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Efficacy of RLY-4008

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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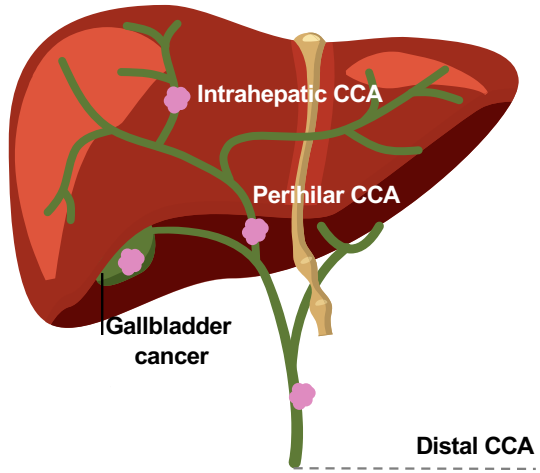
Declaration of Interests

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

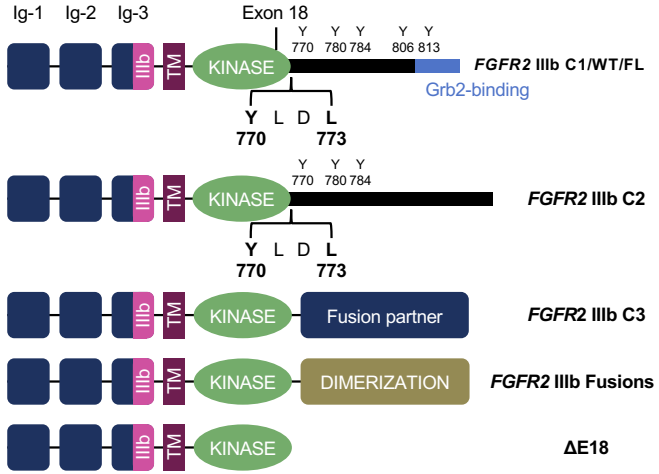
Cholangiocarcinoma and Oncogenic *FGFR2* Fusions

Cholangiocarcinoma (CCA) is a rare malignancy with a dismal prognosis[1]



1st Line: Gemcitabine/Cisplatin +/- Durvalumab mOS ~1 year[3-4]
2nd Line: FOLFOX mOS ~6m[5]

***FGFR2* fusions/rearrangements drive ~10-15% of intrahepatic cholangiocarcinoma[2]**



2nd Line Emerging pan-FGFRi:
Infigratinib, Pemigatinib,Futibatinib
Off-isoform toxicities; On-target resistance mutations[6-13]

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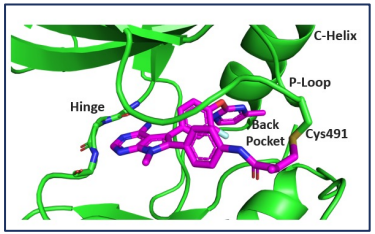
RLY-4008: The First Highly Selective FGFR2 Inhibitor

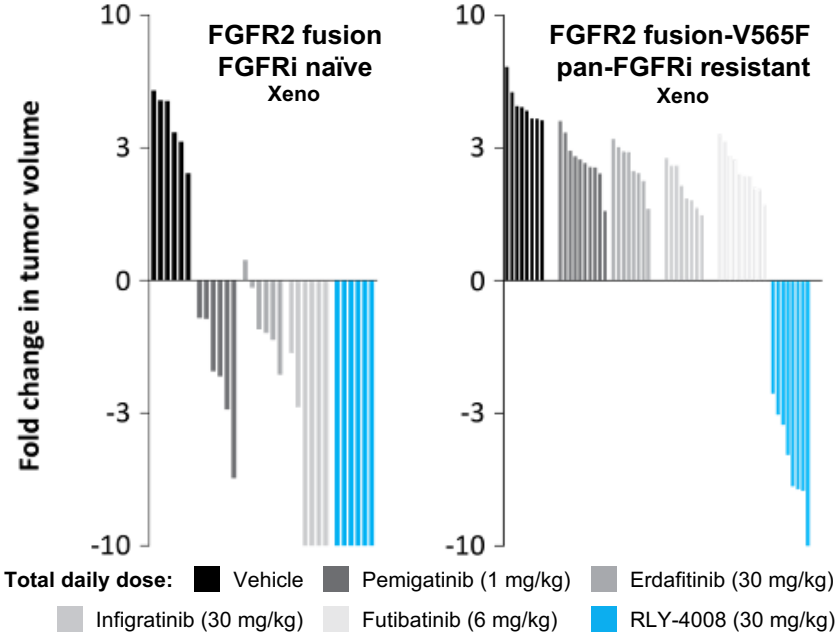
In contrast to pan-FGFRi, RLY-4008 is a potent and selective FGFR2 inhibitor



