mutation)

E. FGFR2-amplification+
   - (Copy Number=39)

**Note:** 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.

- CC6702 cholangiocarcinoma xenograft with FGFR2-TTC28 fusion (Figure A); ICC13-7 cholangiocarcinoma xenograft harboring FGFR2-OPTN fusion with an V565F gatekeeper resistance mutation introduced by CRISPR (Figure B); Gastric adenocarcinoma PDX, FGFR2-WDR11 fusion (Figure C); AN3 CA endometrial adenocarcinoma xenograft, with FGFR2 N550K activating mutation (Figure D); and SNU-16 gastric carcinoma xenograft with FGFR2 amplification (FGFR2 copy number=39) (Figure E).

ICC: Intrahepatic cholangiocarcinoma.
**RLY-4008 first-in-human (FIH) study design**

**Key Objectives:**
MTD/RP2D, safety, pharmacokinetics, biomarkers (ctDNA, tumor markers), preliminary anti-tumor activity

**Part 1: Dose Escalation - Enrolling**
- Unresectable or metastatic solid tumors
- FGFR2-alterations per local assessment (tumor tissue or blood)
- Both FGFRi-naïve & FGFRi-treated allowed

*First patient treated in Sept 2020*

**Part 2: Dose Expansion – Not Started**
- FGFR2-fusion+ intrahepatic cholangiocarcinoma without prior FGFRi
- FGFR2-fusion+ intrahepatic cholangiocarcinoma with prior FGFRi
- FGFR2-fusion+, non intrahepatic cholangiocarcinoma with/without prior FGFRi
- FGFR2-mutant, advanced solid tumors with/without prior FGFRi
- FGFR2-amplified, advanced solid tumors with/without prior FGFRi

Orally dosed; QD and BID schedules explored using the Bayesian Optimal Interval Escalation (BOIN) design; Starting dose was 50 mg BID

MTD, maximum tolerated dose; RP2D: recommended phase 2 dose.
# RLY-4008 FIH Study: Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29 (59%)</td>
</tr>
<tr>
<td>Male</td>
<td>20 (41%)</td>
</tr>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>60 (23-87)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (78%)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>46 (94%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>Prior lines of systemic therapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>2</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>3+</td>
<td>29 (59%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor types, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma (CCA)</td>
<td>40 (82%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Prostate adenocarcinoma</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Soft-tissue sarcoma*</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Uterus</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Melanoma (rectum)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Baseline sum of target lesions (RECIST v1.1, cm), median (range)</strong></td>
<td>9.3 (1.4-22.0)</td>
</tr>
<tr>
<td><strong>FGFR2 oncogenic alteration, n (%)</strong></td>
<td>48/49 (98%)</td>
</tr>
<tr>
<td>FGFR2 fusion</td>
<td>32 (67%)</td>
</tr>
<tr>
<td>FGFR2 mutation</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>FGFR2 amplification</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>


*Soft tissue sarcoma patient enrolled in dose escalation without a documented oncogenic FGFR2 genomic alteration.

Preliminary data as of 09-Sept-2021
**Cholangiocarcinoma population**

**FGFR2-Fusion**

- N=32 (80%)

**FGFR2-Mutation**

- N=6 (15%)

**FGFR2-Amplification**

- N=2 (5%)

---

**FGFR2 Resistance Mutations at Baseline in Fusion+ Patients**

N=25 evaluable by ctDNA

<table>
<thead>
<tr>
<th>FGFR2-Fusion; FGFRi-naïve (n=6)</th>
<th>FGFR2-Fusion 1 prior FGFRi* (n=12)</th>
<th>FGFR2-Fusion 2+ prior FGFRi* (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N550X (molecular brake)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>V565X (gatekeeper)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>E566X (molecular brake)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>L618X</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total patients with any FGFR2 resistance mutation

- 1 of 6 (17%)
- 5 of 12 (42%)
- 6 of 7 (86%)

* Note: all patients discontinued the prior FGFR inhibitor lines of therapy because of disease progression.

ctDNA, circulating DNA; FGFRi, fibroblast growth factor receptor inhibitor.

Preliminary data as of 09-Sept-2021
RLY-4008 FIH Study: Pharmacokinetics and predicted receptor occupancy support QD dosing

RLY-4008 shows ≥ 85 % predicted median receptor occupancy (based on modeling) across all dose levels
Half-life ~15-30h supports QD dosing

Predicted receptor occupancy: projected level of engagement of oncogenic FGFR2 at given plasma concentration. Error bars correspond to the standard deviation measures. BID, twice a day; QD, once a day; RO, receptor occupancy.
FGFR1 sparing: Hyperphosphatemia: n=9/49 (18%) patients, all low grade (Grade 1-2). Only 1/49 (2%) patients was prescribed phosphate binders.

