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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

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Disclosures

Speaker Name: Dr. Lipika Goyal

I have the following financial relationships to disclose:

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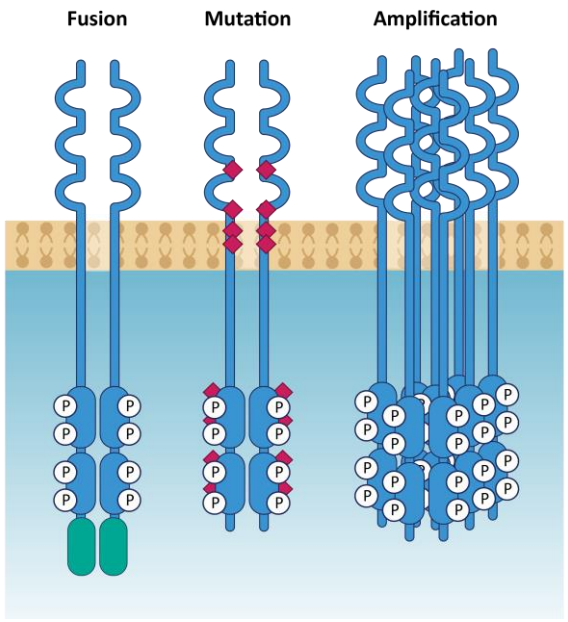
Data Safety Monitoring Committee: AstraZeneca.

I will not discuss off label use and/or investigational use in my presentation.

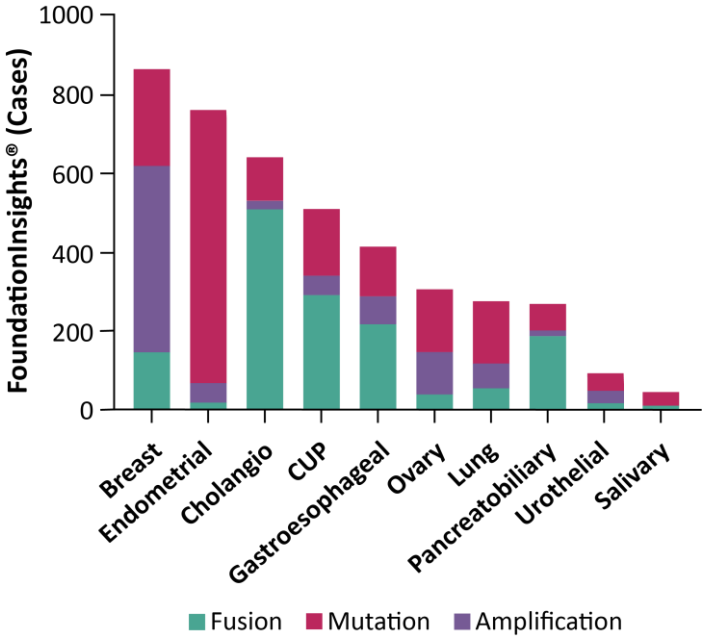
FGFR2 is a clinically validated therapeutic target

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

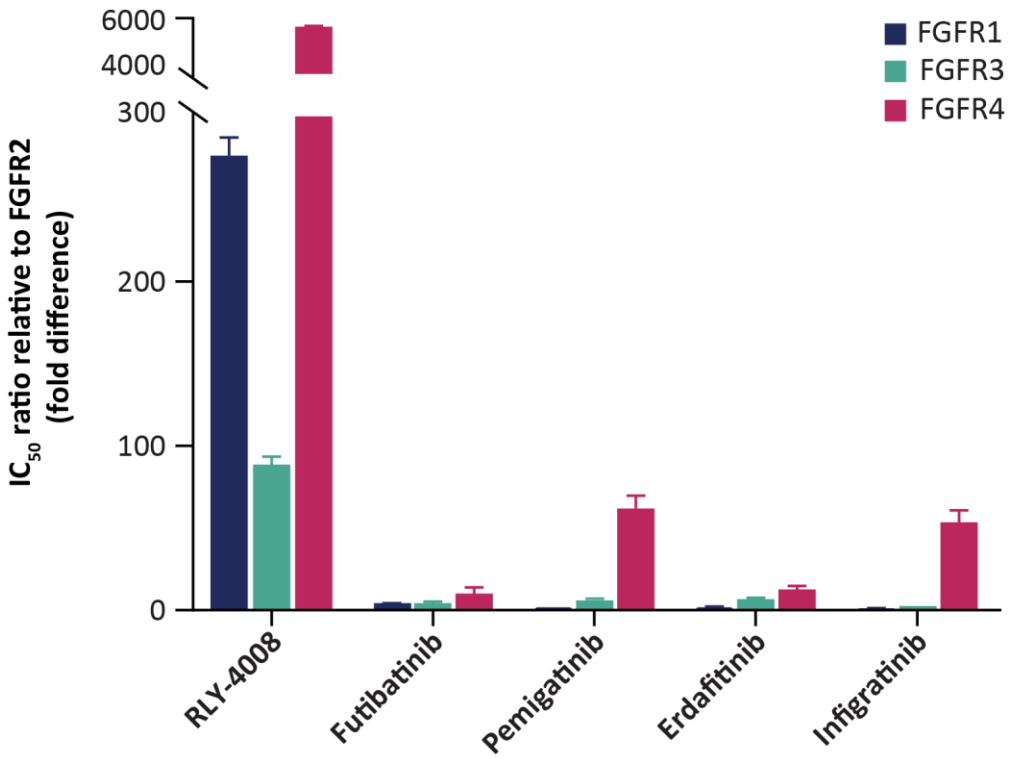
Current FDA Accelerated Approvals (AA) for FGFR2-Altered Cancers

Tumor Type	FGFR2 Fusion & Rearrangement	FGFR2 Oncogenic Mutation	FGFR2 Amplification
FGFRi-naïve Cholangiocarcinoma	Pemigatinib Infigratinib	No effective targeted therapy	
FGFRi-naïve Urothelial	Erdafitinib		
FGFRi-resistant Cholangiocarcinoma			
Other FGFR2-altered solid tumors			

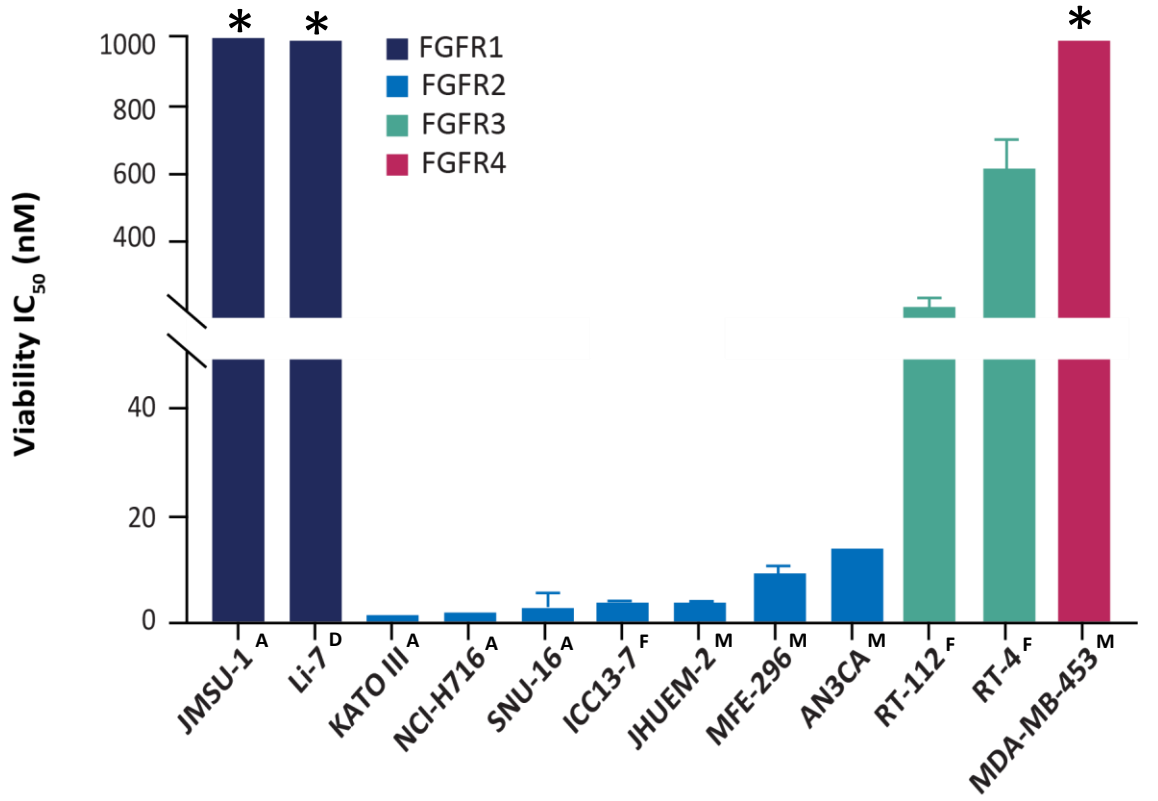
*Data source: FoundationInsights® database, using 8 copies as the threshold for amplification, and including only mutations with known or likely functional significance.
Cholangio, cholangiocarcinoma; CUP, carcinoma unknown primary; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor.