RLY-4008 selectively inhibits FGFR2 based on unique conformational dynamics[1]

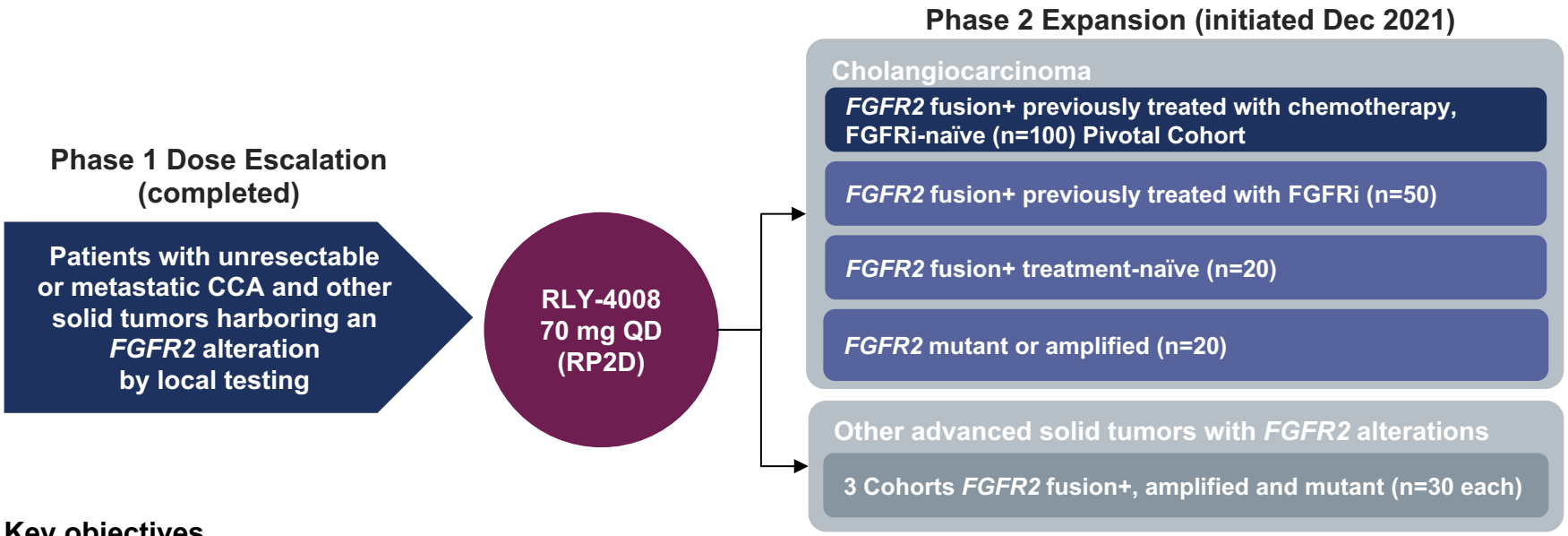
Inhibitor	Mechanism of Action	Biochemical IC50 (nM)[2-5]			
		FGFR1	*FGFR2*	*FGFR3*	*FGFR4*
RLY-4008	Irreversible FGFR2 selective	864.3	3.1	274.1	17,633
Infigratinib	Reversible Pan-FGFRi	1.1	1	2	61
Pemigatinib	Reversible Pan-FGFRi	0.39	0.46	1.2	30
Futibatinib	Irreversible Pan-FGFRi	1.8	1.4	1.6	3.7

Potent in-vivo activity against FGFRi-sensitive and resistant cholangiocarcinoma[2]



1. Schönherr H. et al. Presented at MedChem GRC meeting; August 7-12,2022. 2. Goyal L. et al. Presented at AACR Annual Meeting; April-9-14;2021. 3.Truseltiq(infigratinib) [package insert]. Brisbane,CA QED Therapeutics; 2021.
4. Pemazyre(pemigatinib) [NDA]. Wilmington, DE;2019. www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213736Orig1s000ChemR.pdf Accessed August 25,2022. 5. Sootome H. et al. *Cancer Res.* 2020;80(22):4986-4997.