FGFR4 sparing: Diarrhea: n=3/49 (6%) patients, all low grade (Grade 1-2) and unrelated.
**RLY-4008 FIH Study: Dose-limiting toxicities (DLTs)**

**BID Schedule (deprioritized)**

<table>
<thead>
<tr>
<th>Dose (mg BID)</th>
<th>DLT evaluable patients* (n)</th>
<th>Dose Limiting Toxicity**</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>3</td>
<td>Gr 3 PPE (1) Gr 3 indirect hyperbili# (1)</td>
</tr>
<tr>
<td>50</td>
<td>7</td>
<td>Gr 2 stomatitis (1) Gr 2 rash (1)</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>Gr 3 stomatitis (1)</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

**QD Schedule (ongoing)**

<table>
<thead>
<tr>
<th>Dose (mg QD)</th>
<th>DLT evaluable patients** (n)</th>
<th>Dose Limiting Toxicity**</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>Gr 2 retinopathy (1)</td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

MTD not reached per protocol, RP2D selection is ongoing with the QD dosing schedule

---

*28-day DLT period (per protocol); **DLT evaluable patients represent patients treated in the escalation and in the enrichment given cohorts per BOIN design; #Patient with preexisting Gilbert’s disease.

BOIN, Bayesian Optimal Interval Design; PPE, Palmar-Plantar erythrodysoesthesia.

Preliminary data as of 09-Sept-2021
RLY-4008 FIH Study: Treatment-emergent adverse events (TEAEs) ≥ 20%

Most AEs are low-grade

TEAEs profile consistent with FGFR1- and FGFR4-sparing

Retinopathy/Retinal Pigment Epithelial Detachment (RPED): 7 cases [BID n=4/17 (24%); QD n=3/32 (9%)]. All events were Gr 1-2, self-limiting or resolved upon treatment interruption

No Grade 4-5 AE

*Included preferred terms of nail disorder, nail discoloration, nail ridging, onychalgia, onychoclasis, onycholysis, onychoma desis, paronychia.

**Included preferred terms of retinal pigment epithelium detachment, retinopathy, blurred vision, subretinal fluid.

Preliminary data as of 09-Sept-2021
RLY-4008 FIH Study: RLY-4008 induces radiographic tumor regression across FGFR2 alterations

N=38 evaluable patients with FGFR2 altered solid tumors

66% patients (25/38) exhibit radiographic tumor reductions of ≥ 10%

Preliminary efficacy observed across FGFR2 alterations (fusions, mutations, amplifications)

*Confirmed PR; #Confirmed PR after data cut; ^PR pending confirmation.

FGFRi, fibroblast growth factor receptor inhibitor.

Preliminary data as of 09-Sept-2021
RLY-4008 induces radiographic tumor regression across FGFR2 alterations, FGFR inhibitor status, tumor types and dose levels

A. Across FGFR2 alteration

B. Across prior FGFR inhibitor status

C. Across tumor type

D. Across starting dose level

FGFRi, fibroblast growth factor receptor inhibitor.
N=48 patients

26/48 patients (54%) ongoing on treatment
- Most treatment discontinuations (73%) due to Progressive Disease

Duration on treatment: range 4-45 weeks

FGFRi, fibroblast growth factor receptor inhibitor; NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease.

Preliminary data as of 09-Sept-2021
Preliminary efficacy of RLY-4008 across specific subpopulations

1. FGFR2 fusion+ cholangiocarcinoma, FGFR inhibitor-naïve

2. FGFR2 fusion+ cholangiocarcinoma, FGFR inhibitor-pretreated

3. FGFR2 mutant or amplified solid tumors

FGFRi, fibroblast growth factor receptor inhibitor; NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease.
RLY-4008 induces radiographic tumor regression in FGFR inhibitor-naïve FGFR2-fusion+ cholangiocarcinoma

3/6 patients exhibit a confirmed PR

*Confirmed PR; #Tumor resection after data cut off.
FGFRi, fibroblast growth factor receptor inhibitor PR, partial response.

