UPDATED DOSE ESCALATION RESULTS FOR REFOCUS, A FIRST-IN-HUMAN STUDY OF HIGHLY SELECTIVE FGFR2 INHIBITOR, RLY-4008, IN CHOLANGIOCARCINOMA AND OTHER SOLID TUMORS

Mitesh J. Borad,1 Alison M. Schram,2 Richard D. Kim,3 Suneel Deepak Kamath,4 Vaibhav Sahai,5 Efrat Dotan,6 Robin Kate Kelley,7 Mariano Ponz-Sarvisé,8, Do-Youn Oh,9 Jeffrey Yachnin,10 Vaia Florou,11 Philippe Cassier,12 Joon Oh Park,13 Chih-Yi Andy Liao,14 Michael Millward,15 Florence (Tianhui) Ramirez,16 Fabien Ricard,16 Antoine Hollebecque,17 Vivek Subbiah,18 Lipika Goyal19

1Mayo Cancer Center, Scottsdale, Arizona, USA; 2Memorial Sloan Kettering Cancer Center, New York, New York, USA; 3H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA; 4The Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio, USA; 5The University of Michigan, Ann Arbor, Michigan, USA; 6Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; 7UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, USA; 8Clinica Universidad Navarra, Navarra, Spain; 9Seoul National University Hospital, Seoul, Republic of Korea; 10Karolinska University Hospital, Stockholm, Sweden; 11Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah, USA; 12Centre Léon Berard, Lyon, France; 13Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 14The University of Chicago, Chicago, Illinois, USA; 15Linear Clinical Research & University of Western Australia, Nedlands, Australia; 16Relay Therapeutics, Cambridge, Massachusetts, USA; 17Institut Gustave Roussy, Paris, France; 18The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; 19Massachusetts General Hospital, Boston, Massachusetts, USA
Disclosures for Mitesh J. Borad, M.D.

- Research funding from Relay Therapeutics
Oncogenic Activation of FGFR2 Drives Multiple Cancers, But Selective Targeting of FGFR2 Has Not Been Achieved

FGFR2 is a clinically validated oncogene\(^1\)

FGFR2 alterations drive multiple solid tumor types\(^2-4\)

Approved pan-FGFR inhibitors solid tumor indications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Phase 2 Response Rate</th>
<th>DoR (mos)</th>
<th>% of patients with... (All grades)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemigatinib(^5)</td>
<td>36% (CCA)</td>
<td>9.1 (CCA)</td>
<td>Hyper phosphatemia(^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FGFR1 off-target toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FGFR4 off-target toxicity</td>
</tr>
<tr>
<td>Futibatinib(^6)</td>
<td>42% (CCA)</td>
<td>9.7 (CCA)</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47%</td>
</tr>
<tr>
<td>Erdafitinib(^7)</td>
<td>32% (Urothelial Carcinoma)</td>
<td>5.4 (CCA)</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47%</td>
</tr>
<tr>
<td>Infigratinib(^8)</td>
<td>23% (CCA)</td>
<td>5.0 (CCA)</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24%</td>
</tr>
</tbody>
</table>


CCA: Cholangiocarcinoma, FGFRi: fibroblast growth factor receptor, FGFRi: fibroblast growth factor receptor inhibitor
In contrast to pan-FGFRi, RLY-4008 is a potent and selective FGFR2 inhibitor

RLY-4008 selectively inhibits FGFR2 based on unique conformational dynamics

Potent in-vivo activity against FGFRi-sensitive and resistant cholangiocarcinoma

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Mechanism of Action</th>
<th>FGFR1 IC50 (nM)</th>
<th>FGFR2 IC50 (nM)</th>
<th>FGFR3 IC50 (nM)</th>
<th>FGFR4 IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLY-4008</td>
<td>Irreversible FGFR2 selective</td>
<td>864.3</td>
<td>3.1</td>
<td>274.1</td>
<td>17,633</td>
</tr>
<tr>
<td>Infgratinib</td>
<td>Reversible Pan-FGFRi</td>
<td>1.1</td>
<td>1</td>
<td>2</td>
<td>61</td>
</tr>
<tr>
<td>Pemigatinib</td>
<td>Reversible Pan-FGFRi</td>
<td>0.39</td>
<td>0.46</td>
<td>1.2</td>
<td>30</td>
</tr>
<tr>
<td>Futibatinib</td>
<td>Irreversible Pan-FGFRi</td>
<td>1.8</td>
<td>1.4</td>
<td>1.6</td>
<td>3.7</td>
</tr>
</tbody>
</table>