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



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

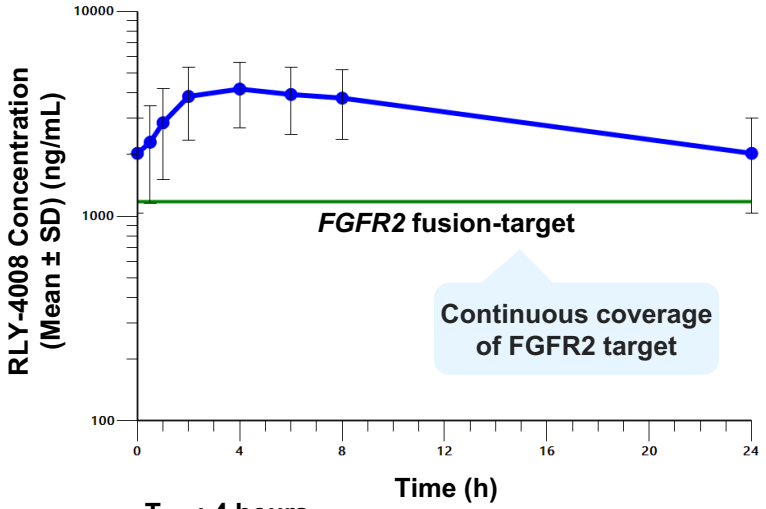
Parameter	CCA, Fusion+, FGFRi-naïve*		Overall** (N=195)
	RP2D, 70 mg QD (N=17)	All doses (N=38)	
Age (years), median (range)	57 (36 to 81)	58 (33 to 81)	59 (23 to 87)
Female, %	59	58	62
Race, %			
White / Asian / Black / Unknown	41 / 24 / 0 / 35	58 / 21 / 3 / 18	63 / 15 / 4 / 18
ECOG PS, %			
0	53	50	38
1	47	50	58
2	0	0	3
Prior lines of systemic therapy, %			
0	0	0	2
1	41	47	20
2	47	32	29
3+	12	21	49
Baseline sum of target lesions (RECIST 1.1, mm), median (range)	57 (10 to 157)	63 (10 to 216)	79 (10 to 274)

* 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.

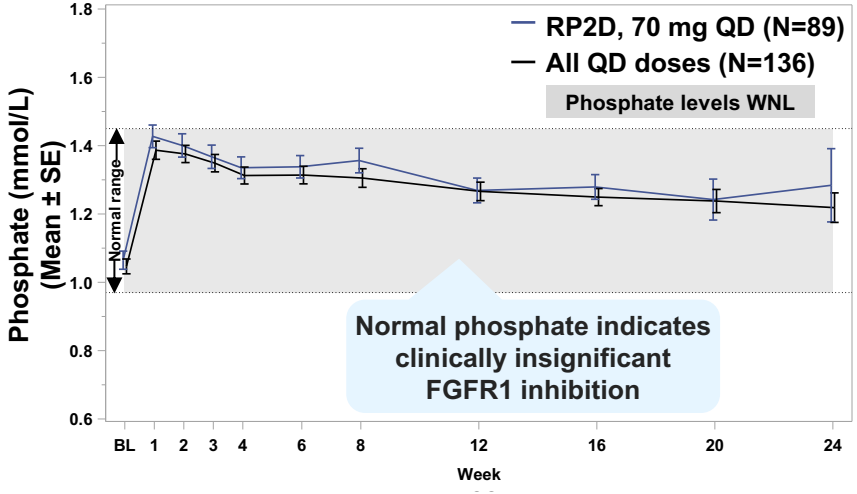
RLY-4008 Provides Potent and Selective FGFR2 Inhibition