RLY-4008 is the first highly selective irreversible FGFR2 inhibitor

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



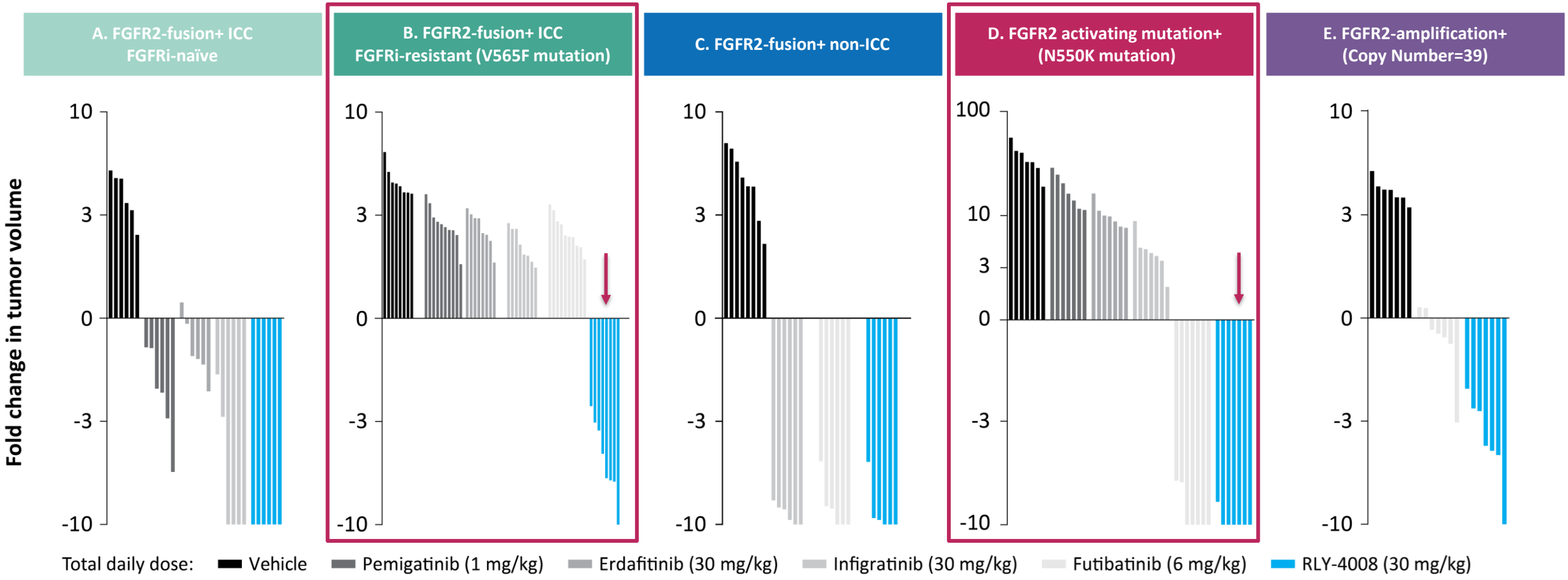
RLY-4008 potently and selectively inhibits FGFR2 driven cellular proliferation



RLY-4008 was designed to selectively bind to FGFR2 to avoid off-isoform toxicities (FGFR1 – hyperphosphatemia; FGFR4 – diarrhea)

*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 has potent *in vivo* antitumor activity against primary FGFR2 alterations and common resistance mutations



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

RP2D

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

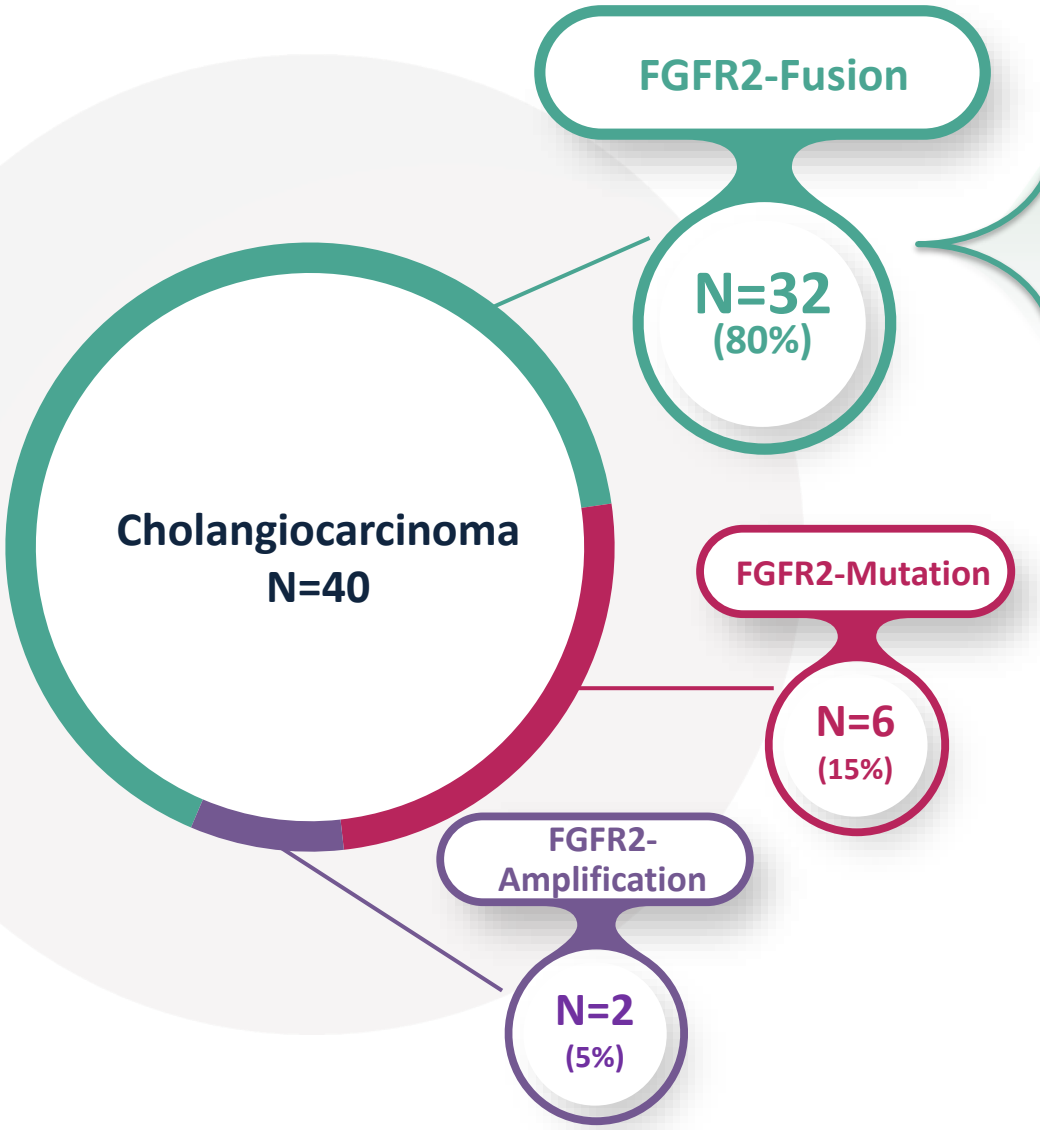
Parameter	Total (N=49)
Sex, n (%)	
Female	29 (59%)
Male	20 (41%)
Age (years), median (range)	**60 (23-87)**
Race, n (%)	
White	38 (78%)
Asian	6 (12%)
Black/African American	4 (8%)
Unknown	1 (2%)
ECOG PS, n (%)	
0-1	46 (94%)
2	3 (6%)
Prior lines of systemic therapy, n (%)	
1	9 (18%)
2	11 (23%)
3+	29 (59%)

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

ECOG, Eastern Cooperative Oncology Group; PS, performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
*Soft tissue sarcoma patient enrolled in dose escalation without a documented oncogenic FGFR2 genomic alteration.

Preliminary data as of 09-Sept-2021

RLY-4008 FIH Study: Cholangiocarcinoma population



FGFR2 Resistance Mutations at Baseline in Fusion+ Patients
N=25 evaluable by ctDNA