ReFocus: A Phase 1 / 2 Open Label Study (NCT04526106)

Focus for today

Phase 1: Dose Escalation*
*Dose Optimization and Proof-of-Mechanism (completed)

Phase 2: Dose Expansion
Definitive Efficacy with registrational intent (initiated Dec 2021)

Ongoing

Safety
PK/PD
Efficacy

FGFR2-altered solid tumors

Pivotal FGFR2-fusion+ Cholangiocarcinoma
FGFR2-altered tumor agnostic cohorts

*Dose escalation followed a BOIN design with enrichment (additional accrual to dose levels declared tolerable); dose modifications including intra-patient dose escalation were permitted per protocol based on tolerability.

Data for Phase 1 Dose Escalation as of 01/30/2023.

BOIN: Bayesian Optimal Interval, DoR: Duration of Response, ORR: Overall Response Rate, RP2D: Recommended Phase 2 Dose
## ReFocus Phase 1 Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cholangiocarcinoma (CCA)</th>
<th>Other Tumors (N=25)</th>
<th>Overall (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pan-FGFRi Naïve (N=36)</td>
<td>Pan-FGFRi Refractory (N=55)</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>59 (33–78)</td>
<td>56 (23–87)</td>
<td>61 (37–81)</td>
</tr>
<tr>
<td>Female, %</td>
<td>58%</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White / Asian / Black or African American / Other</td>
<td>75% / 14% / 3% / 8%</td>
<td>78% / 9% / 5% / 7%</td>
<td>64% / 20% / 12% / 4%</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 / 1 / 2</td>
<td>47% / 53% / 0%</td>
<td>29% / 62% / 9%</td>
<td>48% / 52% / 0%</td>
</tr>
<tr>
<td>Prior chemotherapy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 / 1 / 2 / 3+ lines</td>
<td>100%</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Prior FGFRi, %</td>
<td>0%</td>
<td>100%</td>
<td>12%</td>
</tr>
<tr>
<td>0 / 1 / 2 / 3 lines</td>
<td>100% / 0% / 0% / 0%</td>
<td>0% / 71% / 25% / 4%</td>
<td>88% / 12% / 0% / 0%</td>
</tr>
<tr>
<td>FGFR2 alteration, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion</td>
<td>69%</td>
<td>91%</td>
<td>28%</td>
</tr>
<tr>
<td>Mutation</td>
<td>28%</td>
<td>7%</td>
<td>52%</td>
</tr>
<tr>
<td>Amplification</td>
<td>3%</td>
<td>2%</td>
<td>16%</td>
</tr>
<tr>
<td>No FGFR2 Alteration</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Mutation status per local assessment. Amplification cut-off: FGFR2 locus, copy number ≥ 8 (FGFR2 probe: reference ratio ≥ 4 per FISH) in tumor tissue or defined as amplified by NGS test. No amplification cutoff is defined for ctDNA.

Data for Phase 1 Dose Escalation as of 01/30/2023.

ECOG PS: Eastern Cooperative Oncology Group Performance Status.
Phase 1 BOIN Design Defines 70mg QD as RP2D

- **Maximum Tolerated Dose (MTD) not reached per protocol**
- **Based on PK, PD, safety & efficacy, 70mg QD selected as RP2D and advanced to pivotal testing**

**RLY-4008 QD (daily) Advanced to Phase 2**
- Starting dose: 30 mg QD
- 20 mg QD
- 60 mg QD
- 70 mg QD
- Dose Limiting Toxicities (DLT)*

**RLY-4008 BID (2x per day)**
- Starting dose: 50 mg BID
- 20 mg BID
- 30 mg BID
- 100 mg BID
- DLTs

**RLY-4008 QDi (daily, 3 weeks on, 1 week off)**
- Starting dose: 50 mg QDi
- 60 mg QDi
- 100 mg QDi
- Dose Interruption (%)
- Dose Reduction (%)
- Discontinuation due to AE (%)

*28-day DLT period (per protocol); DLT evaluable patients represent patients treated in escalation & enrichment cohorts per BOIN design. DLTs include Retinopathy, Rash maculo-popular, Rash erythematous, Stomatitis, Hyperbilirubinemia.