Steady state pharmacokinetics at RP2D



T_{max}: 4 hours
Effective half-life: 23 hours

Serum phosphate over time at RP2D and all QD doses



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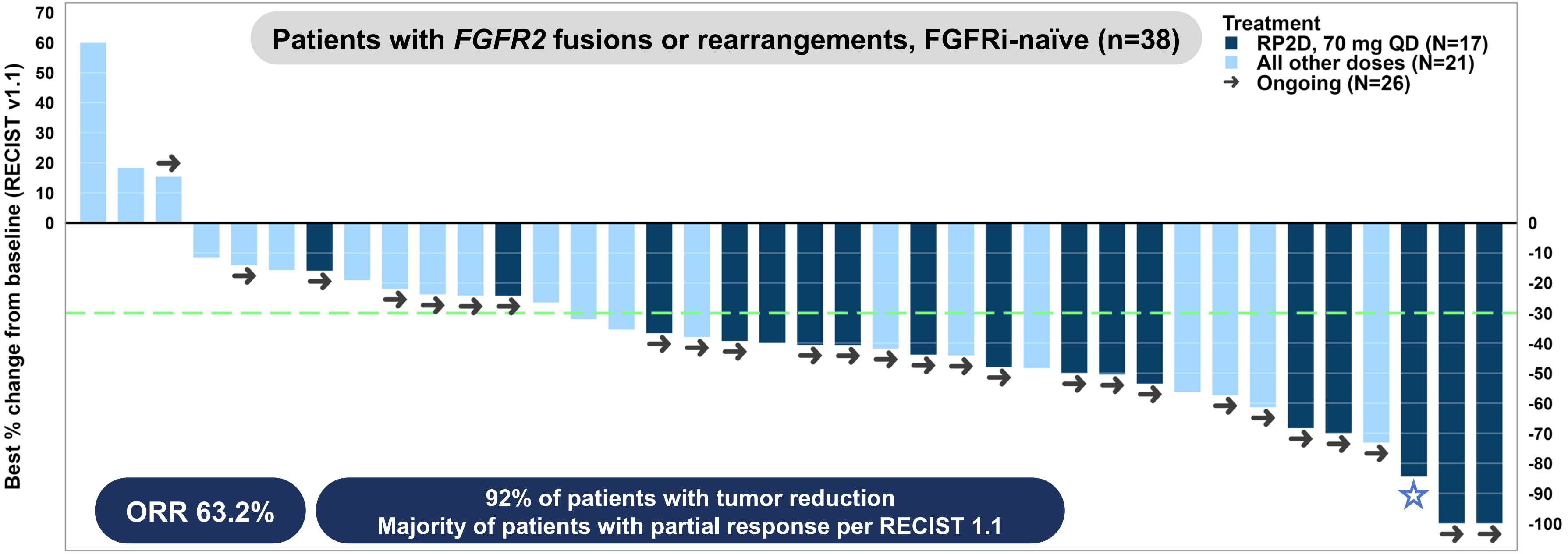
Radiographic Tumor Regression and Response per RECIST 1.1 Across All Doses



Dose (mg)	30 QD	20 QD	100 QDi	50 QD	50 QDi	50 QDi	70 QD	40 QD	50 QDi	70 QDi	100 QDi	70 QD	50 QD	60 QDi	60 QD	70 QD	90 QDi	70 QD	70 QD	70 QD	70 QD	90 QDi	70 QD	100 QDi	70 QD	40 QD	70 QD	70 QD	70 QD	50 QD	60 QD	100 BID	70 QD	70 QD	60 QDi	70 QD	70 QD	70 QD
BOR	PD	PD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	PR	SD	uPR	PR	PR	PR	PR	PR	uPR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR

QDi = once daily dosing on an intermittent schedule; BID = twice daily dosing; ☆ = resection with curative intent   Confirmed ORR 57.9% 2/24 unconfirmed PR

