2023 ASCO® ANNUAL MEETING

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

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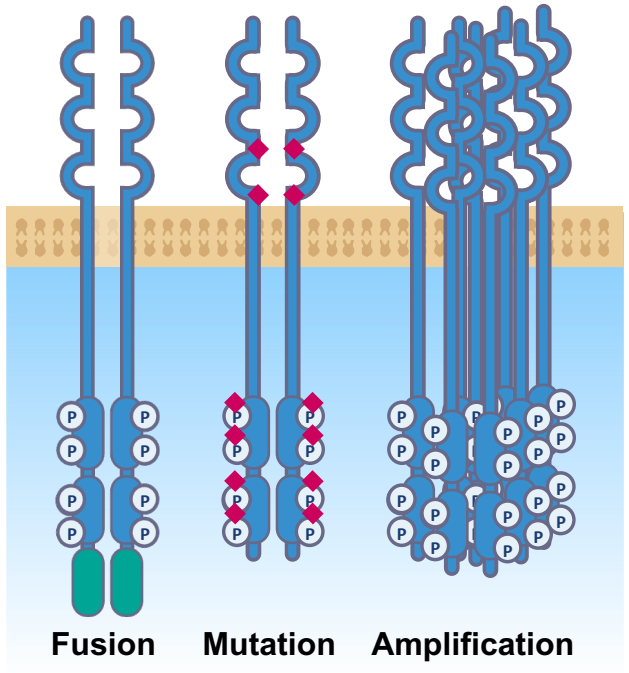
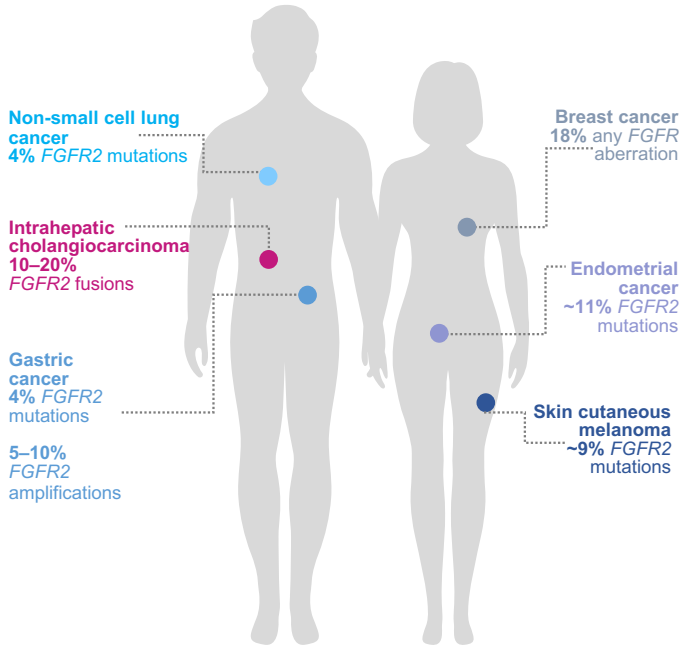
Oncogenic Activation of FGFR2 Drives Multiple Cancers, But Selective Targeting of FGFR2 Has Not Been Achieved

FGFR2 is a clinically validated oncogene[1]



FGFR2 alterations drive multiple solid tumor types[2-4]



Approved pan-FGFR inhibitors solid tumor indications

	Phase 2 Response Rate	DoR (mos)	% of patients with… (All grades)	
			Hyper phosphatemia[9] (FGFR1 off-isoform toxicity)	Diarrhea (FGFR4 off-isoform toxicity)
Pemigatinib[5]	36% (CCA)	9.1 (CCA)	94%	47%
Futibatinib[6]	42% (CCA)	9.7 (CCA)	88%	39%
Erdafitinib[7]	32% (Urothelial Carcinoma)	5.4 (Urothelial Carcinoma)	76%	47%
Infigratinib[8]	23% (CCA)	5.0 (CCA)	90%	24%

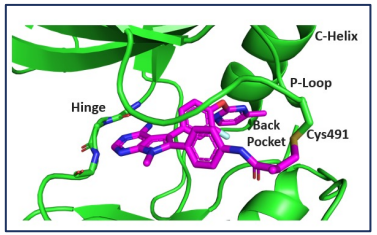
Infigratinib withdrawn

1. Babina IS and Turner NC. *Nat Rev Cancer*. 2017;17:318–332; 2. Krook MA, et al. *Br J Cancer* 2021;124:880–892; 3. Helsten T, et al. *Clin Cancer Res*. 2016;22:259–267; 4. Li J et al, *Front Oncol* 2021; 11: DOI=10.3389/fonc.2021.644854 5. PEMAZYRE® (pemigatinib). Highlights of prescribing information; Pemazyre (pemigatinib) [package insert]. Wilmington, DE Incyte; 2020; ESMO 2019; 6. LYTGOBI® (futibatinib). Highlights of prescribing information; Lytgobi (futibatinib) [package insert]. Princeton, NJ Taiho Oncology; 2022 7. BALVERSA (erdafitinib) Highlights of prescribing information; Balversa (erdafitinib) [package insert]. Horsham, PA Janssen. 8. Truseltiq(infigratinib) [package insert]. Brisbane,CA QED Therapeutics; 2021 9. As defined by increased serum phosphate except for infigratinib which is not specified

CCA: Cholangiocarcinoma, FGFRi: fibroblast growth factor receptor, FGFRi: fibroblast growth factor receptor inhibitor

RLY-4008: The First Highly Selective FGFR2 Inhibitor

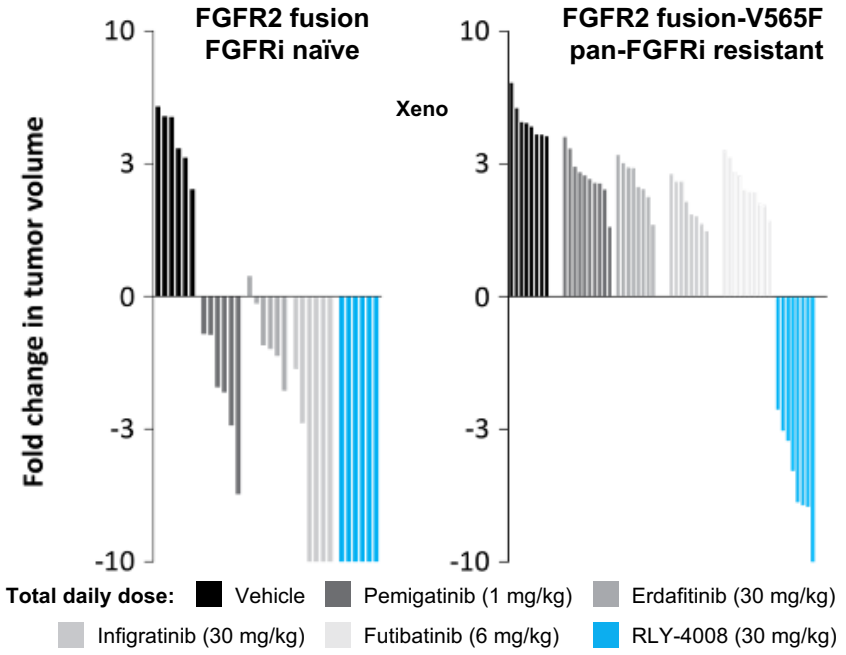
In contrast to pan-FGFRi, RLY-4008 is a potent and selective FGFR2 inhibitor