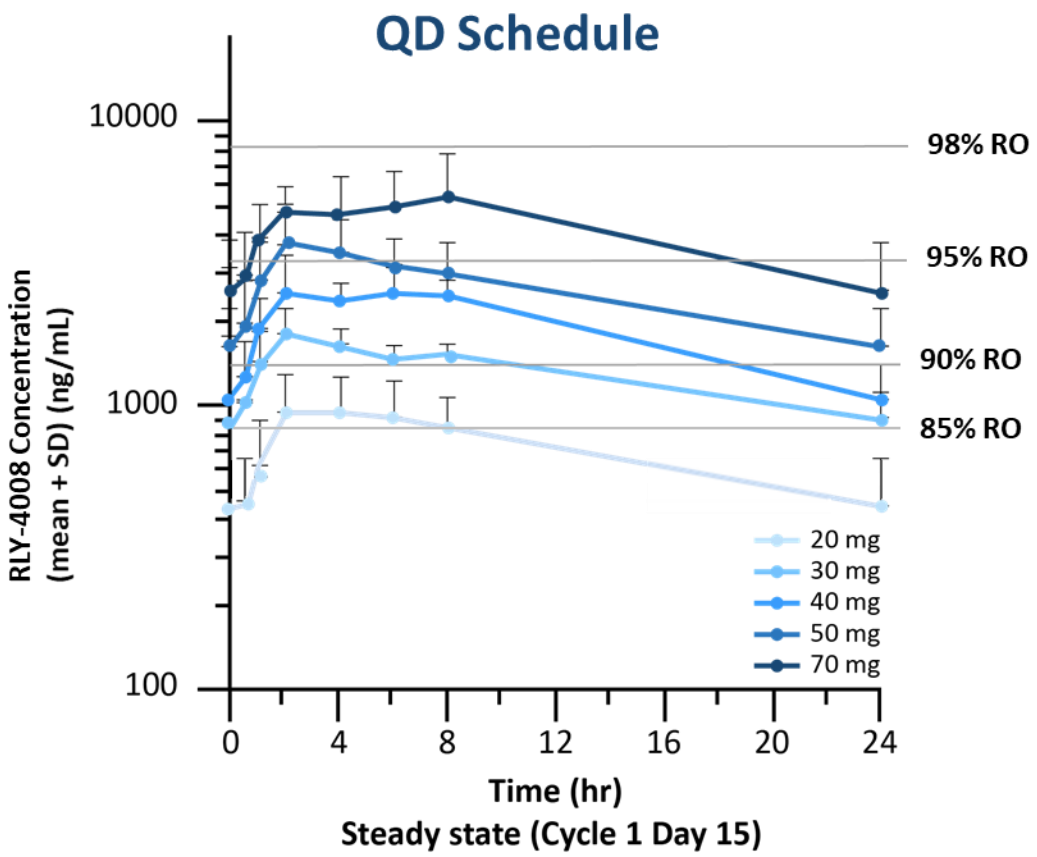
	FGFR2-Fusion; FGFRi-naïve (n=6)	FGFR2-Fusion 1 prior FGFRi* (n=12)	FGFR2-Fusion 2+ prior FGFRi* (n=7)
N550X (molecular brake)	0	4	6
V565X (gatekeeper)	1	1	3
E566X (molecular brake)	0	1	1
L618X	0	0	3
Total patients with any FGFR2 resistance mutation	1 of 6 (17%)	5 of 12 (42%)	6 of 7 (86%)

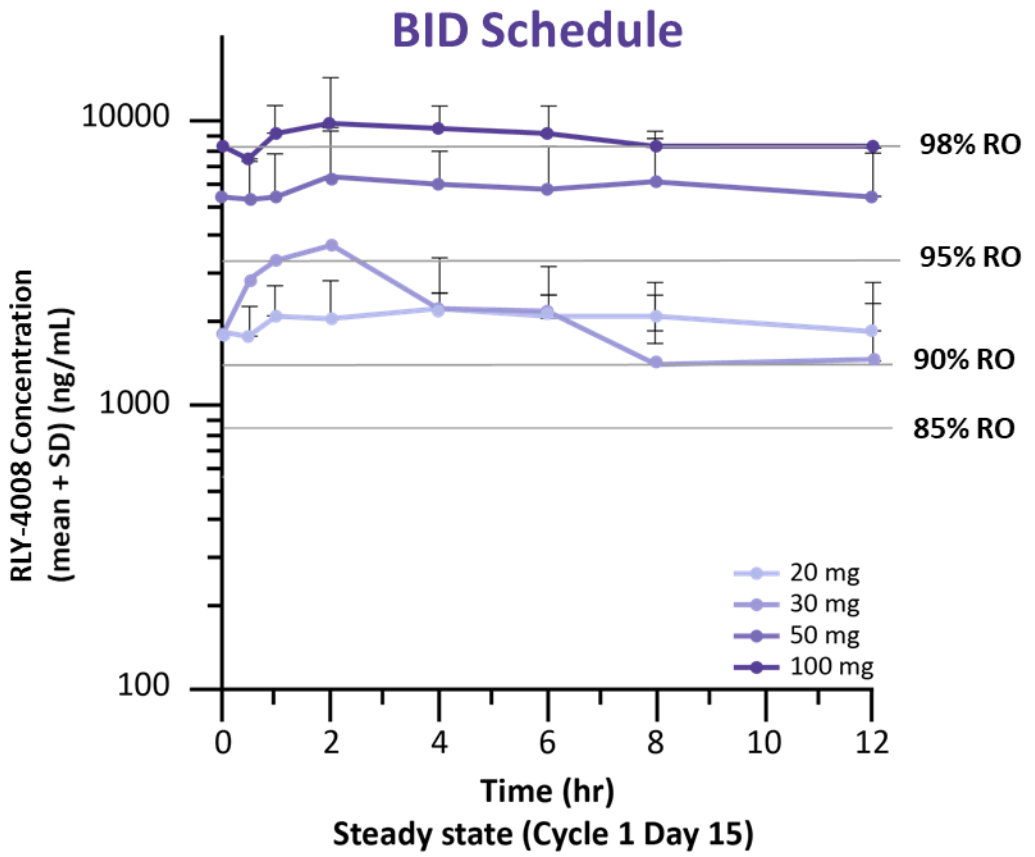
* Note: all patients discontinued the prior FGFR inhibitor lines of therapy because of disease progression.

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





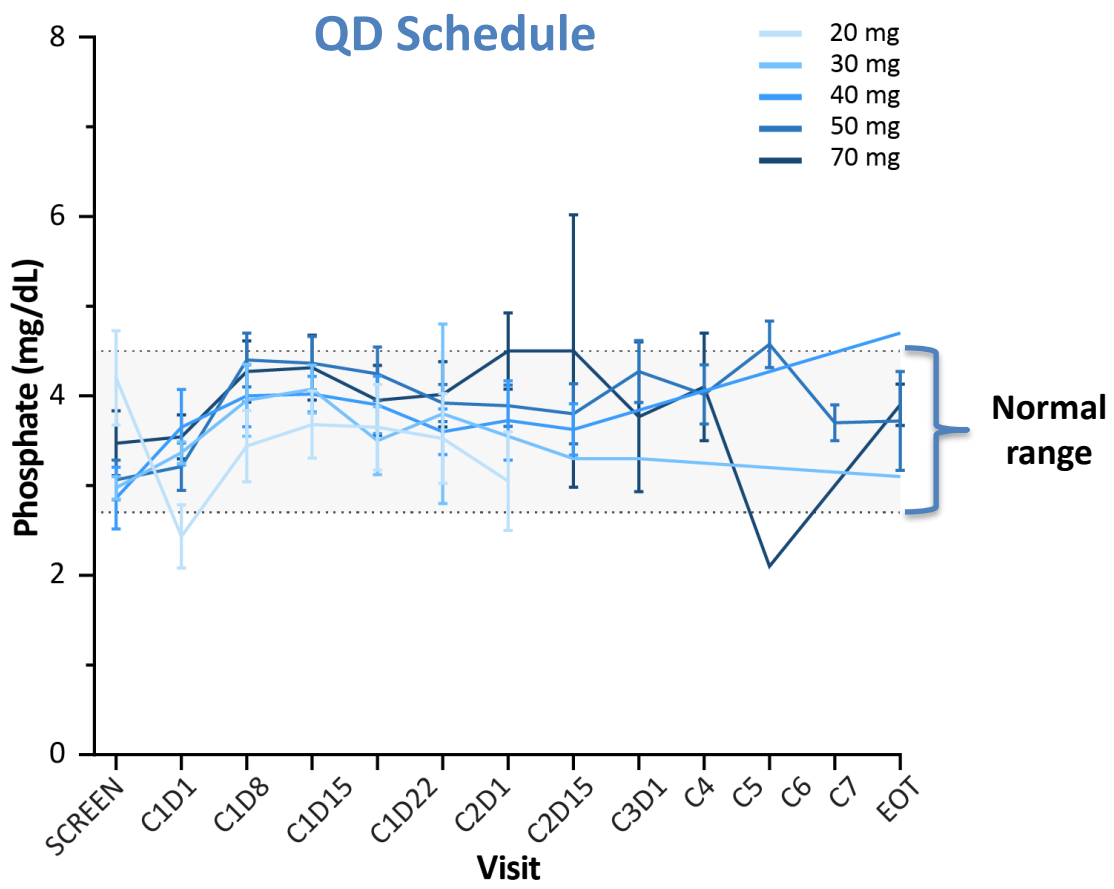
RLY-4008 shows ≥ 85 % predicted median receptor occupancy (based on modeling) across all dose levels