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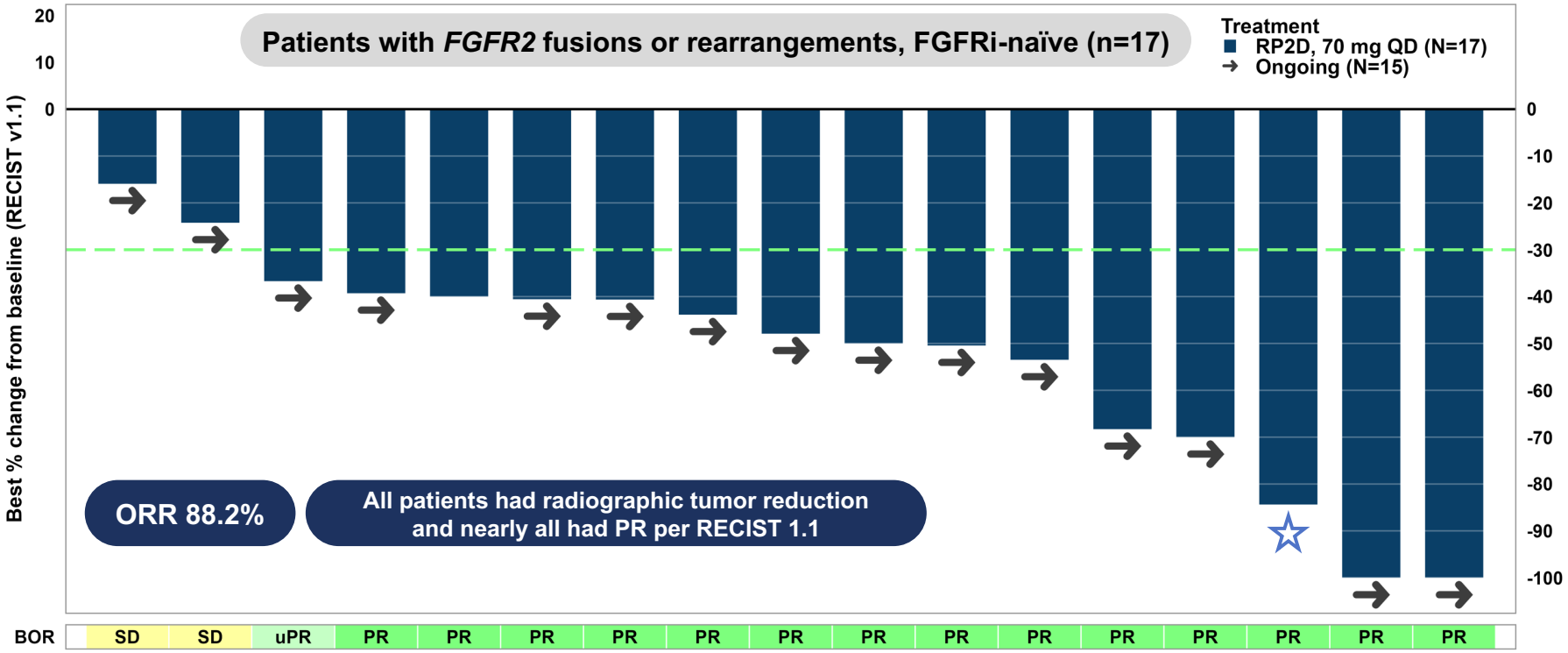
Radiographic Tumor Regression and Response per RECIST 1.1 at RP2D (70 mg QD)



☆ = resection with curative intent

Confirmed ORR 82.4% 1/15 unconfirmed PR

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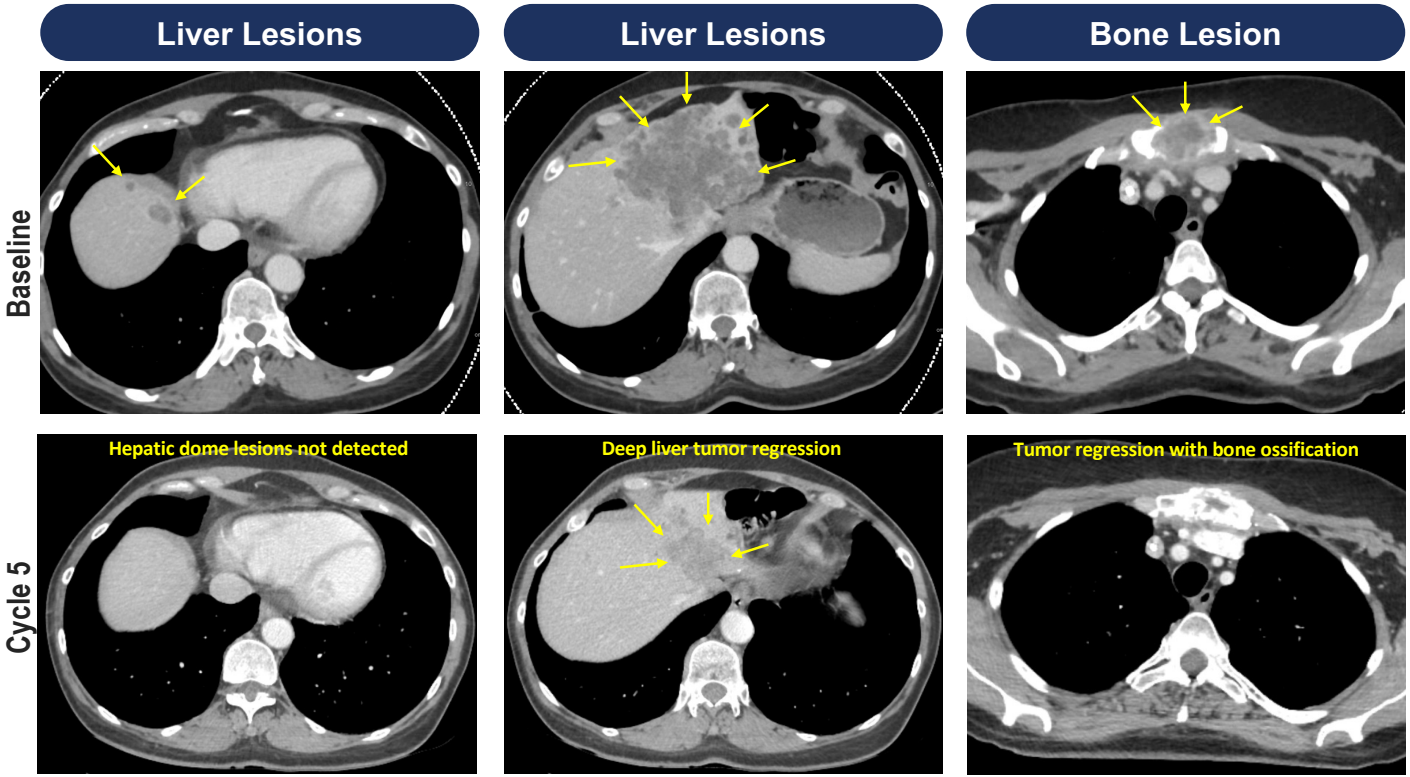
RLY-4008 Induces Marked Radiographic Response per RECIST 1.1