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

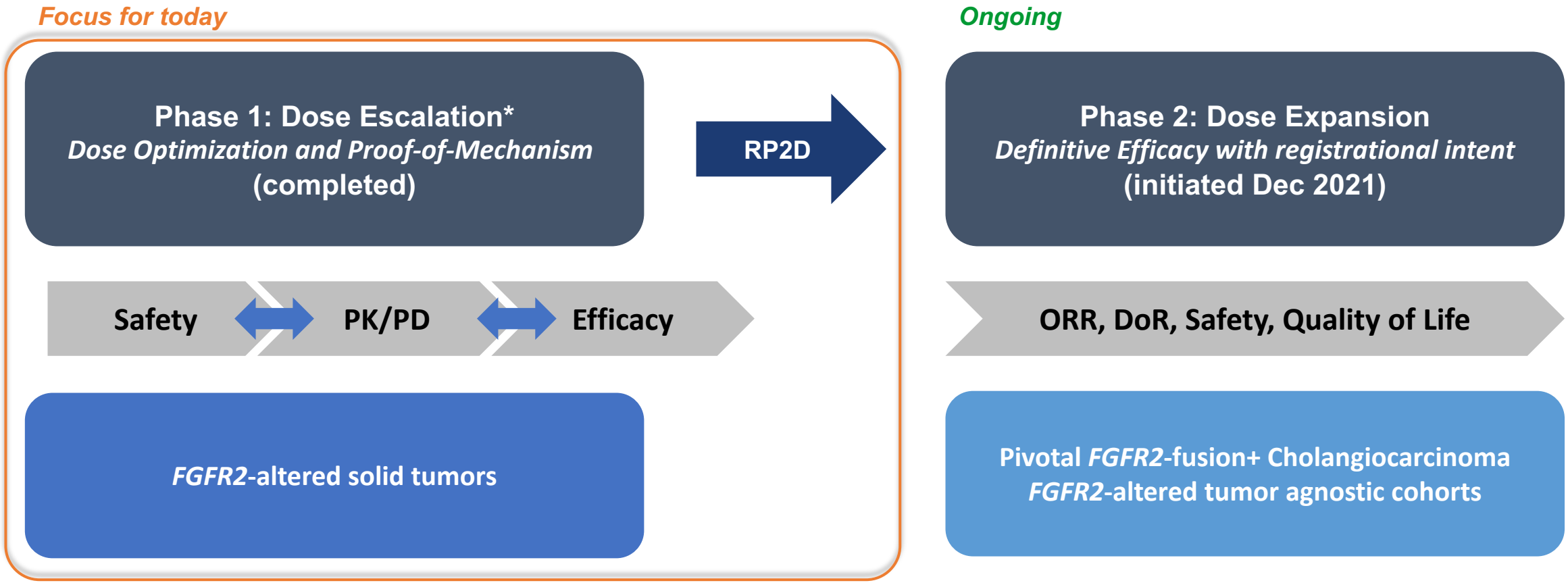
Inhibitor	Mechanism of Action	Biochemical IC50 (nM)[2-5]			
		FGFR1	*FGFR2*	*FGFR3*	*FGFR4*
RLY-4008	Irreversible FGFR2 selective	864.3	3.1	274.1	17,633
Infigratinib	Reversible Pan-FGFRi	1.1	1	2	61
Pemigatinib	Reversible Pan-FGFRi	0.39	0.46	1.2	30
Futibatinib	Irreversible Pan-FGFRi	1.8	1.4	1.6	3.7

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.
FGFRi: fibroblast growth factor receptor inhibitor

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



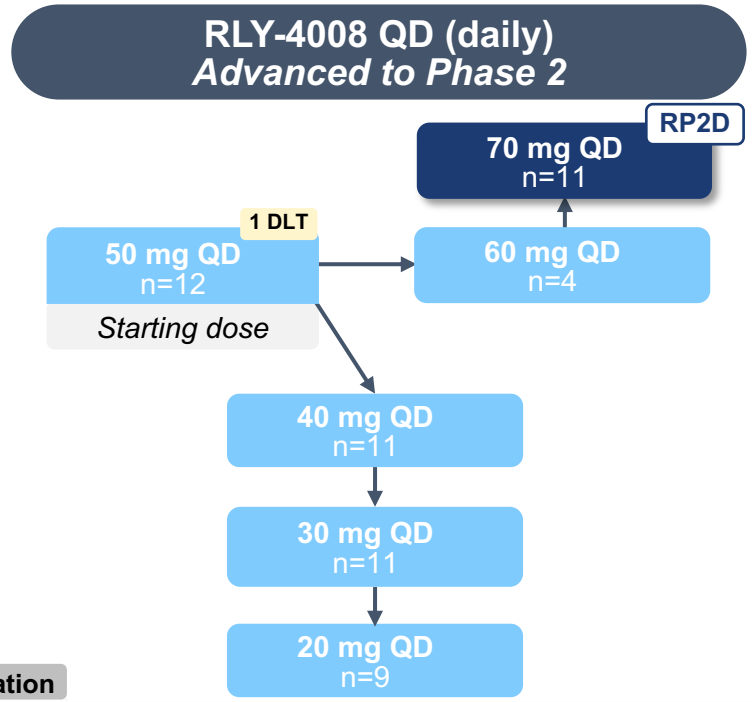
*Dose escalation followed a BOIN design with enrichment (additional accrual to dose levels declared tolerable); dose modifications including intra-patient dose escalation were permitted per protocol based on tolerability.
Data for Phase 1 Dose Escalation as of 01/30/2023.
BOIN: Bayesian Optimal Interval, DoR: Duration of Response, ORR: Overall Response Rate, RP2D: Recommended Phase 2 Dose

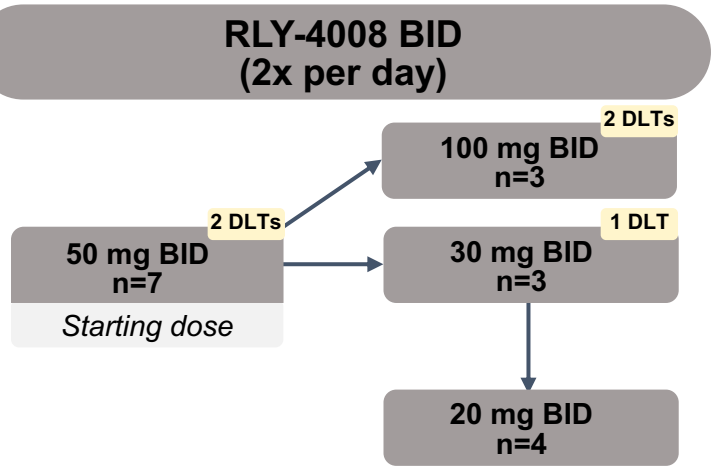
ReFocus Phase 1 Demographics and Baseline Characteristics