BOIN: Bayesian Optimal Interval Design; RP2D: Recommended Phase 2 Dose; TRAE: Treatment-related Adverse Event

Data for Phase 1 Dose Escalation as of 01/30/2023.
ReFocus Phase 1 PK/PD Confirms Selective FGFR2 Targeting

Target Coverage Across FGFR2 Alterations
Cycle 1 Day 15

Serum Phosphate Over Time

≥96% predicted median receptor occupancy at 70mg QD (RP2D)
Effective half-life ~18-26h supports QD dosing

Data for Phase 1 Dose Escalation as of 01/30/2023.
BOIN: Bayesian Optimal Interval Design. QD: Daily; RP2D: Recommended Phase 2 Dose; SD: Standard Deviation, SE: Standard Error
Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org
ReFocus Phase 1 Safety & Efficacy Populations

ReFocus Phase 1 (N=116; Safety Population)

Cholangiocarcinoma (n=91)

- **FGFR2 Fusion+ (fusions/rearrangements)**
  - n=75
  - FGFRi-Naïve n=25
  - FGFRi-Refractory n=50

- **FGFR2 mutations**
  - n=14
  - (FGFRi-Naïve n=10, FGFRi-Refractory n=4)

- **FGFR2 Fusions/rearrangements**
  - (ASCO23-212)

Other Solid Tumors (n=25)

- **FGFR2 amplifications**
  - n=2

Efficacy data presented today

Data for Phase 1 Dose Escalation as of 01/30/2023.
ReFocus Phase 1 Efficacy - FGFRi-Naïve FGFR2 Fusion+ Cholangiocarcinoma

4/4 at 70mg QD (RP2D) had response per RECIST 1.1

ORR 73%

ORR 36%

Across all doses:
92% of patients with tumor reduction

Data for Phase 1 Dose Escalation as of 01/30/2023.
ORR: Overall Response Rate; RP2D: Recommended Phase 2 Dose
ReFocus Phase 1 - Duration of Exposure & Responses: FGFRi-Naïve FGFR2 Fusion+ Cholangiocarcinoma

Data for Phase 1 Dose Escalation as of 01/30/2023. BID: Twice daily, DCR: Disease Control Rate, DoR: Duration of Response; NE: not evaluable, ORR: Overall Response Rate; PD: Progressive Disease, PFS: Progression Free Survival; PR: Partial Response; QD: once daily, QDi: once daily, 3 weeks on, 1 week off; SD: Stable Disease

Across all doses: ORR: 52%; Median DoR, 95%CI: 8.2 mos (5.6, NA); 6-mo PFS, 95%CI: 83.2% (61.1, 93.4); DCR: 88% (22/25); Median Time to Response: 1.8 mos; Median DoE (range): 32 weeks (<1 to 108)

ORR: 73%
Median DoR: 11.2 mos
6-mo PFS: 100%
DCR: 100%

ORR: 36%
Median DoR: 5.6 mos
6-mo PFS: 70%
DCR: 79%

PRESENTED BY: Mitesh J. Borad, M.D.

#ASCO23

Presentation is property of the author and ASCO. Permission required for reuse; contact permissions@asco.org
ReFocus Phase 1 Efficacy - FGFRi-Refractory, FGFR2 Fusion+ Cholangiocarcinoma

>70mg All schedules (n=14)

ORR 21%

<70mg All schedules (n=36)*

ORR 11%

Across all doses:
70% of patients with tumor reduction

*Waterfall excludes 2 FGFRi-Refractory patients with clinical progressive disease without post baseline tumor assessment.
N549X and V564X correspond to FGFR2 IIIc isoform; X denotes any amino acid substitution.
** Other includes FGFR2 mutations other than N549X and V564X (pink), no detectable FGFR2 mutation (white)

Data for Phase 1 Dose Escalation as of 01/30/2023.
ReFocus Phase 1 - Duration of Exposure & Responses: FGFRi-Refractory FGFR2 Fusion+ Cholangiocarcinoma

Across all doses: ORR: 14%; Median DoR, 95%CI: 5.6 mos (3.7, NA); 6-mo PFS, 95%CI: 35.5% (22.4, 48.9); DCR: 80% (40/50); Median Time to Response: 3.7 mos; Median DoE (range): 21 weeks (4 to 68)

Data for Phase 1 Dose Escalation as of 01/30/2023. BID: Twice daily; DCR: Disease Control Rate; DoR: Duration of Response; NA: Not available; ORR: Overall Response Rate; PD: Progressive Disease; PFS: Progression Free Survival; PR: Partial Response; QD: once daily; QDI: once daily, 3 weeks on, 1 week off; SD: Stable Disease