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%)



Courtesy A. Hollebecque, IGR.

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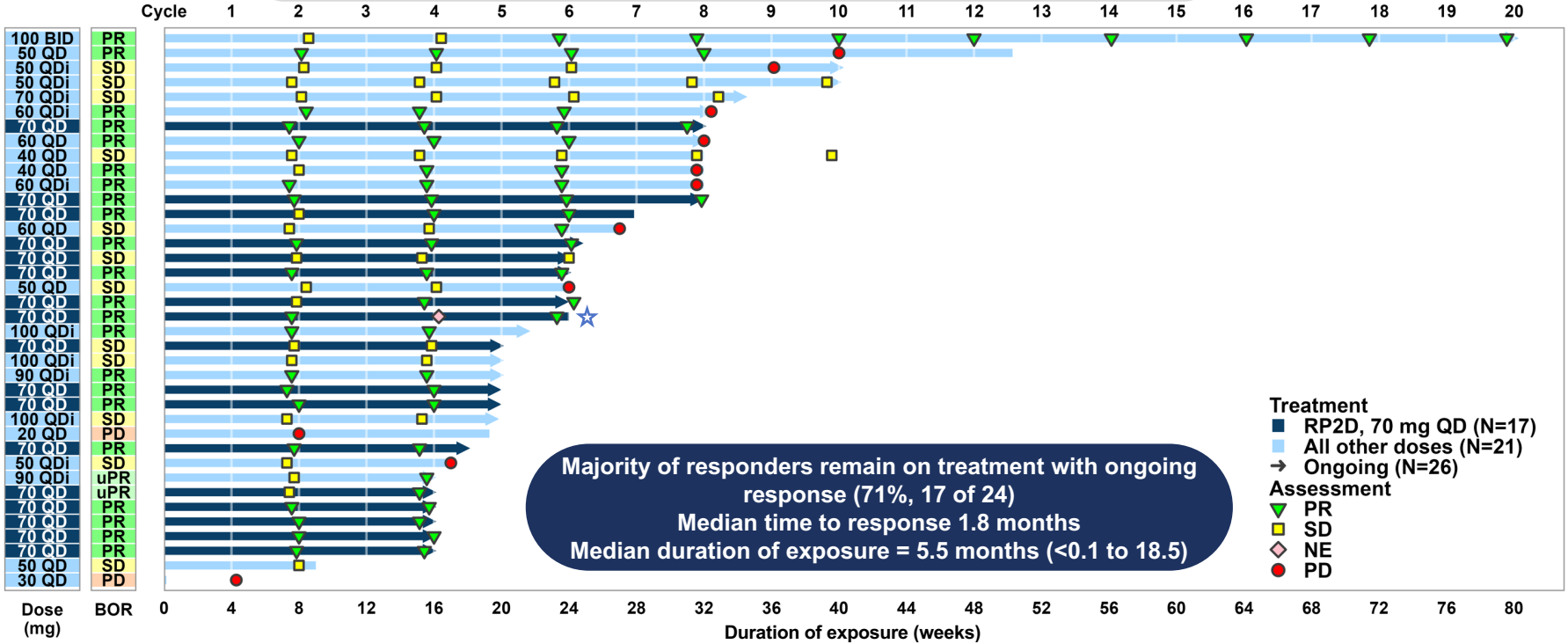
Radiographic Response per RECIST 1.1