3/6 patients ongoing on treatment, and 1 patient had resection in curative intent

Preliminary data as of 09-Sept-2021
35-year-old male with FGFR2-FLIP1 fusion ICC. Prior treatment: Gemcitabine/Cisplatin
70 mg QD dosing (no dose modification). Relevant AEs: Gr 1 dry eye, Gr 1 onycholysis, Gr 2 stomatitis

RLY-4008 results in near complete regression in a patient with FGFR2-fusion, FGFRi-naïve cholangiocarcinoma, leading to surgical resection

Confirmed PR (near CR) -83% by RECIST v1.1
Patient underwent resection in curative intent

Baseline

Target Lesion 1 (liver lesion)
31.9 mm
Lesion not detected

Target Lesion 2 (liver lesion)
13.2 mm
Lesion not detected

Target Lesion 3 (lymph node)
19.0 mm
19.1 mm

Cycle 7

31.9 mm → Not detected
13.2 mm → Not detected
19.0 mm → 10.2 mm

Preliminary data as of 09-Sept-2021
RLY-4008 exhibits activity in pan-FGFR inhibitor resistant FGFR2-fusion cholangiocarcinoma regardless of FGFR2 resistance mutations

13/21 (62%) patients with tumor reduction > 10%

7/10 (70%) patients with FGFR2 resistance mutations at baseline had all identified resistance mutations rendered undetectable at C2D1

cDNA, circulating DNA; FGFRi, fibroblast growth factor receptor inhibitor.
RLY-4008 produces tumor regression in a patient with FGFR2-fusion+ cholangiocarcinoma pretreated with futibatinib

51-year-old female with FGFR2-CIT fusion ICC. Prior treatments: Gemcitabine/Cisplatin, Futibatinib

Antitumor activity:
Sustained tumor reduction at C7 (-21% per RECIST v1.1)

Safety and tolerability
No dose interruption or modification
RLY-4008 treatment is ongoing (50 mg QD)

ctDNA:
Baseline FGFR2-E566V mutation is undetectable at C2D1

Preliminary data as of 09-Sept-2021

Courtesy: Dr. L. Goyal (Mass. General Hospital)
RLY-4008 induces radiographic tumor regression in FGFR2 oncogenic mutations and in FGFR2 amplifications.

**FGFR2 Oncogenic Mutations**

- S252W: 30 QD
- F276C: 70 QD
- N550K: 30 BID
- H167_N173del: 70 QD
- K660E: 70 QD
- N550K: 30 QD
- C383R: 40 QD

**FGFR2 Amplifications**

- FC 3.0: 70 QD
- CN 4-5: 100 BID
- CN >50: 50 BID

*Confirmed PR with increased tumor reduction after data cut; ^PR pending confirmation.

FC, fold change; CN, copy number.

Preliminary data as of 09-Sept-2021.
RLY-4008 results in confirmed PR in a patient with heavily pretreated FGFR2 N550K mutant breast cancer

60-year-old female with breast cancer ER+ HER2- ESR1 mut PIK3CA mut FGFR2 N550K-mut, 12 prior lines of therapy including Alpelisib (PI3Ki) + Palbociclib (CDKi)

Antitumor activity:
Confirmed PR at Cycle 5: -41% (after data cut off), initial PR at Cycle 3: -30%
Significant reduction in CA 15-3 by Cycle 2: -62%

Safety and tolerability
Relevant AEs: G2 PPE, G1 stomatitis, G1 nail changes
No dose reduction; RLY-4008 treatment is ongoing (70 mg QD)

Courtesy: Dr. A. Schram (MSKCC)
Conclusions

RLY-4008 is the first highly selective FGFR2 inhibitor in the clinic that targets driver alterations and FGFR inhibitor resistance mutations

Robust FGFR2 inhibition with ≥ 85% receptor occupancy and minimal off-isoform toxicity across a wide dose range

Favorable QD PK and safety profile with manageable AE – stomatitis, PPE, dry mouth, and nail toxicities

Encouraging anti-tumor activity
  • FGFRi-naïve, FGFR2-fusion+ cholangiocarcinoma: 3/6 patients with confirmed partial responses
  • FGFRi-resistant, FGFR2-fusion+ cholangiocarcinoma: 62% patients showed tumor shrinkage ≥10%
  • Early signs of activity also observed in FGFR2-mutant and -amplified tumors, beyond cholangiocarcinoma

Overall results validate selective targeting of FGFR2 and suggest RLY-4008 has potential to overcome FGFRi resistance
We thank the participating patients, their families, and all study team members at the following institutions:

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

This study was sponsored by Relay Therapeutics, Inc.

Graphics and editorial assistance was provided by Bio Connections LLC and funded by Relay Therapeutics, Inc.

Please direct any questions to:
lgoyal@partners.org

Copies of this presentation are for personal use only and may not be reproduced without permission from AACR-NCI-EORTC® and the author of this presentation