Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients with an FGFR2 fusion or rearrangement, FGFR inhibitor-naïve cholangiocarcinoma: ReFocus trial

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Dr. Antoine Hollebecque declares participation on safety monitoring or consulting and advisory boards for Amgen, Basilea, BMS, Incyte, Servier, QED Therapeutics, Relay Therapeutics, and Taiho.
Cholangiocarcinoma and Oncogenic FGFR2 Fusions

Cholangiocarcinoma (CCA) is a rare malignancy with a dismal prognosis1

FGFR2 fusions/rearrangements drive ~10-15% of intrahepatic cholangiocarcinoma2

**RLY-4008: The First Highly Selective FGFR2 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.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Mechanism of Action</th>
<th>Biochemical IC50 (nM)</th>
<th>FGFR1</th>
<th>FGFR2</th>
<th>FGFR3</th>
<th>FGFR4</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>
<td></td>
</tr>
<tr>
<td>Infgratinib</td>
<td>Reversible Pan-FGFRi</td>
<td>1.1</td>
<td>1</td>
<td>2</td>
<td>61</td>
<td></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>
<td></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>
<td></td>
</tr>
</tbody>
</table>

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

ReFocus: A Global, Seamless Phase 1/2 Open Label Study

Phase 1: Maximum tolerated dose and Recommended Phase 2 Dose (RP2D), safety, PK and preliminary efficacy

- Phase 1 Dose Escalation (completed)
- Patients with unresectable or metastatic CCA and other solid tumors harboring an FGFR2 alteration by local testing
- RLY-4008 70 mg QD (RP2D)

Phase 2: Objective response rate (ORR) and duration of response (DoR) by independent review committee

- Phase 2 Expansion (initiated Dec 2021)
- Cholangiocarcinoma
  - FGFR2 fusion+ previously treated with chemotherapy, FGFRi-naïve (n=100) Pivotal Cohort
  - FGFR2 fusion+ previously treated with FGFRi (n=50)
  - FGFR2 fusion+ treatment-naïve (n=20)
  - FGFR2 mutant or amplified (n=20)

- Other advanced solid tumors with FGFR2 alterations
  - 3 Cohorts FGFR2 fusion+, amplified and mutant (n=30 each)

Key objectives

- Phase 1: Maximum tolerated dose and Recommended Phase 2 Dose (RP2D), safety, PK and preliminary efficacy
- Phase 2: Objective response rate (ORR) and duration of response (DoR) by independent review committee

Preliminary data, data cut August 1, 2022 (response investigator assessed)
## Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CCA, Fusion+, FGFRi-naïve*</th>
<th>Overall** (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP2D, 70 mg QD (N=17)</td>
<td>All doses (N=38)</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>57 (36 to 81)</td>
<td>58 (33 to 81)</td>
</tr>
<tr>
<td>Female, %</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White / Asian / Black / Unknown</td>
<td>41 / 24 / 0 / 35</td>
<td>58 / 21 / 3 / 18</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prior lines of systemic therapy, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td>3+</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Baseline sum of target lesions (RECIST 1.1, mm), median (range)</td>
<td>57 (10 to 157)</td>
<td>63 (10 to 216)</td>
</tr>
</tbody>
</table>

* Efficacy analysis includes patients who are FGFRi naïve CCA from Phase 1 and Phase 2. Patients with measurable disease who had opportunity for ≥2 tumor assessments to confirm response or discontinued treatment with <2 tumor assessments.

** Safety population includes patients who received ≥1 dose of RLY-4008 at any dose level.
RLY-4008 Provides Potent and Selective FGFR2 Inhibition

Steady state pharmacokinetics at RP2D

- **FGFR2 fusion-target**
- **Continuous coverage of FGFR2 target**
- **Time (h)**
- **T\text{\tiny max}: 4 hours**
- **Effective half-life: 23 hours**

Serum phosphate over time at RP2D and all QD doses

- **Phosphate levels WNL**
- **Normal phosphate indicates clinically insignificant FGFR1 inhibition**

Phosphate (mmol/L) (Mean ± SE)

- **RP2D, 70 mg QD (N=89)**
- **All QD doses (N=136)**

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Radiographic Tumor Regression and Response per RECIST 1.1 Across All Doses

Patients with **FGFR2** fusions or rearrangements, FGFRi-naïve (n=38)

**ORR 63.2%**

92% of patients with tumor reduction

Majority of patients with partial response per RECIST 1.1

**Treatment**
- RP2D, 70 mg QD (N=17)
- All other doses (N=21)
- Ongoing (N=26)

QDi = once daily dosing on an intermittent schedule; BID = twice daily dosing; ★ = resection with curative intent

Confirmed ORR 57.9% 2/24 unconfirmed PR
Patients with FGFR2 fusions or rearrangements, FGFRi-naïve (n=17)