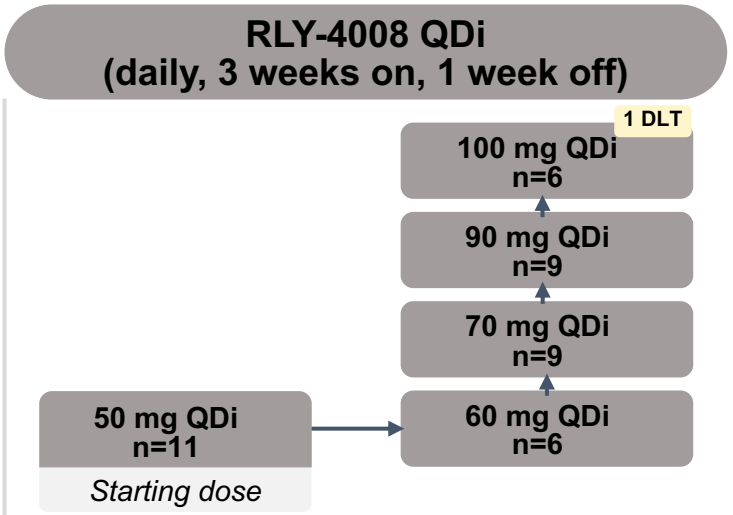
	Cholangiocarcinoma (CCA)		Other Tumors (N=25)	Overall (N=116)
	Pan-FGFRi Naïve (N=36)	Pan-FGFRi Refractory (N=55)		
Age (years), median (range)	59 (33–78)	56 (23–87)	61 (37–81)	58 (23–87)
Female, %	58%	67%	64%	64%
Ethnicity, %				
White / Asian / Black or African American /Other	75% / 14% / 3% / 8%	78% / 9% / 5% / 7%	64% / 20% / 12% / 4%	74% / 13% / 6% / 7%
ECOG PS, %				
0 / 1 / 2	47% / 53% / 0%	29% / 62% / 9%	48% / 52% / 0%	39% / 57% / 4%
Prior chemotherapy, %	100%	95%	96%	97%
0 / 1 / 2 / 3+ lines	0% / 58% / 19% / 22%	5% / 36% / 33% / 25%	4% / 16% / 36% / 44%	3% / 39% / 29% / 29%
Prior FGFRi, %	0%	100%	12%	50%
0 / 1 / 2 / 3 lines	100% / 0% / 0% / 0%	0% / 71% / 25% / 4%	88% / 12% / 0% / 0%	50% / 36% / 12% / 2%
FGFR2 alteration, %				
Fusion	69%	91%	28%	71%
Mutation	28%	7%	52%	23%
Amplification	3%	2%	16%	5%
No FGFR2 Alteration	0%	0%	4%	1%

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







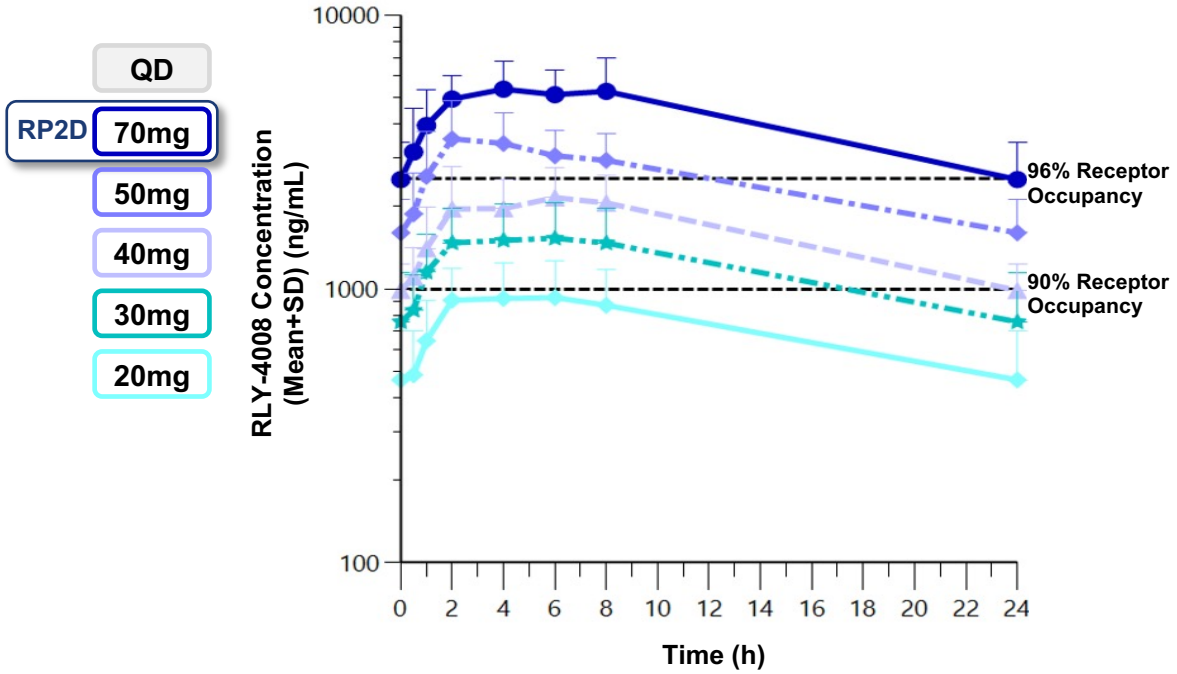
TRAE Dose Modification	Dose Limiting Toxicities (DLT)*		
Dose Interruption (%)	30 (51.7)	14 (82.4)	24 (58.5)
Dose Reduction (%)	22 (37.9)	12 (70.6)	20 (48.8)
Discontinuation due to AE (%)	2 (3.4)	0	1 (2.4)

