ASCO® Gastrointestinal Cancers Symposium

Efficacy and safety of lirafugratinib in patients with FGFRi-naïve cholangiocarcinoma harboring *FGFR2* fusions/rearrangements

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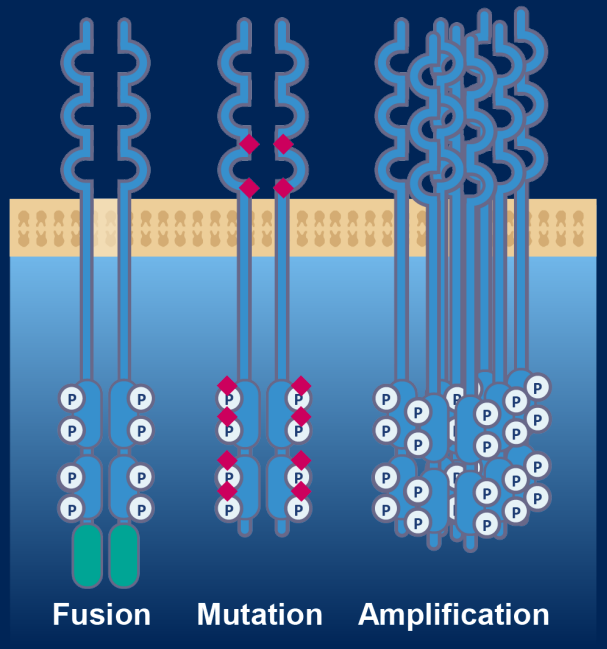
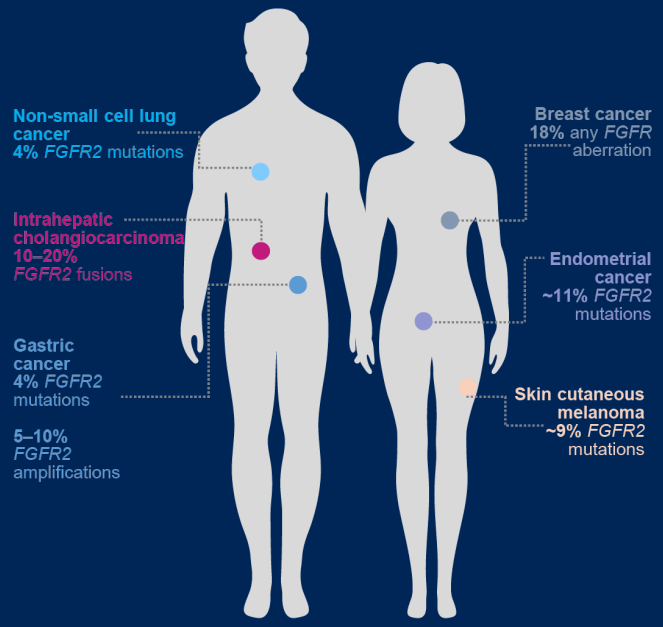
Oncogenic Activation of *FGFR2* Drives Multiple Cancers, But Selective Targeting of *FGFR2* Has Not Been Achieved

FGFR2 is a clinically validated oncogene[1]



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



Approved pan-FGFR inhibitors solid tumor indications

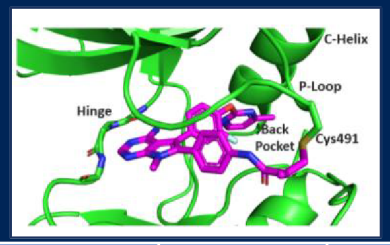
	Phase 2 Response Rate	DoR (mos)	% of patients with… (All grades)	
			Hyper phosphatemia[9]	Diarrhea
			FGFR1 off-isoform toxicity	FGFR4 off-isoform toxicity
Pemigatinib[5]	36% (CCA)	9.1 (CCA)	94%	47%
Futibatinib[6]	42% (CCA)	9.7 (CCA)	88%	39%
Erdafitinib[7]	32% (Urothelial Carcinoma)	5.4 (Urothelial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Infigratinib withdrawn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