	Patients with *FGFR2* fusions or rearrangements, FGFRi-naïve	
Parameter	**RP2D, 70 mg QD (N=17)**	**All doses (N=38)**
Objective response rate (ORR), n (% [95% CI])	15 (88.2 [63.6 - 98.5])	24 (63.2 [46.0 - 78.2])
• Confirmed ORR, n (% [95% CI])	14 (82.4 [56.6 - 96.2])	22 (57.9 [40.8 - 73.7])
Best overall response, %		
• Partial response	82.4	57.9
• Unconfirmed partial response	5.9	5.3
• Stable disease	11.8	31.6
• Progressive disease	—	5.3
• Response ongoing, n/N (%)*	15/15 (100.0)	19/24 (79.2)
Disease control rate, n (% [95% CI])	17 (100.0 [80.5 - 100.0])	36 (94.7 [82.3 - 99.4])
Remain on treatment, n (%)	15 (88.2)	26 (68.4)

* 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



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.

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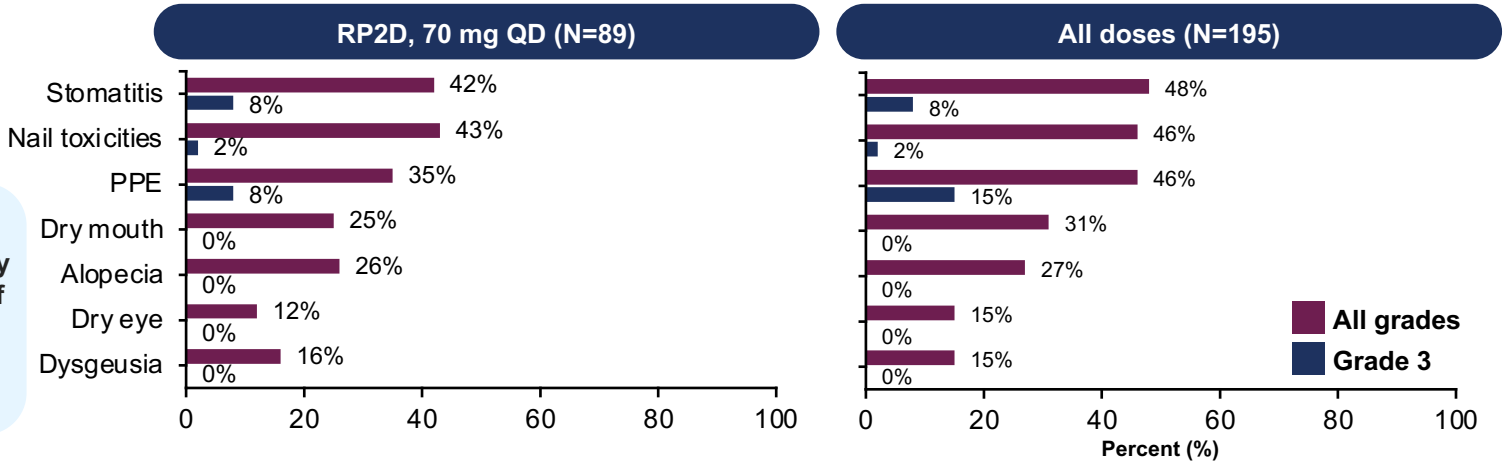
Treatment-Related Adverse Events (TRAEs) ≥ 15%

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



TRAE Dose Modification	RP2D, 70mg QD (N=89)	All Doses (N=195)
Interruption, n (%)	37 (42)	92 (47)
Reduction, n (%)	24 (27)	65 (33)
Discontinuation, n (%)	1 (1)	2* (1)

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

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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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