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

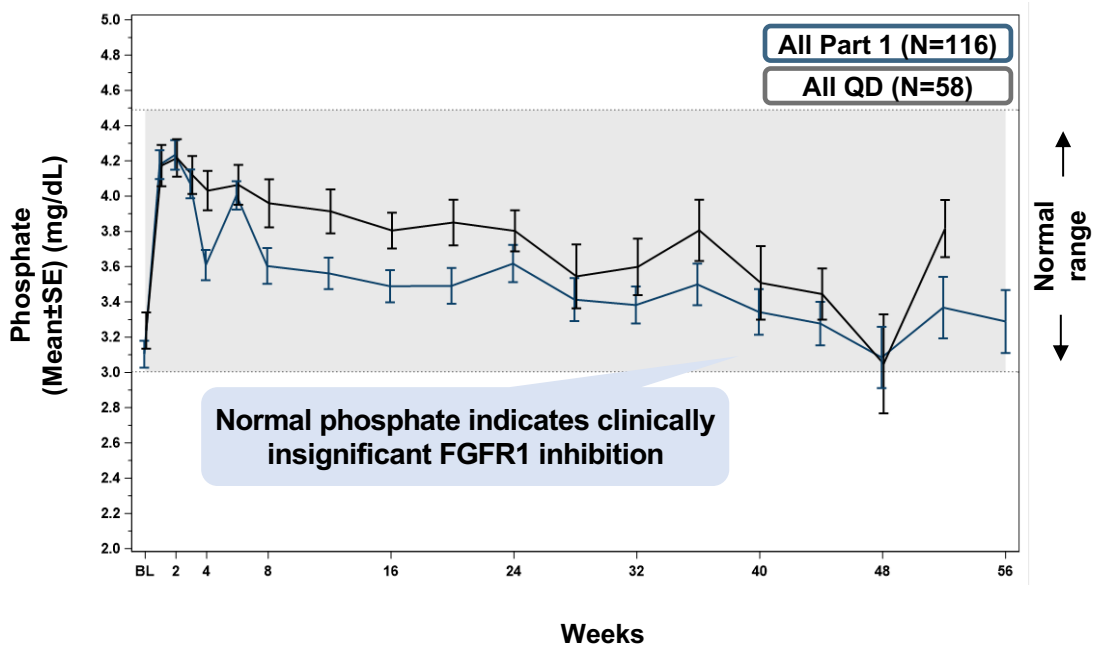
*28-day DLT period (per protocol); DLT evaluable patients represent patients treated in escalation & enrichment cohorts per BOIN design. DLTs include Retinopathy, Rash maculo-popular, Rash erythematous, Stomatitis, Hyperbilirubinemia
BOIN: Bayesian Optimal Interval Design. RP2D: Recommended Phase 2 Dose, 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



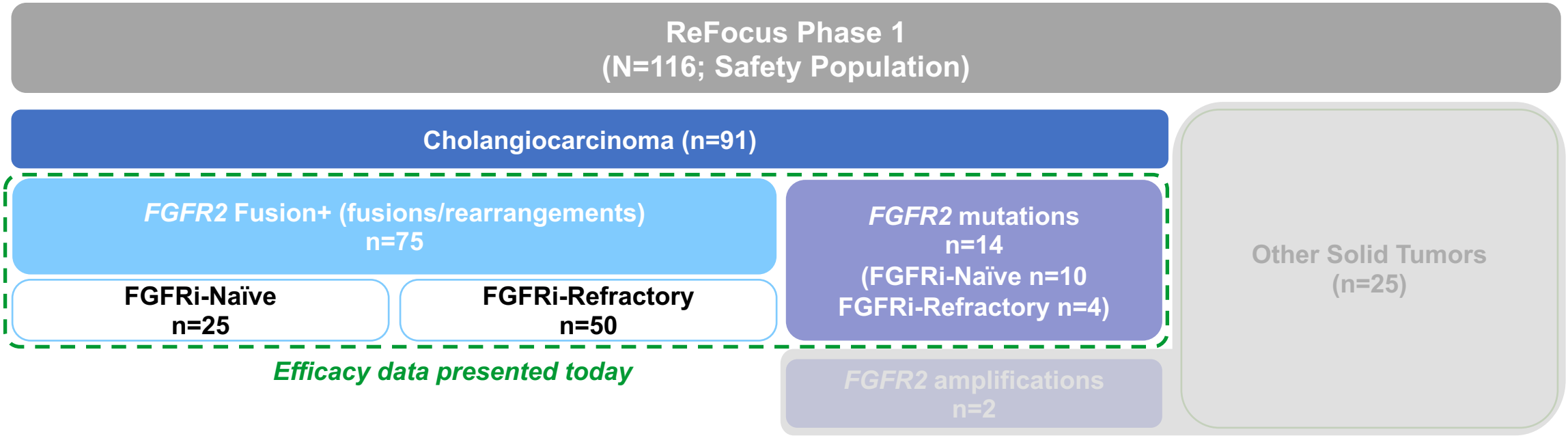
Serum Phosphate Over Time



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

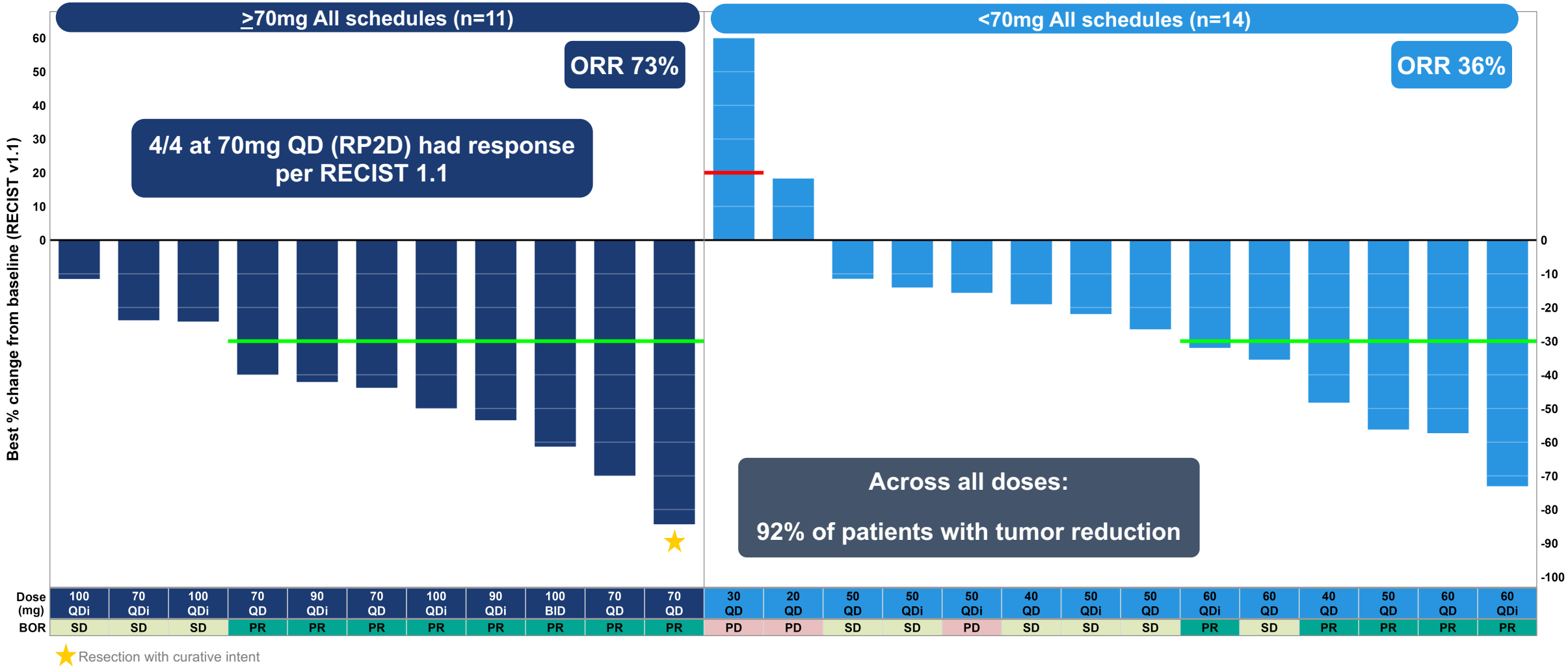
Data for Phase 1 Dose Escalation as of 01/30/2023.
BOIN: Bayesian Optimal Interval Design. QD: Daily; RP2D: Recommended Phase 2 Dose; SD: Standard Deviation, SE: Standard Error