Lirafugratinib: The First Highly Selective FGFR2 Inhibitor

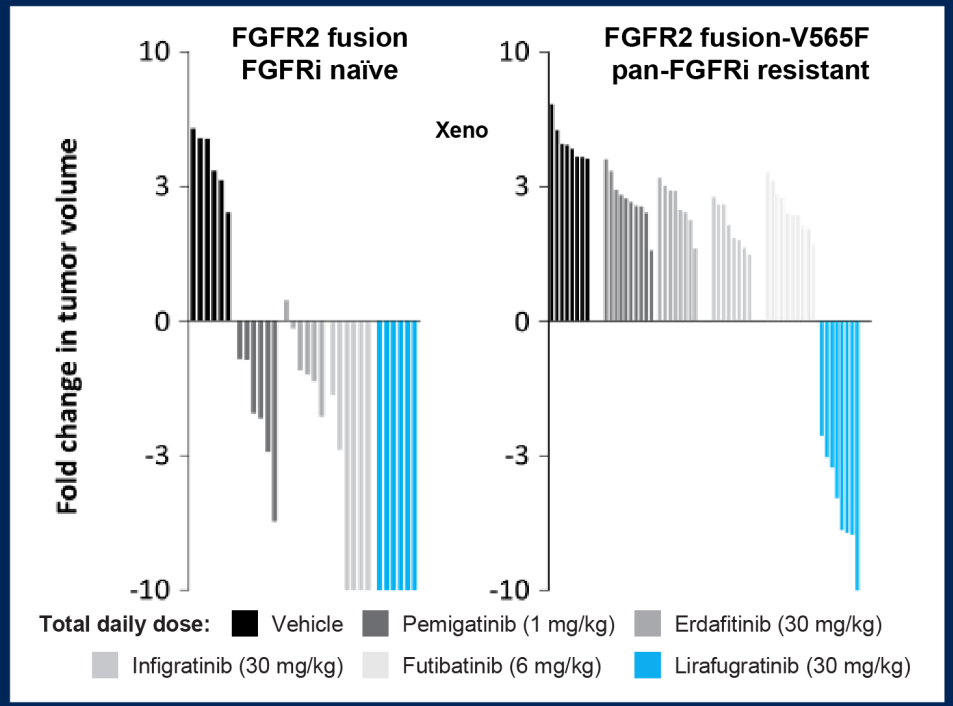
In contrast to pan-FGFRi, lirafugratinib is a potent and selective FGFR2 inhibitor



Lirafugratinib selectively inhibits FGFR2 based on unique conformational dynamics[1]

Inhibitor	Mechanism of Action	Biochemical IC50 (nM)[2-5]			
		FGFR1	*FGFR2*	*FGFR3*	*FGFR4*
Lirafugratinib	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)

Part 1
Dose Escalation (Completed): All Solid Tumors[a]

Cohort 1
QDC (N=58); QDD (N=41); BID (N=17)

Cohort 2 (N=4)

Completed
(*RP2D defined as 70 mg QDC*)

Part 2
Dose Expansion (Completed): Cholangiocarcinoma (CCA)

Group 1A (QDC): *FGFR2*-f/r + CCA with prior chemotherapy + prior FGFRi (N=53)

Group 2A (QDC): *FGFR2*-f/r + CCA with prior chemotherapy with no prior FGFRi (N=26)

Group 6 (QDC): *FGFR2*-f/r + CCA naïve to prior chemotherapy and FGFRi (N=11)

Group 7 (QDC): *FGFR2*-mutant or amplified CCA with no prior FGFRi (N=42)[b]

Non-CCA

Group 3 (QDC): *FGFR2*-f/r naïve to prior FGFRi (N=46)[b]
Group 4 (QDC): *FGFR2*-amplified naïve to prior FGFRi (N=46)[b]
Group 5 (QDC): *FGFR2*-mutant naïve to prior FGFRi (N=37)[b]

Part 3
Extension(s) (Completed)

Group 2A Extension (QDC): *FGFR2*-f/r + CCA with prior chemotherapy with no prior FGFRi (N=86)