ORR: 21%
Median DoR: 5.6 mos
6-mo PFS: 43%
DCR: 93%

ORR: 11%
Median DoR: 6.0 mos
6-mo PFS: 33%
DCR: 75%
ReFocus Phase 1 Efficacy - FGFR2-Mutated Cholangiocarcinoma

29% ORR

64% of patients with tumor reduction

Median DoE: 26.4 weeks (2 – 62 weeks)

FGFRi-pretreated patients

Mutation based on local/central assessment; Data for Phase 1 Dose Escalation as of 01/30/2023. DoE: Duration of Exposure, ORR: Overall Response Rate
Differentiated Safety Profile Confirms Selective FGFR2 Targeting

AEs are on-target events; mostly low grade and reversible, no Gr 4 or Gr 5

Most common TRAEs were stomatitis, PPE, dry mouth, and nail toxicities; minimal hyperphosphatemia and diarrhea

Overall, 3/116 (2.6%) patients discontinued treatment due to AEs

Data for Phase 1 Dose Escalation as of 01/30/2023. AE: Adverse Event; TRAE: Treatment-related Adverse Event
ReFocus Next Steps: Phase 2 Pivotal Cholangiocarcinoma Ongoing


ORR 88%
All patients had radiographic tumor reduction and nearly all had PR per RECIST 1.1

Pivotal enrollment anticipated completion: 2H 2023
ReFocus Next Steps: Phase 2 Tumor Agnostic Enrollment Ongoing

Partial response per RECIST 1.1 (-67%)

Baseline

First Assessment (8 weeks)

Liver

Data anticipated 2H 2023

46-year-old male; FGFR2 Y375C metastatic salivary gland carcinoma
Previously treated with carboplatin/paclitaxel, lenvatinib
RLY-4008 70mg QD (RP2D)

Subbiah et al, Cancer Disc 2023; in press. DOI: 10.1158/2159-8290.CD-23-0475; QD: once daily, RP2D: Recommended Phase 2 Dose
Conclusions

ReFocus dose escalation data validate RLY-4008 as the first highly selective FGFR2 inhibitor that targets driver alterations and FGFRi resistance mutations

Promising initial efficacy and durability confirm highly potent FGFR2 targeting
- 73% ORR with mDoR 11.2 months in FGFRi-naïve, FGFR2 f/r cholangiocarcinoma patients treated ≥70mg
- 21% ORR, 93% DCR and 43% 6-month PFS in FGFRi-refractory FGFR2 f/r cholangiocarcinoma patients treated ≥70mg
- 70% DCR including 3 durable PR in FGFRi-naïve, FGFR2-mutated cholangiocarcinoma

PK/PD and differentiated safety profile confirm highly selective FGFR2 inhibition
- Favorable PK/PD provides continuous target inhibition ≥ 96% at the 70mg QD RP2D
- Most AEs are low grade, largely reversible on-target AEs

Pivotal testing continues in Phase 2 of ReFocus; anticipating tumor-agnostic data 2H 2023
Foundational preclinical and translational research published in Cancer Discovery today

RLY-4008, THE FIRST HIGHLY SELECTIVE FGFR2 INHIBITOR WITH ACTIVITY ACROSS FGFR2 ALTERATIONS AND RESISTANCE MUTATIONS

Vivek Subbiah,1* Vaibhav Sahai,2* Dejan Maglic,3 Kamil Bruderek,3 B. Barry Touré,3† Songping Zhao,3 Roberto Valverde,3 Patrick J. O’Hearn,3 Demetri T. Moustakas,3 Heike Schönherr,3 Nastaran Gerami-Moayed,3 Alexander M. Taylor,3 Brandi M. Hudson,3† Damian J. Houde,3 Dejanjai Pal,3 Lindsey Foster,3 Hakan Gunaydin,3 Pelin Ayaz,4 Dina A. Sharron,4 Lipika Goyal,5† Alison M. Schram,6 Suneel Kamath,7 Cori Ann Sherwin,3 Oleg Schmidt-Kittler,3 Kai Yu Jen,3 Fabien Ricard,3 Beni B. Wolf,3 David E. Shaw,4,8 Donald A. Bergstrom,3 James Watters,3 Jessica B. Casaletto3