ORR 88.2%

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

Confirmed ORR 82.4% 1/15 unconfirmed PR

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RLY-4008 Induces Marked Radiographic Response per RECIST 1.1

56-year-old female with FGFR2-PLETHA4 rearrangement ICC
Refractory to Gemcitabine/Cisplatin
RLY-4008 70 mg QD
Ongoing confirmed partial response per RECIST 1.1 (-68%)

Hepatic dome lesions not detected
Deep liver tumor regression
Tumor regression with bone ossification

Courtesy A. Hollebecque, IGR.
## Radiographic Response per RECIST 1.1

### Patients with *FGFR2* fusions or rearrangements, FGFRi-naïve

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RP2D, 70 mg QD (N=17)</th>
<th>All doses (N=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate (ORR), n (% [95% CI])</strong></td>
<td>15 (88.2 [63.6 - 98.5])</td>
<td>24 (63.2 [46.0 - 78.2])</td>
</tr>
<tr>
<td>• Confirmed ORR, n (% [95% CI])</td>
<td>14 (82.4 [56.6 - 96.2])</td>
<td>22 (57.9 [40.8 - 73.7])</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Partial response</td>
<td>82.4</td>
<td>57.9</td>
</tr>
<tr>
<td>• Unconfirmed partial response</td>
<td>5.9</td>
<td>5.3</td>
</tr>
<tr>
<td>• Stable disease</td>
<td>11.8</td>
<td>31.6</td>
</tr>
<tr>
<td>• Progressive disease</td>
<td>—</td>
<td>5.3</td>
</tr>
<tr>
<td>• Response ongoing, n/N (%)*</td>
<td>15/15 (100.0)</td>
<td>19/24 (79.2)</td>
</tr>
<tr>
<td><strong>Disease control rate, n (% [95% CI])</strong></td>
<td>17 (100.0 [80.5 - 100.0])</td>
<td>36 (94.7 [82.3 - 99.4])</td>
</tr>
<tr>
<td><strong>Remain on treatment, n (%)</strong></td>
<td>15 (88.2)</td>
<td>26 (68.4)</td>
</tr>
</tbody>
</table>

* Includes 2 patients who came off treatment while still in response without disease progression.*
Duration of Exposure and Responses Across All Doses

Patients with FGFR2 fusions or rearrangements, FGFRi-naïve

Duration of exposure (weeks)

12/38 (32%) Discontinued - 1 resection (✓) with curative intent, 8 PD, 1 AE, 2 withdrawal of consent.

Majority of responders remain on treatment with ongoing response (71%, 17 of 24)
Median time to response 1.8 months
Median duration of exposure = 5.5 months (<0.1 to 18.5)

QDi = once daily dosing on an intermittent schedule; BID = twice daily dosing

12/38 (32%) Discontinued - 1 resection (✓) with curative intent, 8 PD, 1 AE, 2 withdrawal of consent.
Treatment-Related Adverse Events (TRAEs) ≥ 15%

AEs are low-grade, manageable, and largely reversible; Indicative of selective FGFR2 inhibition and sparing FGFR1 & FGFR4

<table>
<thead>
<tr>
<th>TRAE Dose Modification</th>
<th>RP2D, 70mg QD (N=89)</th>
<th>All Doses (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interruption, n (%)</td>
<td>37 (42)</td>
<td>92 (47)</td>
</tr>
<tr>
<td>Reduction, n (%)</td>
<td>24 (27)</td>
<td>65 (33)</td>
</tr>
<tr>
<td>Discontinuation, n (%)</td>
<td>1 (1)</td>
<td>2* (1)</td>
</tr>
</tbody>
</table>

*1 hypersensitivity, 1 retinal pigment epithelial detachment, both resolved
PPE: palmar plantar erythrodysesthesia syndrome; relatedness determined by investigator
Conclusions

RLY-4008 is the first highly selective, irreversible inhibitor designed to target oncogenic FGFR2 driver alterations and resistance mutations

ReFocus validates this novel MOA and supports expedited development for the treatment of patients with FGFRi-naïve CCA harboring an FGFR2 fusion or rearrangement

High response rates and encouraging durability confirm highly potent FGFR2 targeting

- At the RP2D 70 mg QD, ORR is 88% (15/17, 15 with response ongoing)
- Across doses, ORR is 63% (24/38, 19 with response ongoing)

PK/PD and differentiated safety profile confirm highly selective FGFR2 inhibition

- Robust target inhibition
- Most AEs are low grade, largely reversible on-target AEs
- No clinically significant off-isoform toxicity

Results suggest that RLY-4008 has potential to transform CCA treatment paradigm and strongly support seamless expansion of ReFocus with registrational intent
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