Pivotal Cohort (N=116)[c]
Part 1 Cohort 2 +
Part 2 Group 2A + Part 3 Group 2A Extension

Key Eligibility Criteria:
- 18 years or older
- Histologically or cytologically confirmed diagnosis of unresectable or metastatic CCA or other solid tumors per RECIST v1.1 that were refractory to or inadequately responded to standard therapy, or for which no standard therapy exists or was declined
- ECOG PS of 0–1
- Documented *FGFR2* genomic alteration (fusion, mutation, or amplification) per local assessment of blood and/or tumor tissue

Primary Endpoint:
- Confirmed ORR per RECIST v1.1 by IRC

Key Secondary Endpoints:
- Duration of response
- Disease control rate
- Progression-free survival
- Overall survival
- Safety
- Quality of life per EORTC QLC-C30

BID, twice daily; CCA, cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR2, fibroblast growth factor receptor 2; FGFRi, fibroblast growth factor receptor inhibitor; f/r, fusion/rearrangement; mRNA, messenger RNA; QDC, once daily on a continuous dosing schedule (referred to as QD on subsequent slides); QDD, once daily on a discontinuous dosing schedule; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose.
[a]Including FGFR2 genomic alteration (fusion, amplification, or mutation) or other potentially oncogenic FGFR2 alterations (eg, FGFR2 protein or mRNA overexpression) and other tumor types.
[b]Additional 27 patients who received prior FGFRi were enrolled in Groups 3 (n=10), 4 (n=3), 5 (n=8), and 7 (n=6). These patients were not included in the efficacy analyses but were included in the safety analyses.
[c]As of 27SEP2024, the primary efficacy analysis of IRC-assessed data (n=114) and the secondary analysis of investigator-assessed data (n=116) set was done. The primary efficacy analysis excluded 2 patients as not available.

Baseline Characteristics (Primary Efficacy Analysis Set)

Characteristics	CCA f/r FN CP (Pivotal Cohort; N=114)
Median age, years (range)	57 (29, 81)
Sex, n (%)	
Male	44 (38.6)
Female	70 (61.4)
Race, n (%)	
American Indian or Alaskan Native	0
Asian	26 (22.8)
Black or African American	2 (1.8)
Native Hawaiian or Other Pacific Islander	0
White	62 (54.4)
Other/Multiple	1 (0.9)
Not Reported/Unknown[a]	23 (20.2)
Geographic Region, n (%)	
North America	47 (41.2)
Europe	40 (35.1)
Asia-Pacific	27 (23.7)
Baseline ECOG PS, n (%)	
0	57 (50.0)
1	57 (50.0)
Median prior lines of systemic therapy, n (range)	1 (1-5)
Lines of prior systemic therapy, n (%)	
1	72 (63.2)
2	31 (27.2)
3	5 (4.4)
4	4 (3.5)
5	2 (1.8)
Prior systemic therapy, n (%)	
Chemotherapy	114 (100)
Gem Platinum Based Without ICI	66 (57.9)
Gem Platinum Based With ICI	38 (33.3)
Fluoropyrimidine Based	37 (32.5)
Other	5 (4.4)
ICI	42 (36.8)
Without Gem Platinum	4 (3.5)

CCA, cholangiocarcinoma; CP, chemotherapy pretreated; ECOG PS, Eastern Cooperative Oncology Group performance status; f/r, fusion/rearrangement; FN, fibroblast growth factor receptor inhibitor treatment naïve; Gem, gemcitabine; ICI, immune checkpoint inhibitor. [a]Not reported/unknown includes patients who did not disclose or were unsure of their race or ethnicity.