ReFocus Phase 1 Safety & Efficacy Populations



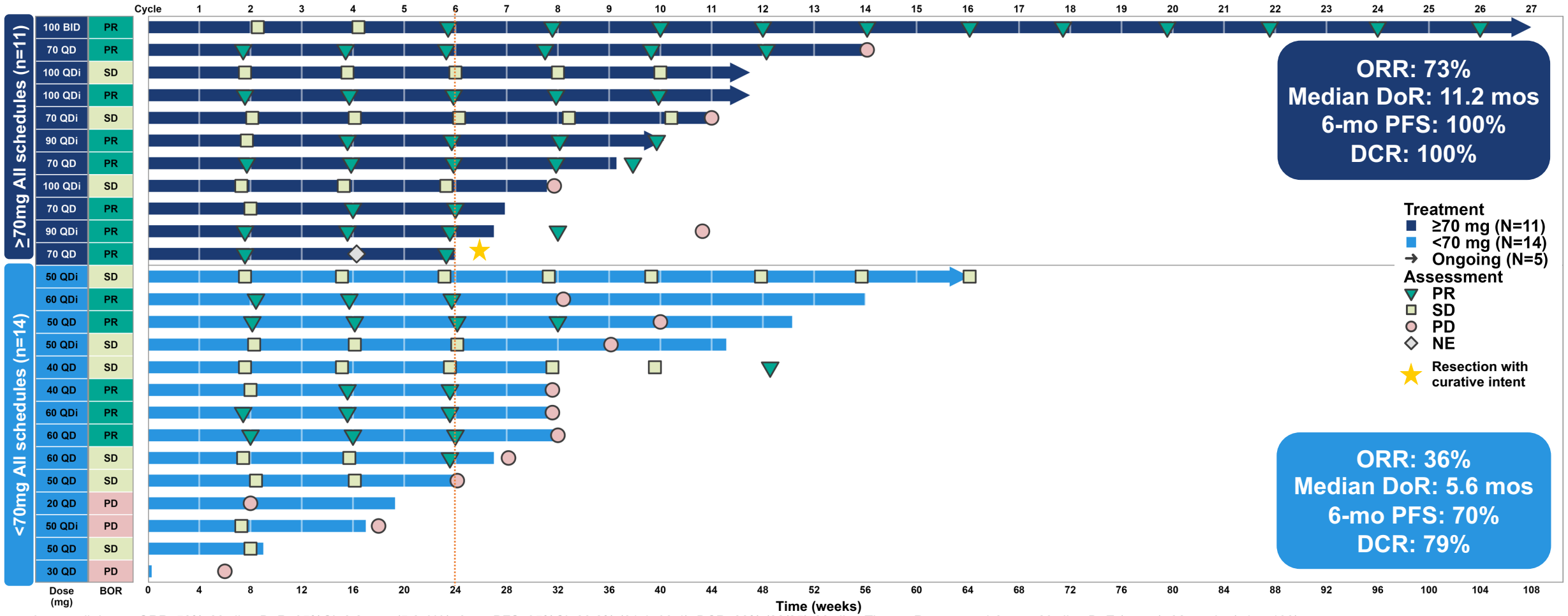
Data for Phase 1 Dose Escalation as of 01/30/2023.

ReFocus Phase 1 Efficacy - FGFRi-Naïve *FGFR2* Fusion+ Cholangiocarcinoma



Data for Phase 1 Dose Escalation as of 01/30/2023.
ORR: Overall Response Rate; RP2D: Recommended Phase 2 Dose

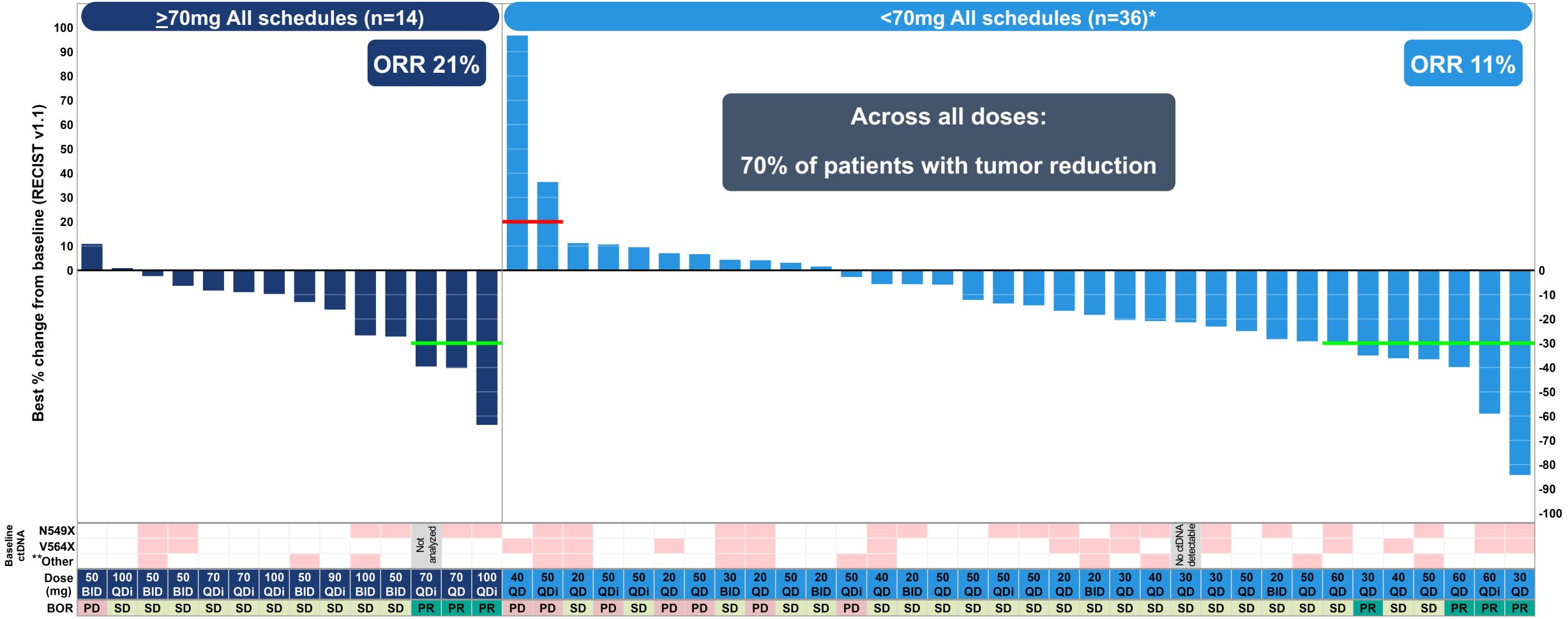
ReFocus Phase 1 - Duration of Exposure & Responses: FGFRi-Naïve *FGFR2* Fusion+ Cholangiocarcinoma