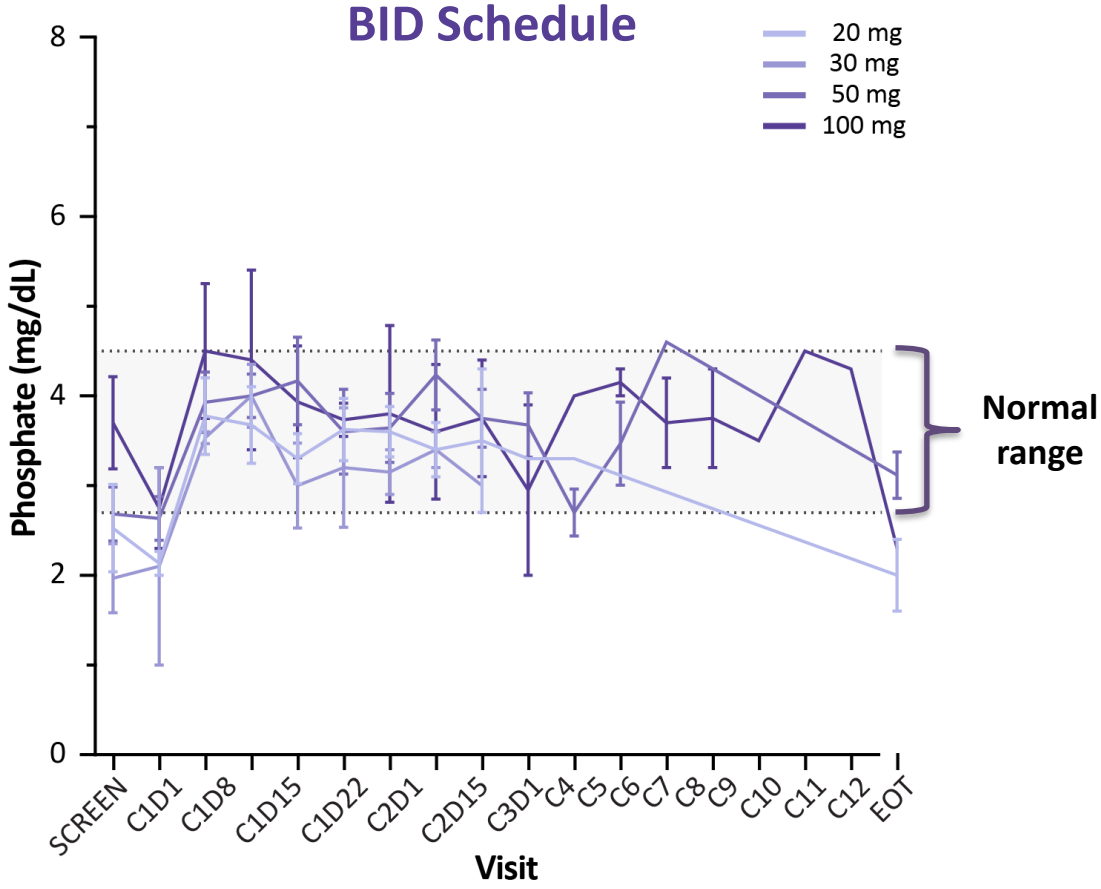
Half-life ~15-30h supports QD dosing

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.

Preliminary data as of 09-Sept-2021

RLY-4008 FIH Study: Confirmation of FGFR1- and FGFR4-sparing in the clinic





FGFR1 sparing: Hyperphosphatemia: n=9/49 (18%) patients, all low grade (Grade 1-2). Only 1/49 (2%) patients was prescribed phosphate binders.

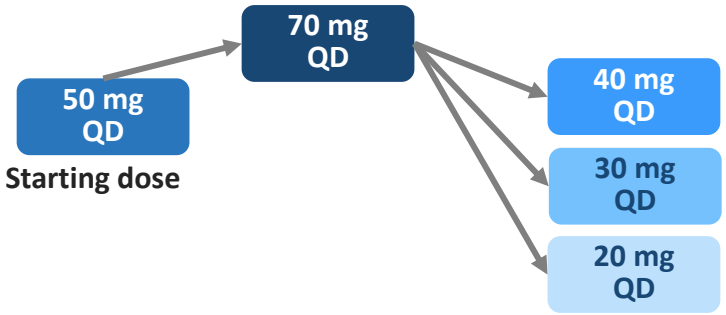
FGFR4 sparing: Diarrhea: n=3/49 (6%) patients, all low grade (Grade 1-2) and unrelated.

EOT, End of Treatment

Preliminary data as of 09-Sept-2021

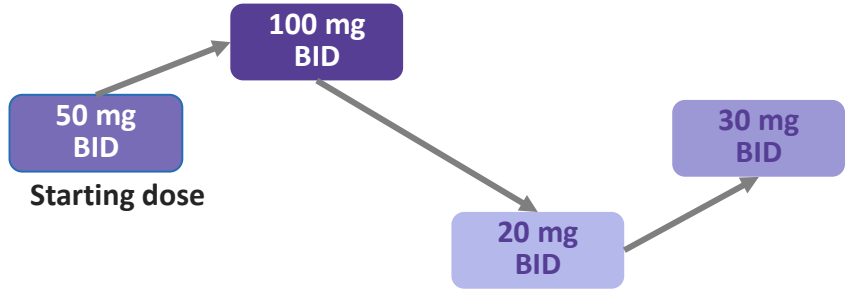
RLY-4008 FIH Study: Dose-limiting toxicities (DLTs)

QD Schedule (ongoing)



Dose (mg QD)	DLT evaluable patients**(n)	Dose Limiting Toxicity**
70	6	0
50	10	Gr 2 retinopathy (1)
40	4	0
30	4	0
20	4	0

BID Schedule (deprioritized)



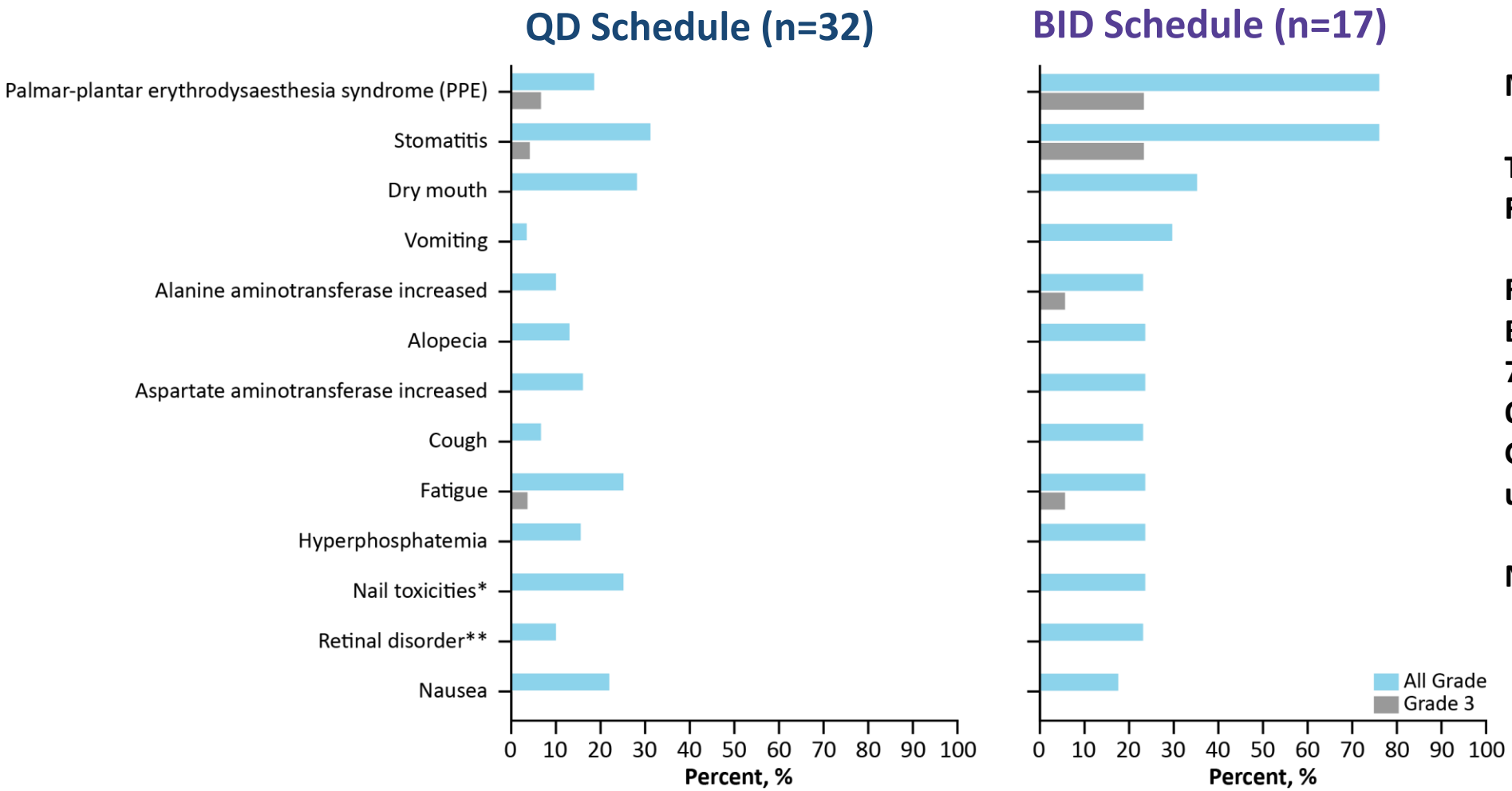
Dose (mg BID)	DLT evaluable patients* (n)	Dose Limiting Toxicity**
100	3	Gr 3 PPE (1) Gr 3 indirect hyperbili# (1)
50	7	Gr 2 stomatitis (1) Gr 2 rash (1)
30	3	Gr 3 stomatitis (1)
20	4	0

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 erythrodysaesthesia.