Summary of Efficacy by IRC (Primary Efficacy Analysis Set)

	CCA f/r FN CP (Pivotal Cohort; N=114)
Confirmed BOR, n (%)	
Complete response	3 (2.6)
Partial response	50 (43.9)
Stable disease	57 (50.0)
Progressive disease	3 (2.6)
Not evaluable[a]	1 (0.9)
ORR[b], n (%) [95% CI]	53 (46.5) [37.1, 56.1]
DCR[c], n (%) [95% CI]	110 (96.5) [91.3, 99.0]
Median DOR, months [95% CI]	11.8 [7.5, 13.0]
Median PFS, months [95% CI]	11.3 [9.2, 14.8]
Median OS[d], months [95% CI]	22.8 [18.1, 27.2]

BOR, best overall response; CCA, cholangiocarcinoma; CP, chemotherapy pretreated; DCR, disease control rate; DOR, duration of response; FN, fibroblast growth factor receptor inhibitor treatment naïve; f/r, fusion/rearrangement; IRC, Independent Review Committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
Note: Percentages are based on the number of patients in the primary efficacy analysis set for the CCA f/r FN CP population. Note: 95% CI is based on the exact Clopper-Pearson method.
[a]No valid post-baseline assessment. [b]ORR is defined as the proportion of patients achieving a confirmed response of complete response or partial response per RECIST v1.1. [c]DCR is defined as the proportion of patients with a confirmed response of complete response, partial response, or stable disease per RECIST v1.1. [d]Safety analysis set (N=116) is used for the overall survival analysis because the safety analysis set is equal to the full analysis set, which includes all enrolled patients who had received at least 1 dose of study drug.

Summary of Efficacy by IRC (Supportive Efficacy Populations in Primary Efficacy Analysis Set)

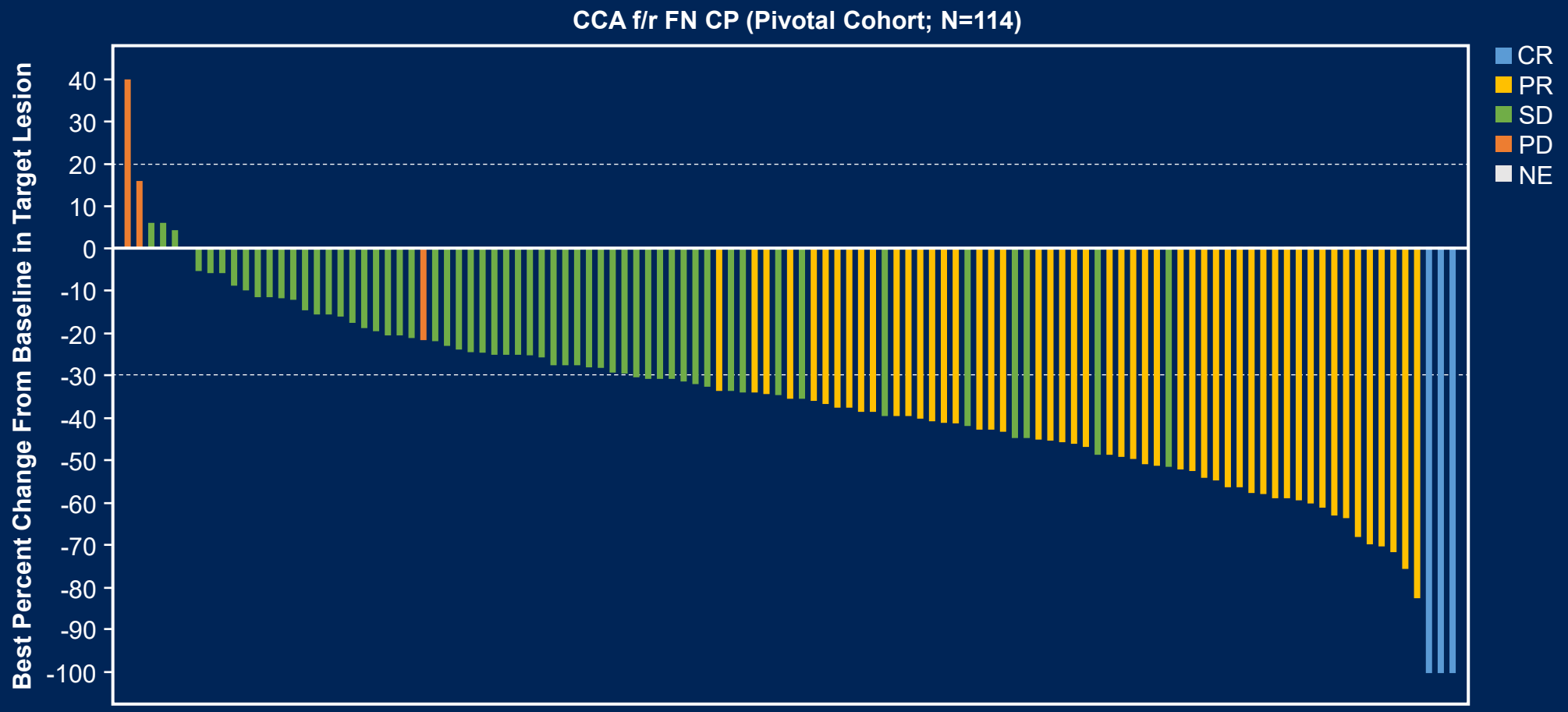
	CCA f/r FP CP (Group 1A; N=53)	CCA f/r FN CN (Group 6; N=11)
Confirmed BOR, n (%)		
Complete response	0	1 (9.1)
Partial response	12 (22.6)	6 (54.5)
Stable disease	29 (54.7)	4 (36.4)
Progressive disease	10 (18.9)	0
Not evaluable[a]	2 (3.8)	0
ORR[b], n (%) [95% CI]	12 (22.6) [12.3, 36.2]	7 (63.6) [30.8, 89.1]
DCR[c], n (%) [95% CI]	41 (77.4) [63.8, 87.7]	11 (100) [71.5, 100]
Median DOR, months [95% CI]	5.6 [3.8, NE]	9.2 [5.6, NE]
Median PFS, months [95% CI]	5.6 [3.7, 7.4]	11.0 [3.7, NE]
Median OS[d], months [95% CI]	10.9 [6.6, 18.2]	NE [12.6, NE]