1The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; 2University of Michigan, Ann Arbor, Michigan, USA; 3Relay Therapeutics, Cambridge, Massachusetts, USA; 4D. E. Shaw Research, New York, New York, USA; 5Massachusetts General Hospital, Boston, Massachusetts, USA; 6Memorial Sloan Kettering Cancer Center, New York, New York, USA; 7The Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio, USA, 8Department of Biochemistry and Molecular Biophysics, Columbia University, New York, New York, USA

*co-first authors
†Research conducted while employed by this institution

https://doi.org/10.1158/2159-8290.CD-23-0475
Acknowledgments

We would like to thank the patients and their families, all study investigators, sub-investigators, and research staff at the following institutions:

Australia
- Jia Liu - St. Vincent's Hospital Sydney, New South Wales
- Jermaine Coward - Icon Cancer Care South Brisbane, Queensland
- Michael Millward - Linear Clinical Research Ltd, Western Australia

France
- François Ghiringhelli - Centre Georges François Leclerc, Côte-d'Or
- Antoine Italiano - EDOG - Institut Bergonie - PPDS, Gironde
- Philippe Cassier - Centre Leon Bérard, Rhône
- Antoine Hollebecque - Institut Gustave Roussy, Val-de-Marne

Hong Kong
- Thomas Yau - Queen Mary Hospital

Italy
- Giovanni Luca Frassineti - Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l - PPDS, Emilia-Romagna
- Federico Cappuzzo - Istituto Nazionale Tumori Regina Elena, Lazio
- Giuseppe Curigliano - Istituto Europeo Di Oncologia, Lombardia

Republic of Korea
- Joon Oh Park - Samsung Medical Center - PPDS, Seoul Teugbyeolsi
- Changhoon Yoo - Asan Medical Center - PPDS, Seoul Teugbyeolsi
- Do-Youn Oh - Seoul National University Hospital, Seoul Teugbyeolsi

Netherlands
- Frans Opdam - Het Nederlands Kanker Instituut Antoni Van Leeuwenhoek Ziekenhuis, Noord-Holland
- David Tai - National Cancer Centre

Singapore
- Elisa Fontana

Spain
- Elena Garralda - Hospital Universitario Vall d'Hebron - PPDS, Barcelona
- Victor Moreno - START MADRID_Hospital Universitario Fundacion Jimenez Diaz, Madrid
- Irene Moreno - START MADRID_Hospital Universitario HM Sanchinarro - CIOCC, Madrid
- Spain, cont’d
- Mariano Ponz-Sarvisé - Clinica Universidad Navarra, Navarra
- Desamparados Roda Perez - Hospital Clinico Universitario de Valencia, Valencia

Sweden
- Jeffrey Yachnin - Karolinska Universitetssjukhuset Solna

Taiwan
- Li-Yuan Bai - China Medical University Hospital, , Taiwan

United Kingdom
- Matthew Krebs - The Christie NHS Foundation Trust - PPDS, Lancashire
- Elisa Fontana - Sarah Cannon Research Institute UK - SCRI - PPDS, City of London

United States
- Mitesh Borad - Mayo Clinic Scottsdale - PPDS, Arizona
- Robin Kate Kelley - UCSF Helen Diller Family Comprehensive Cancer Center, California
- Anthony El-Khoueiry - USC Norris Cancer Center, California
- Hani Babiker - Mayo Clinic Jacksonville - PPDS, Florida
- Richard Kim - H. Lee Moffitt Cancer Center and Research Institute, Florida
- Chih-Yi (Andy) Liao - University of Chicago Medical Center, Illinois
- Lipika Goyal - Massachusetts General Hospital, Massachusetts
- Vaibhav Sahai - University of Michigan, Michigan
- Zhaohui Jin - Mayo Comprehensive Cancer Center - PPDS, Minnesota
- Alison Schram - Memorial Sloan Kettering Cancer Center, New York
- Suneel Kamath - The Cleveland Clinic Foundation, Ohio
- Efrat Dotan - Fox Chase Cancer Center, Pennsylvania
- Vivek Subbiah - University of Texas MD Anderson Cancer Center, Texas
- Andrew Paulson - Texas Oncology-Baylor Charles A. Sammons Cancer Center - USOR, Texas
- Vaia Florou - University of Utah - Huntsman Cancer Institute - PPDS, Utah
- Bruce Lin - Virginia Mason Medical Center, Washington

This study was sponsored by Relay Therapeutics, Inc. Medical writing support was provided by Christine Etliner of BOLDSCIENCE Inc., funded by Relay Therapeutics.

PRESENTED BY: Mitesh J. Borad, M.D.