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

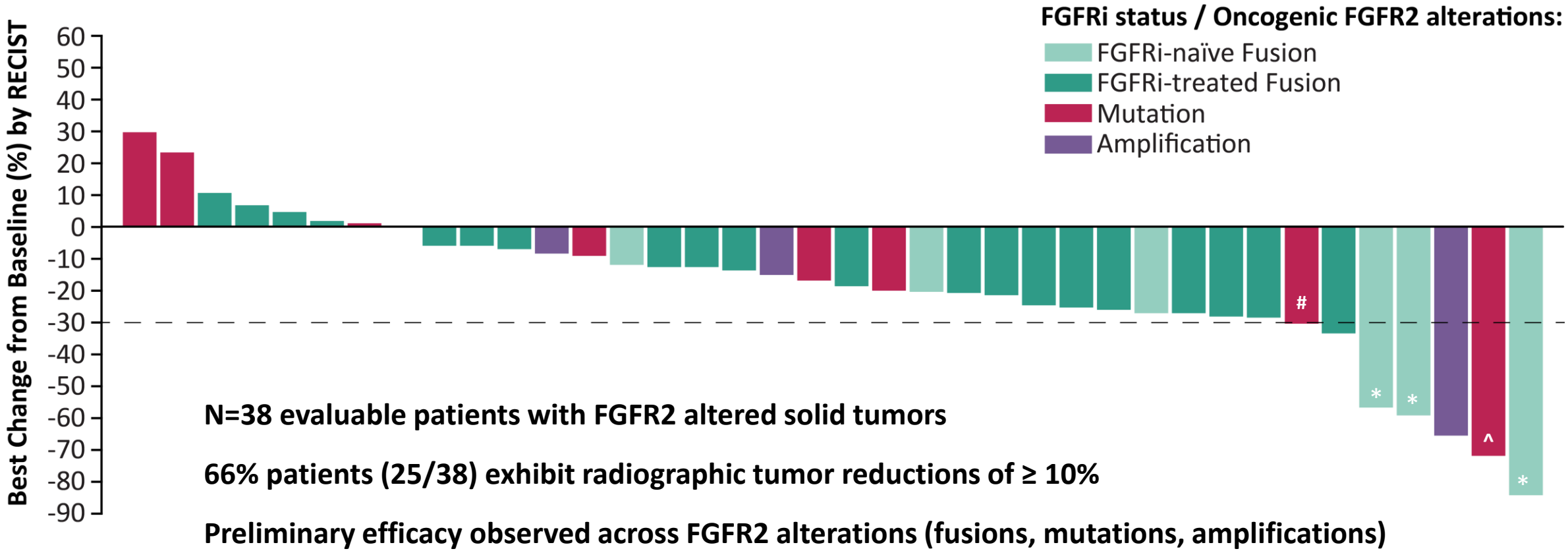
Retinopathy/Retinal Pigment Epithelial Detachment (RPED): 7 cases [BID n=4/17 (24%); QD n=3/32 (9%)]. All events were Gr 1-2, self-limiting or resolved upon treatment interruption

No Grade 4-5 AE

*Included preferred terms of nail disorder, nail discoloration, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, 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

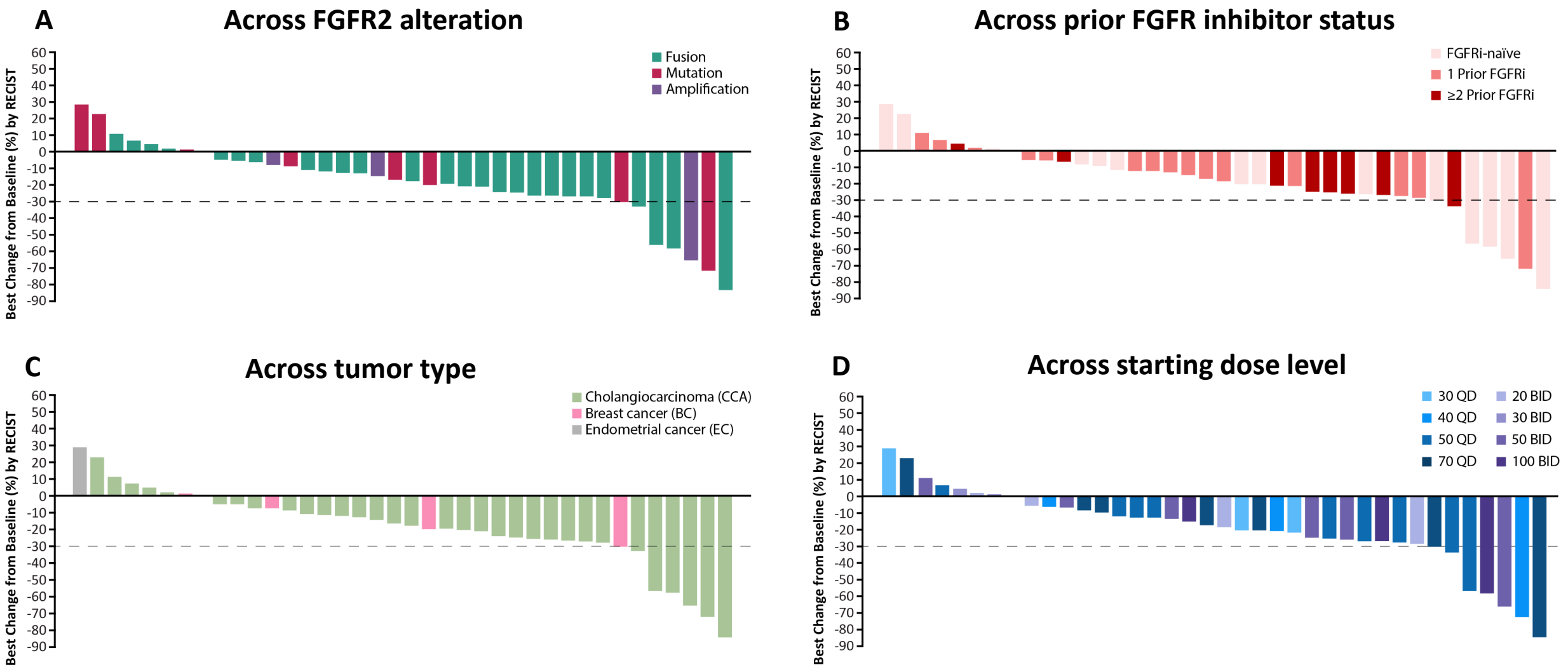
66% patients (25/38) exhibit radiographic tumor reductions of ≥ 10%

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

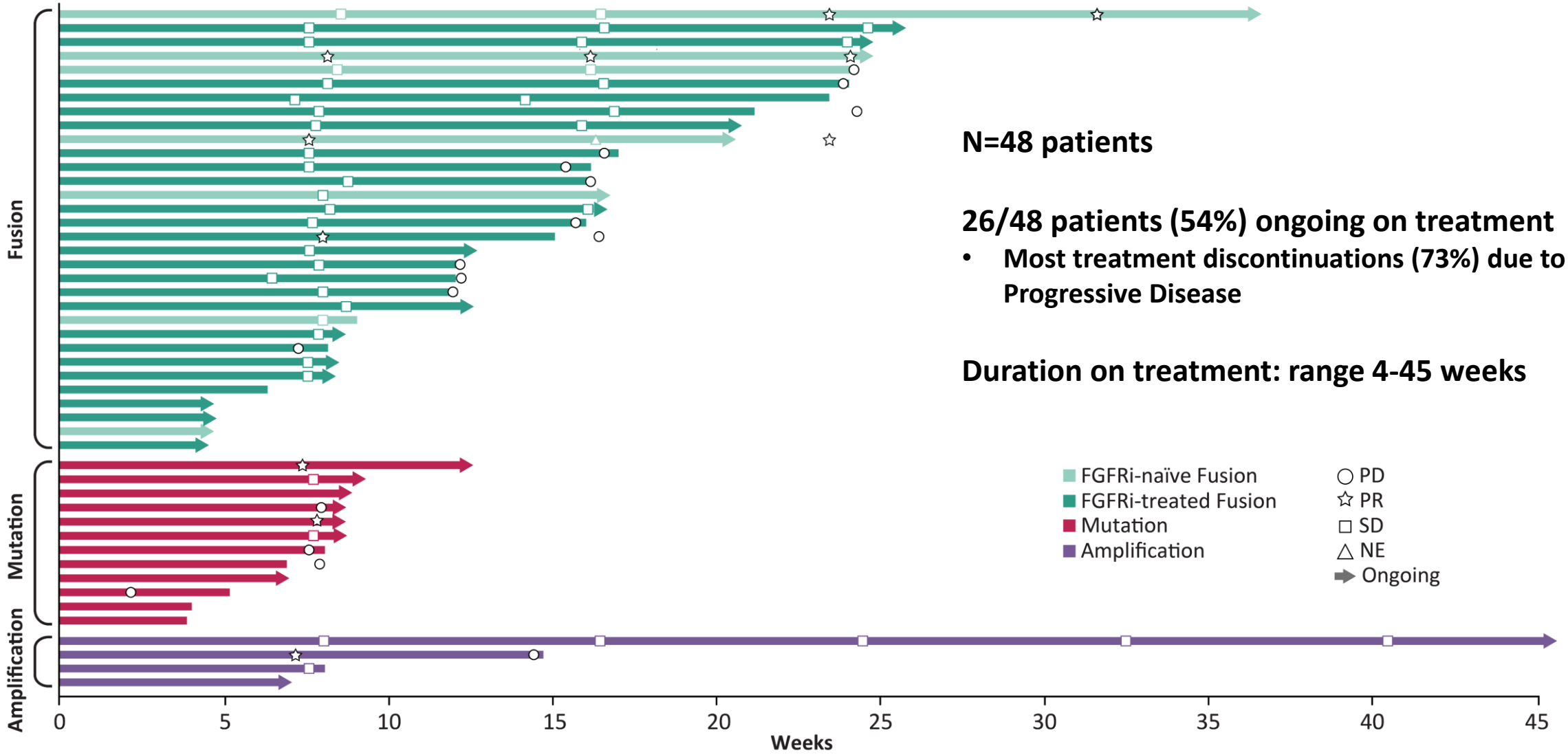
RLY-4008 induces radiographic tumor regression across FGFR2 alterations, FGFR inhibitor status, tumor types and dose levels



FGFRi, fibroblast growth factor receptor inhibitor.