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)

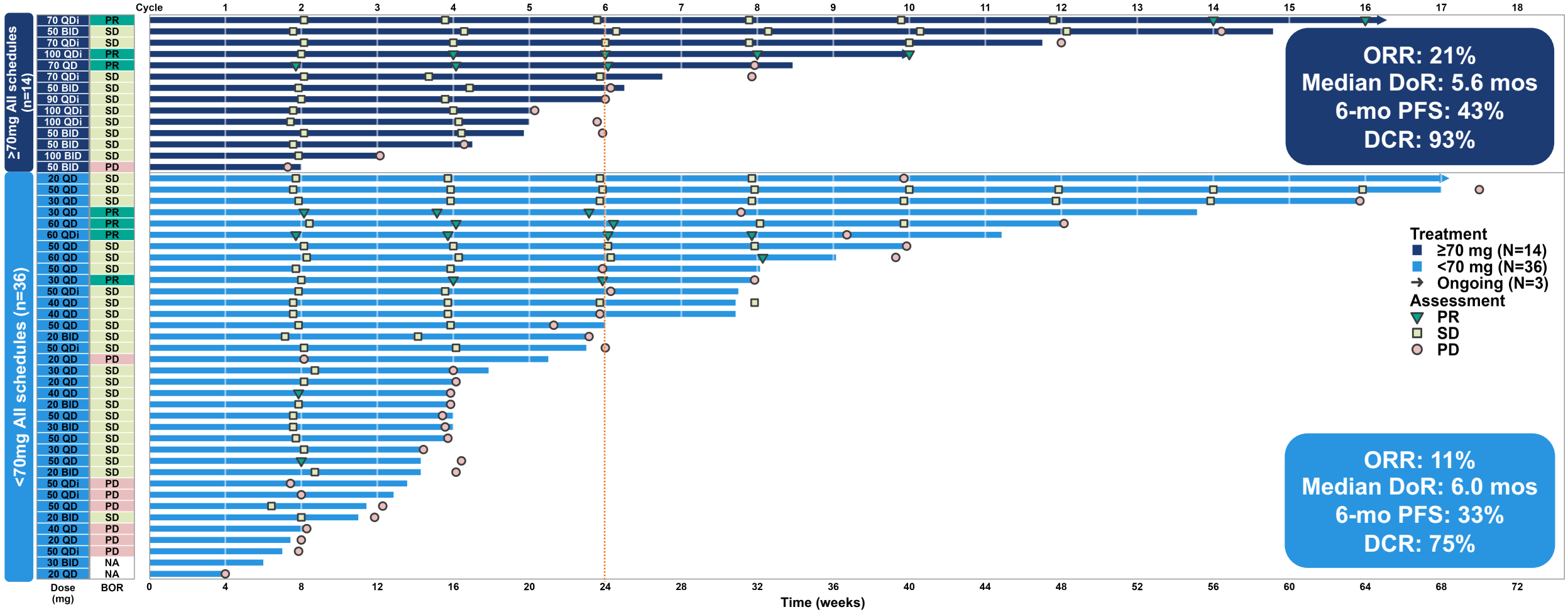
Data for Phase 1 Dose Escalation as of 01/30/2023. BID: Twice daily, DCR: Disease Control Rate, DoR: Duration of Response; NE: not evaluable, ORR: Overall Response Rate, PD: Progressive Disease, PFS: Progression Free Survival; PR: Partial Response; QD: once daily; QDi: once daily, 3 weeks on, 1 week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

ReFocus Phase 1 Efficacy - FGFRi-Refractory, *FGFR2* Fusion+ Cholangiocarcinoma



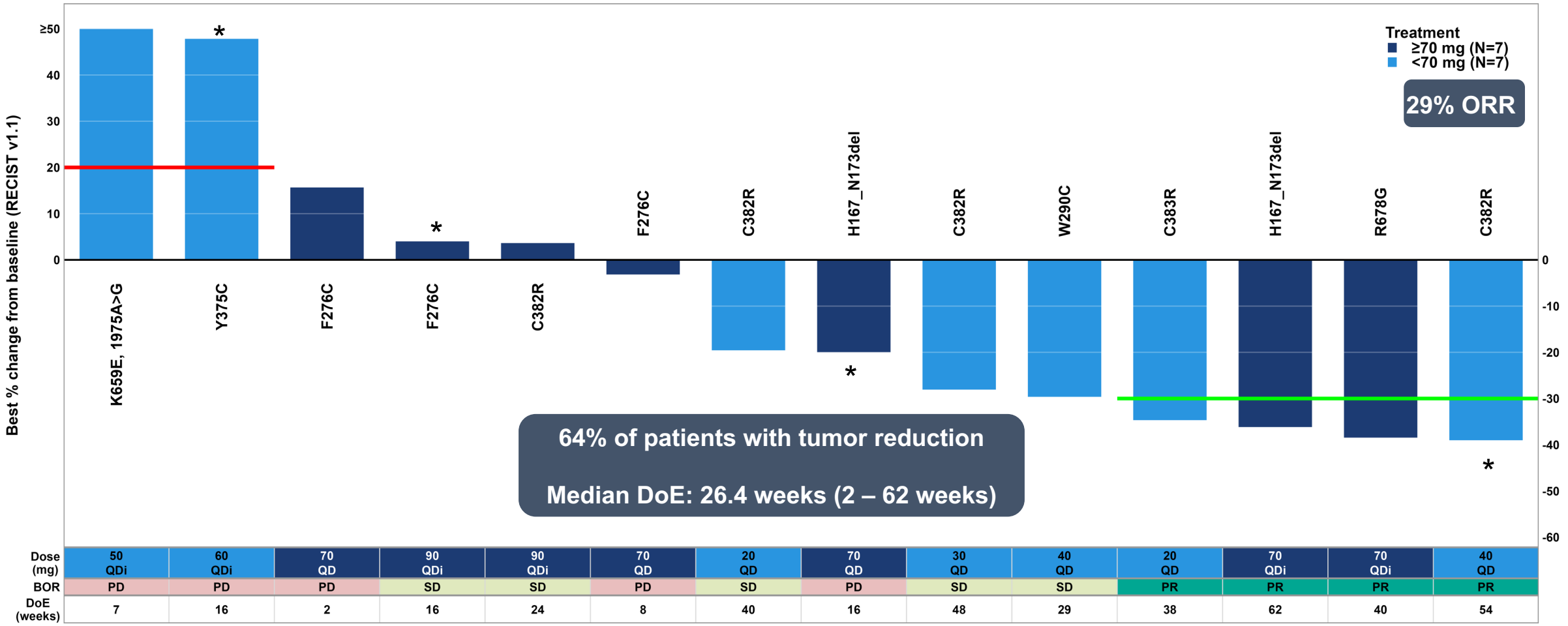
*Waterfall excludes 2 FGFRi-Refractory patients with clinical progressive disease without post baseline tumor assessment.
N549X and V564X correspond to FGFR2 IIIc isoform; X denotes any amino acid substitution
** Other includes FGFR2 mutations other than N549X and V564X (pink), no detectable FGFR2 mutation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