Preliminary data as of 09-Sept-2021

RLY-4008 FIH Study: Time on treatment and response by FGFR2-alteration



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**

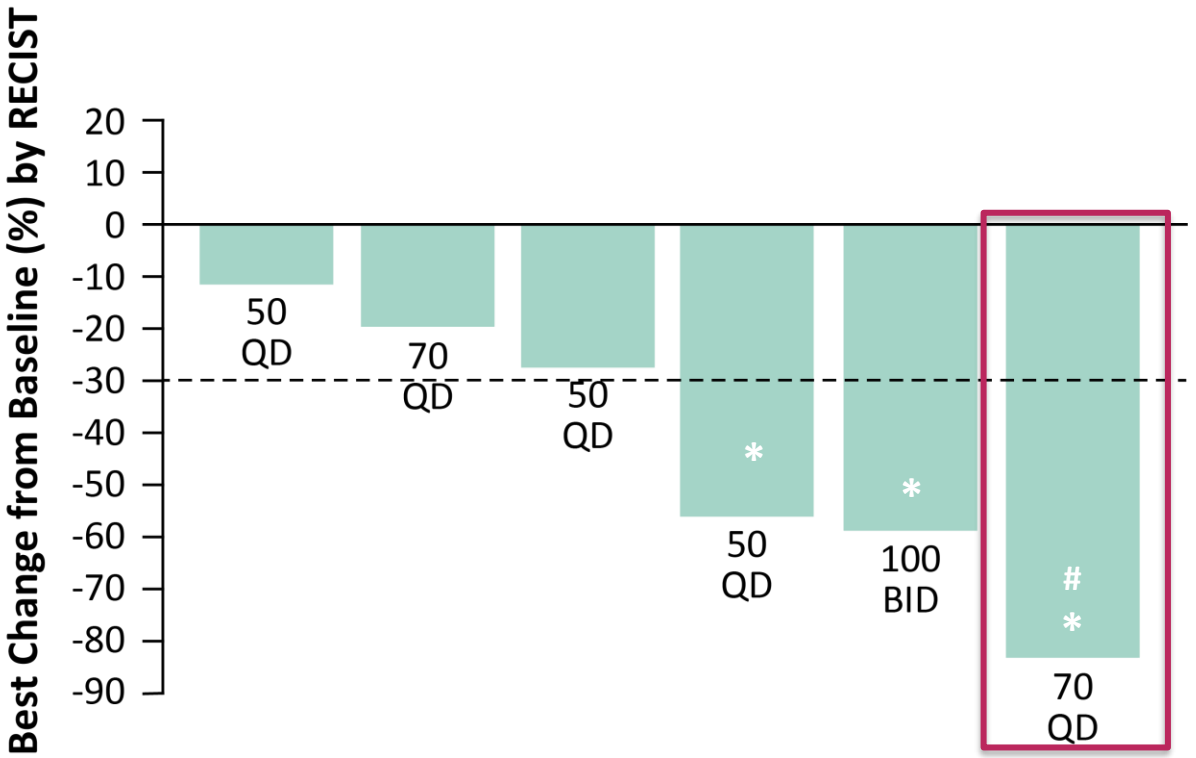
3. **FGFR2 mutant or amplified solid tumors**

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

Preliminary data as of 09-Sept-2021

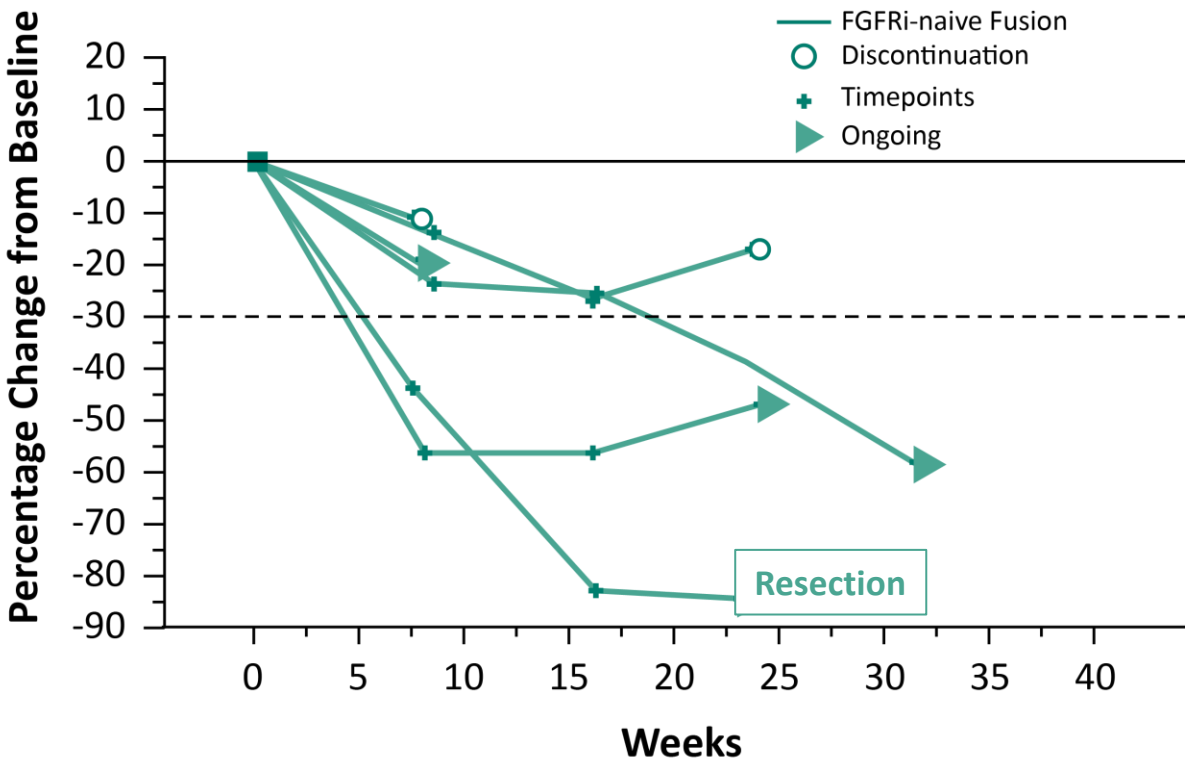
RLY-4008 induces radiographic tumor regression in FGFR inhibitor-naïve FGFR2-fusion+ cholangiocarcinoma

Best RECIST change from baseline



3/6 patients exhibit a confirmed PR

Relative change from baseline in tumor size



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

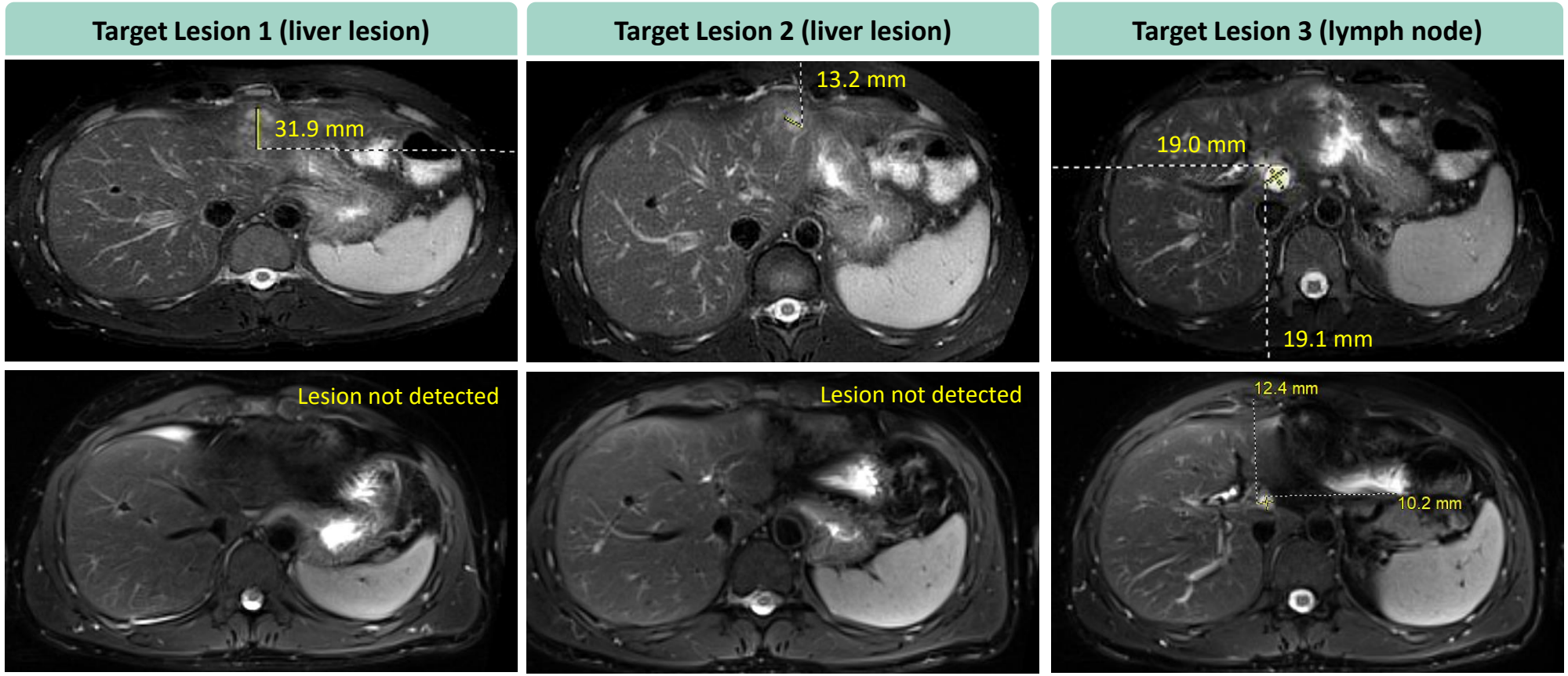
*Confirmed PR; #Tumor resection after data cut off.
FGFRi, fibroblast growth factor receptor inhibitor PR, partial response.