ReFocus Phase 1 Efficacy - *FGFR2*-Mutated Cholangiocarcinoma

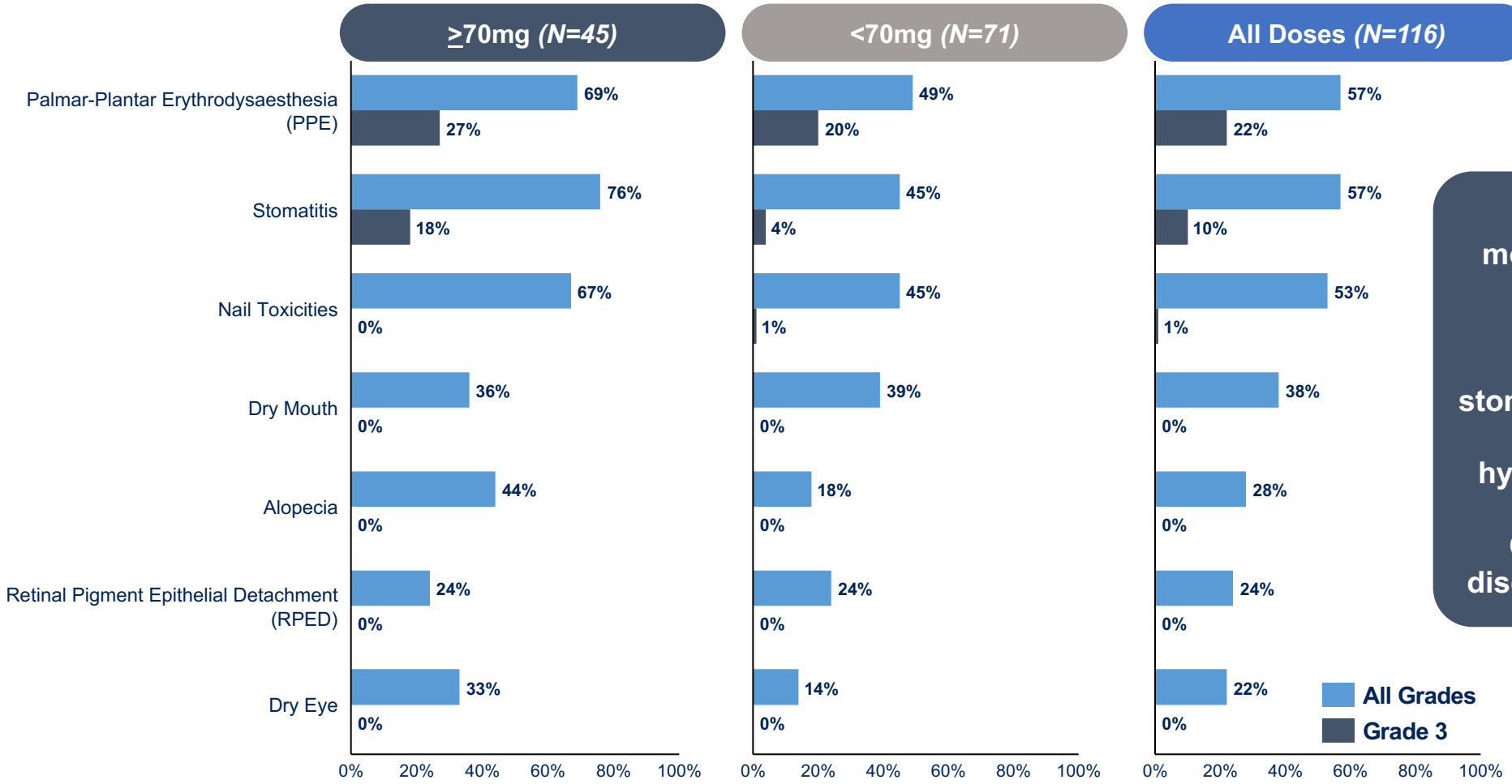


Dose (mg)	50 QDi	60 QDi	70 QD	90 QDi	90 QDi	70 QD	20 QD	70 QD	30 QD	40 QD	20 QD	70 QDi	70 QDi	40 QD
BOR	PD	PD	PD	SD	SD	PD	SD	PD	SD	SD	PR	PR	PR	PR
DoE (weeks)	7	16	2	16	24	8	40	16	48	29	38	62	40	54