Preliminary data as of 09-Sept-2021

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

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



31.9 mm → Not detected

13.2 mm → Not detected

19.0 mm → 10.2 mm

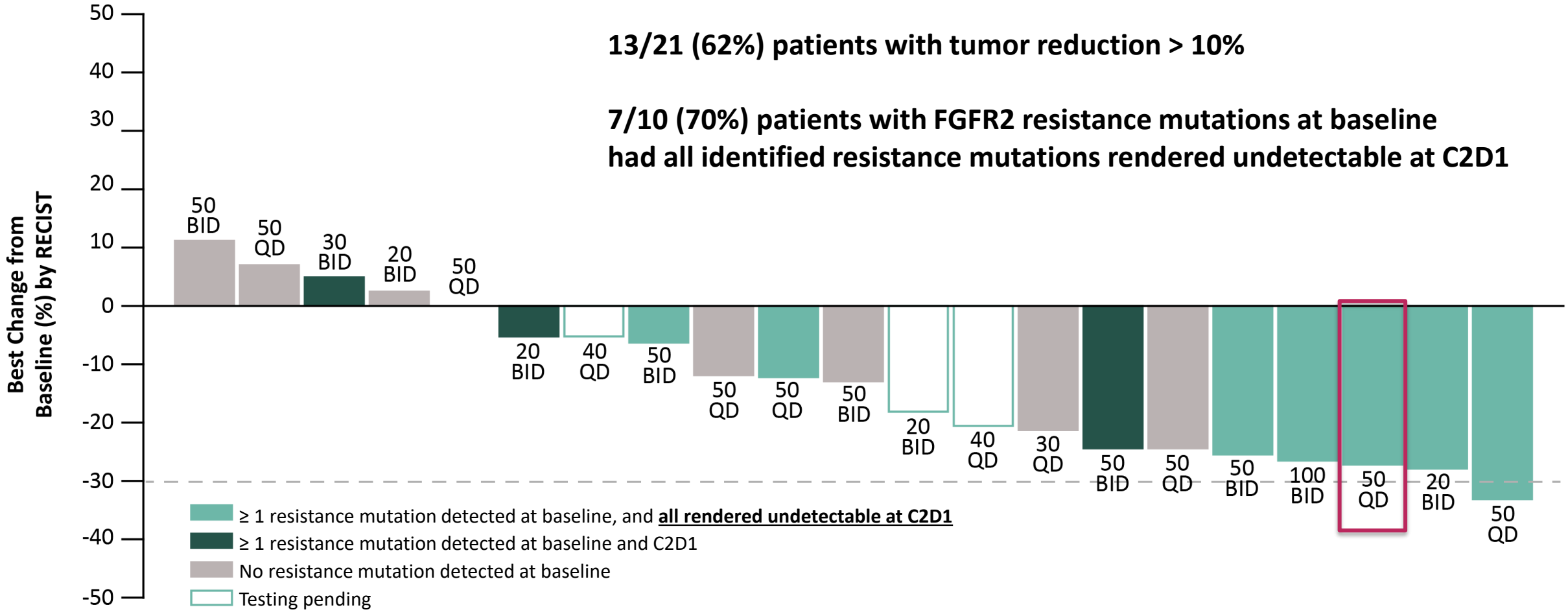
Confirmed PR (near CR) -83% by RECIST v1.1

Patient underwent resection in curative intent

Courtesy: Dr. V. Sahai (U Michigan)

Preliminary data as of 09-Sept-2021

RLY-4008 exhibits activity in pan-FGFR inhibitor resistant FGFR2-fusion cholangiocarcinoma regardless of FGFR2 resistance mutations



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

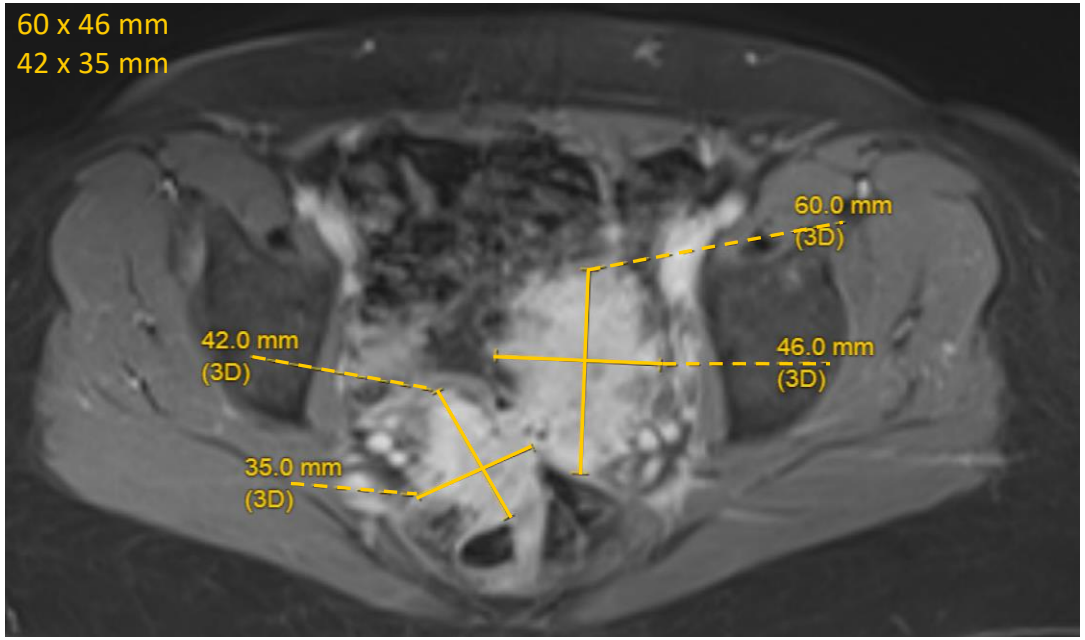
Preliminary data as of 09-Sept-2021

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

Baseline

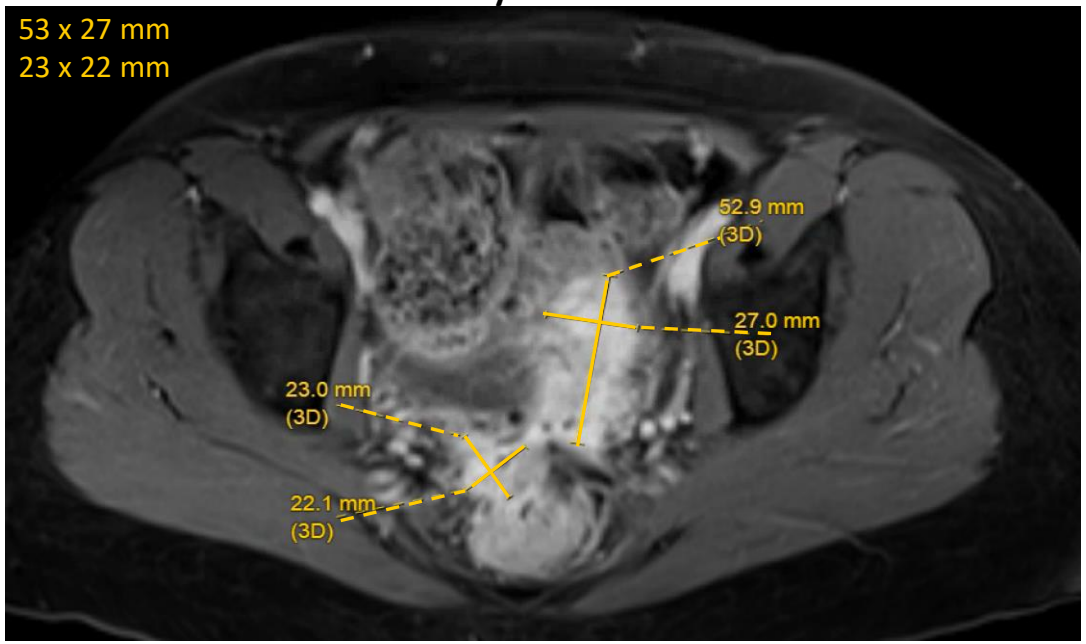
Pelvic lesions



Sustained tumor reduction at Cycle 7

- 21% by RECIST v1.1

Cycle 7

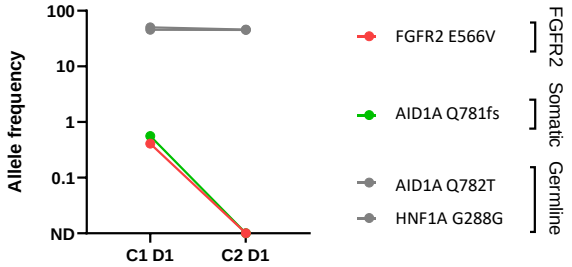


<u>Antitumor activity:</u>
Sustained tumor reduction at C7 (-21% per RECIST v1.1)

<u>Safety and tolerability</u>
No dose interruption or modification

RLY-4008 treatment is ongoing (50 mg QD)