* 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



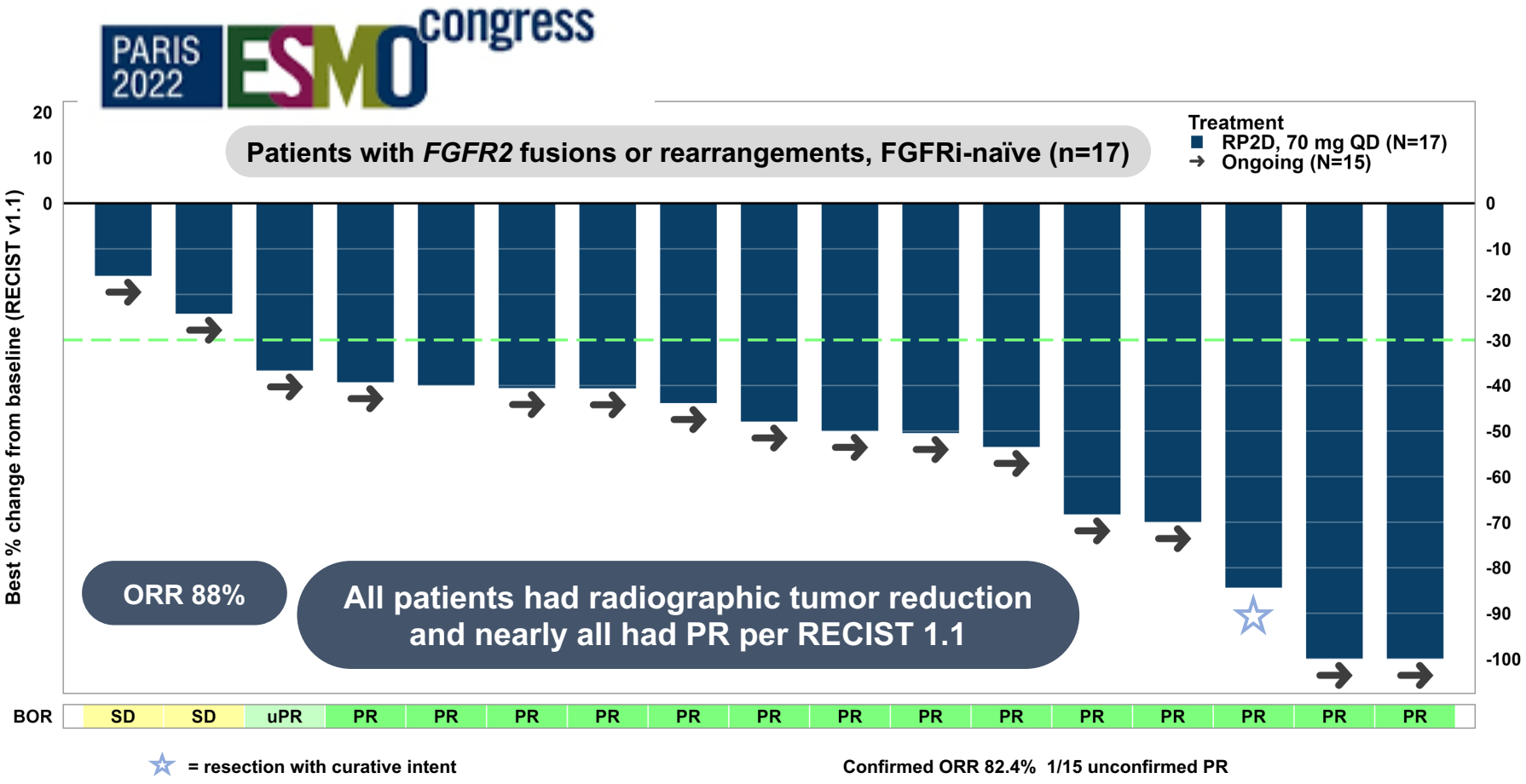
AEs are on-target events; mostly low grade and reversible, no Gr 4 or Gr 5

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

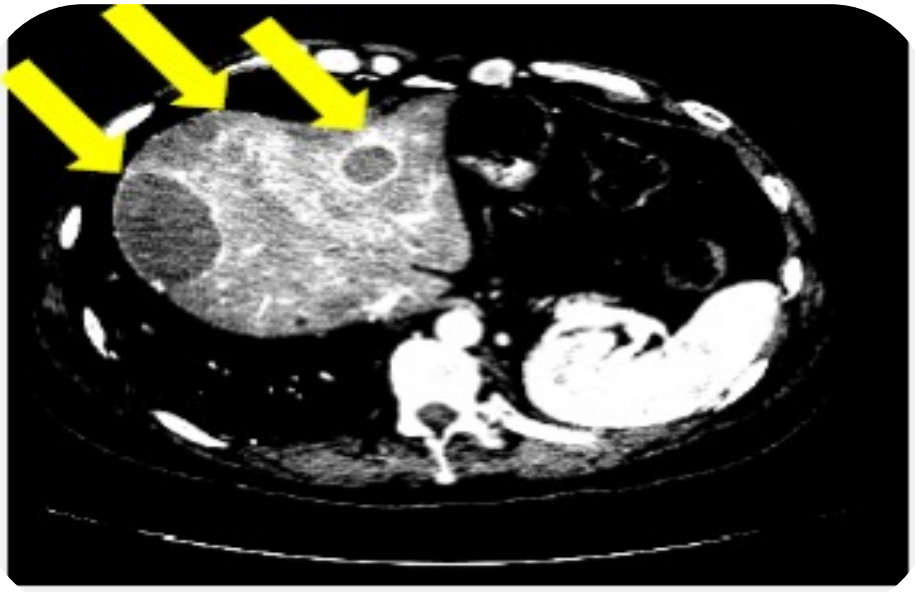
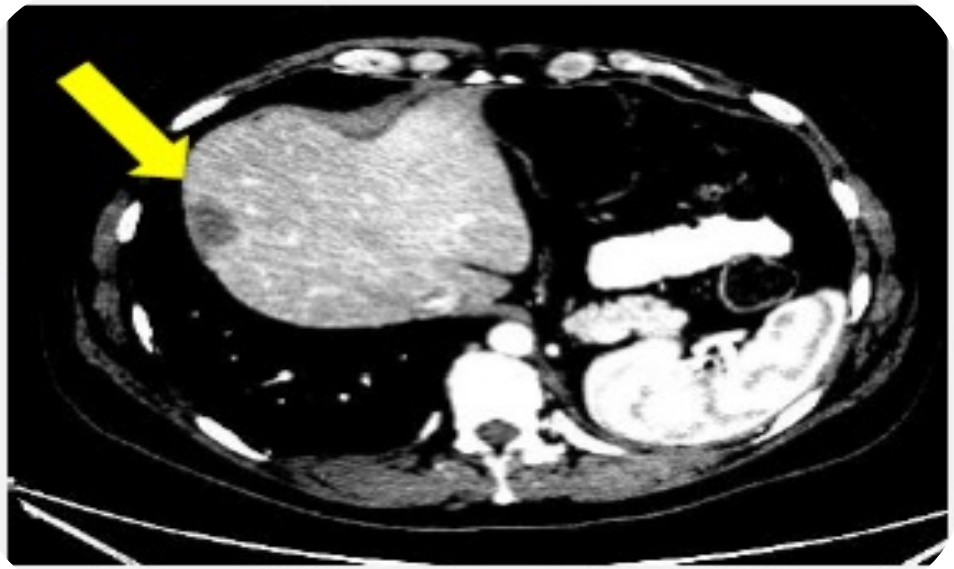


Pivotal enrollment anticipated completion: 2H 2023

Hollebecque et al. Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients (pts) with a FGFR2-fusion or rearrangement (f/r), FGFR inhibitor (FGFRi)-naïve cholangiocarcinoma (CCA): ReFocus trial. Oral Presentation. European Society for Molecular Oncology 2022, Paris, 9-13 October 2022. Data cut-off for ESMO 2022 as of 08/01/2022. ORR: Overall Response Rate, QD: once daily, PR: partial response, uPR: unconfirmed partial response, SD: Stable Disease

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

Data for Phase 1 Dose Escalation as of 01/30/2023. AE: Adverse Event; DCR: Disease Control Rate, FGFR2 f/r: fibroblast growth factor receptor inhibitor 2, fusions or rearrangements, FGFRi: fibroblast growth factor receptor inhibitor, mDoR: median Duration of Response, ORR: Overall Response Rate, PFS: Progression-free Survival, QD: once daily, RP2D: Recommended Phase 2 Dose

Foundational preclinical and translational research published in *Cancer Discovery* today

CANCER DISCOVERY

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

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- 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
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