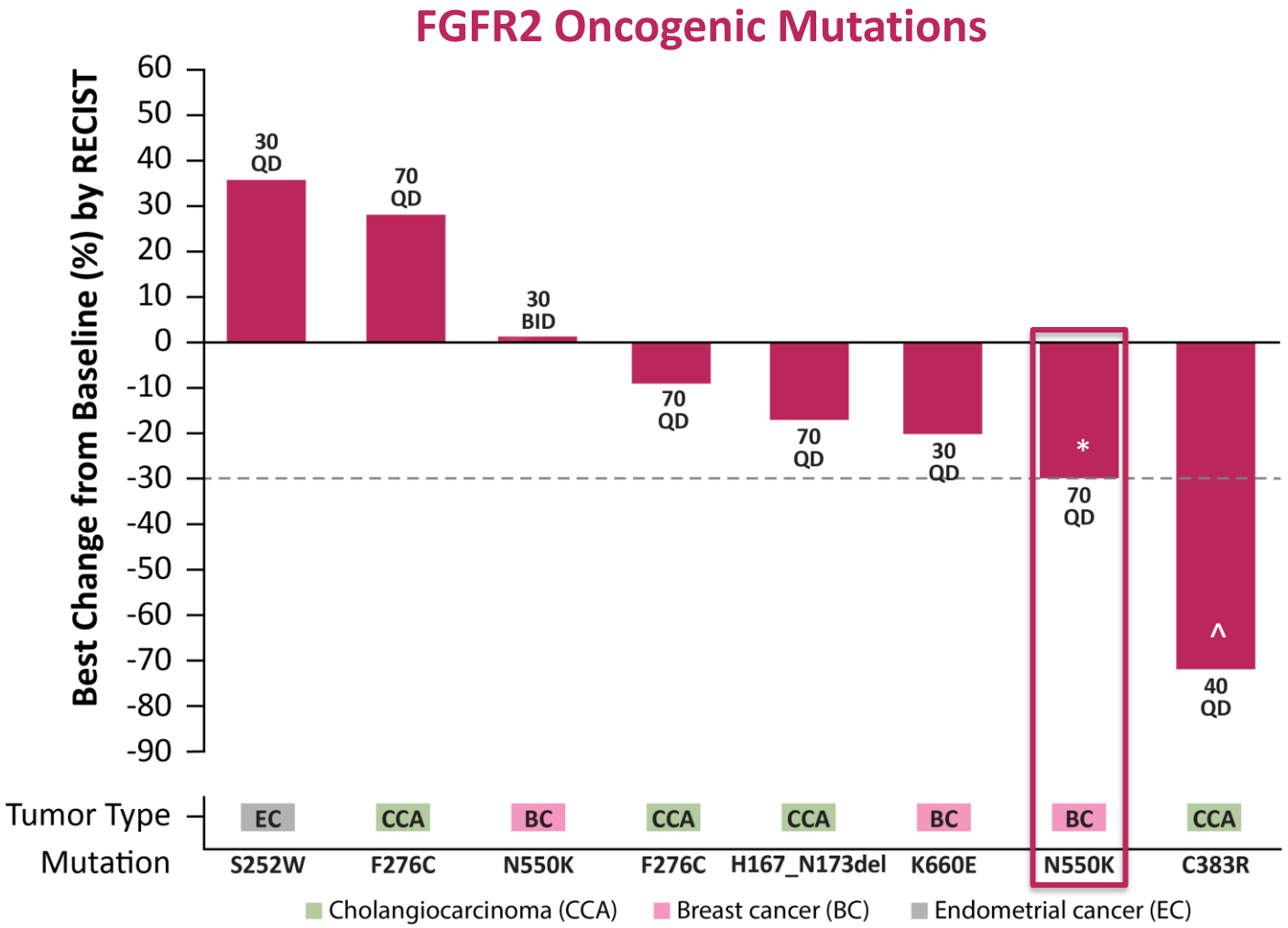
<u>ctDNA:</u>
Baseline FGFR2-E566V mutation is undetectable at C2D1

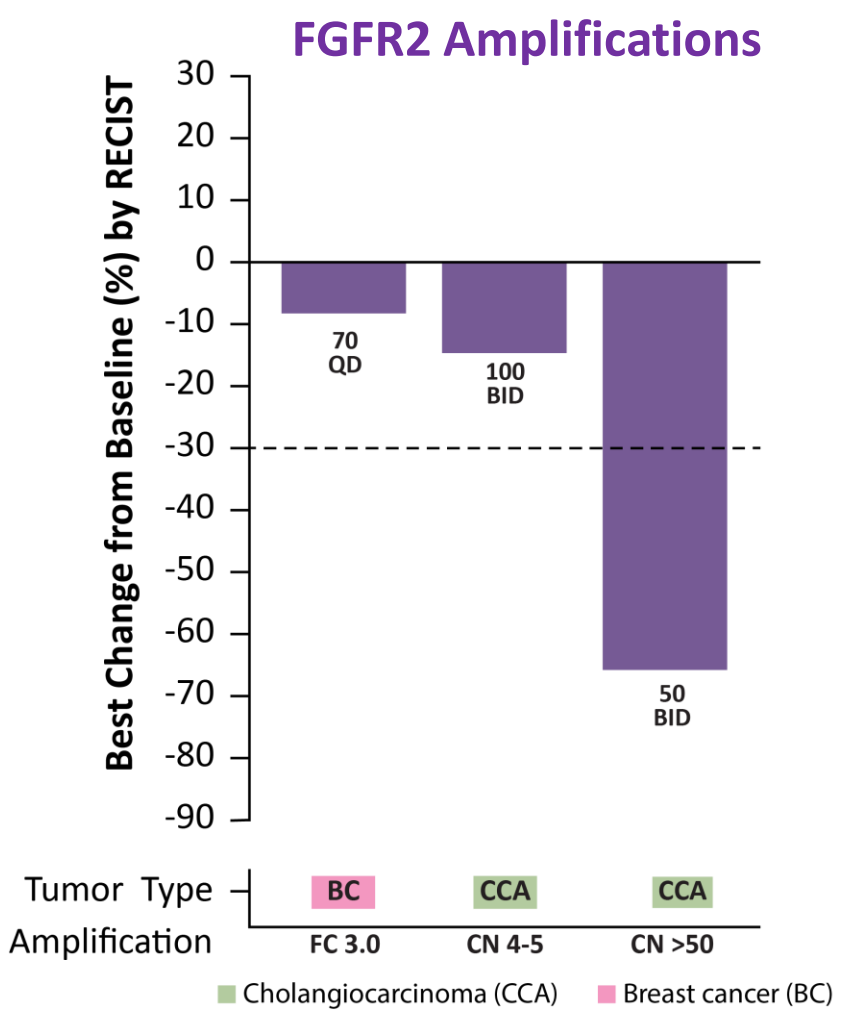


Courtesy: Dr. L. Goyal (Mass. General Hospital)

Preliminary data as of 09-Sept-2021

RLY-4008 induces radiographic tumor regression in FGFR2 oncogenic mutations and in FGFR2 amplifications



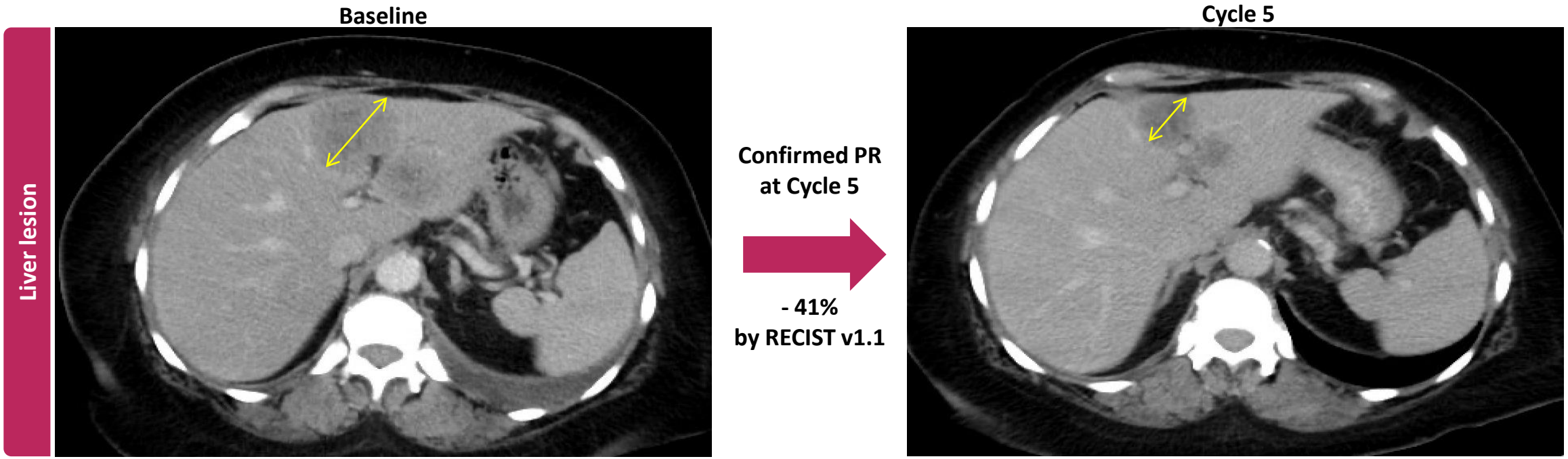


*Confirmed PR with increased tumor reduction after data cut; ^PR pending confirmation.
FC, fold change; CN, copy number.

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)

Preliminary data as of 09-Sept-2021

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

Preliminary data as of 09-Sept-2021

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- **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**

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