BOR, best overall response; CCA, cholangiocarcinoma; CN, chemotherapy naïve; CP, chemotherapy pretreated; DCR, disease control rate; DOR, duration of response; FN, fibroblast growth factor receptor inhibitor treatment naïve; FP, fibroblast growth factor receptor inhibitor pretreated; f/r, fusion/rearrangement; IRC, Independent Review Committee; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Note: Percentages are based on the number of patients in the primary efficacy analysis set for the CCA f/r FN CP population. Note: 95% CI is based on the exact Clopper-Pearson method.

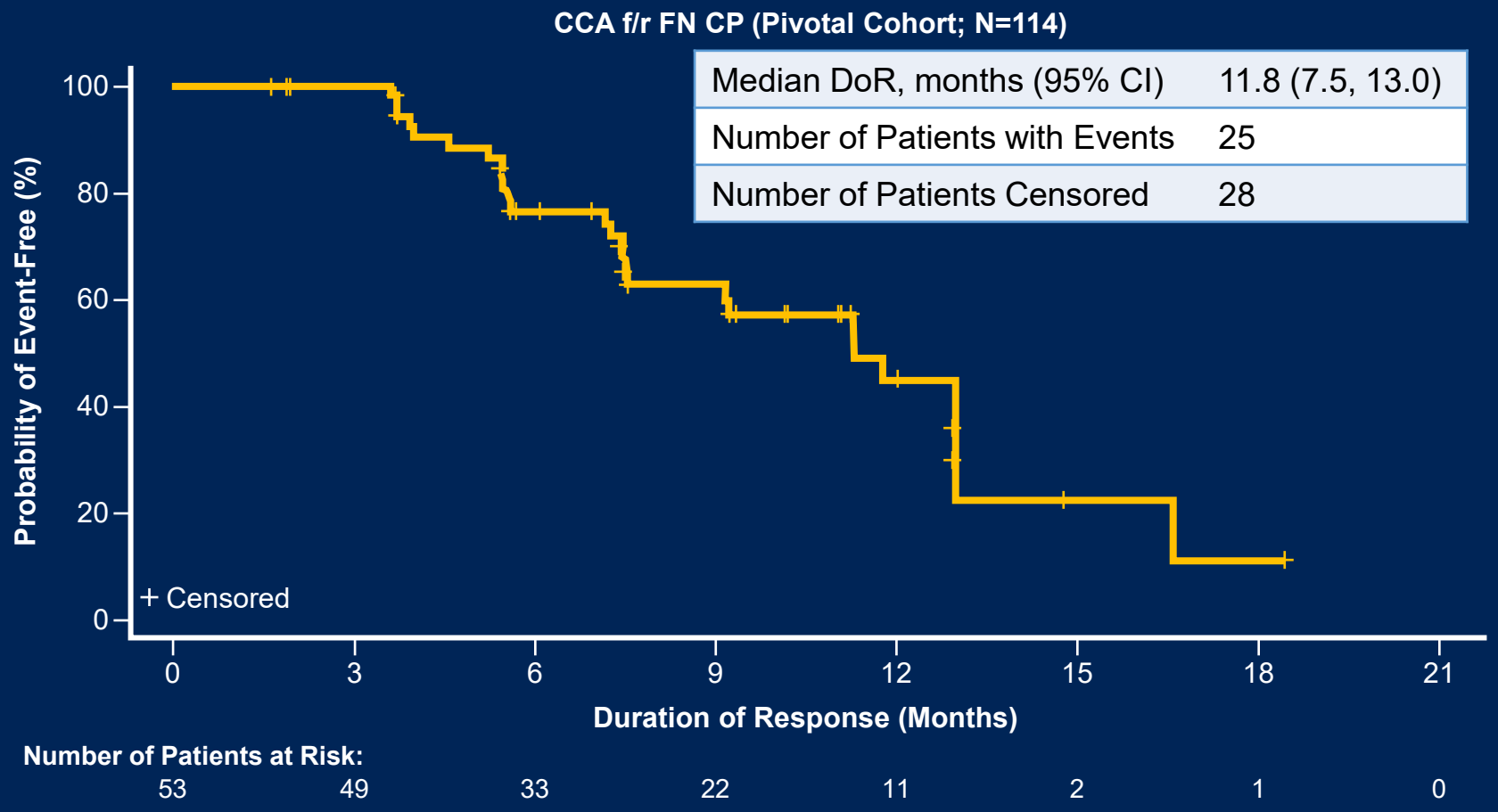
[a]No valid post-baseline assessment. [b]ORR is defined as the proportion of patients achieving a confirmed response of complete response or partial response per RECIST v1.1. [c]DCR is defined as the proportion of patients with a confirmed response of complete response, partial response, or stable disease per RECIST v1.1. [d]Safety analysis set (N=116) is used for the overall survival analysis because the safety analysis set is equal to the full analysis set, which includes all enrolled patients who had received at least 1 dose of study drug.

Waterfall Plot for BOR From Baseline by IRC (Primary Efficacy Analysis Set)



BOR, best overall response; CCA, cholangiocarcinoma; CP, chemotherapy pretreated; CR, complete response; FN, fibroblast growth factor receptor inhibitor treatment naïve; f/r, fusion/rearrangement; IRC, Independent Review Committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response by IRC (Primary Efficacy Analysis Set)



DoR, duration of response; IRC, Independent Review Committee.

Duration of Treatment (Pivotal Efficacy Population and Supportive Efficacy Populations in Primary Efficacy Analysis Set)

	CCA f/r FN CP (Pivotal Cohort; N=114)	CCA f/r FP CP (Group 1A; N=53)	CCA f/r FN CN (Group 6; N=11)
Median duration of treatment, weeks (range)	41 (4, 138)	27 (2, 96)	36 (16, 55)

CCA, cholangiocarcinoma; CN, chemotherapy naïve; CP, chemotherapy pretreated; FN, fibroblast growth factor receptor inhibitor treatment naïve; FP, fibroblast growth factor receptor inhibitor pretreated; f/r, fusion/rearrangement.
[a]Duration of treatment (weeks) = (last dose date – first dose date +1)/7.

Summary of TRAEs (Safety Analysis Set)

	All Solid Tumors (70 mg QD Safety Population; N=385)	CCA f/r FN CP (Pivotal Safety Population; N=116)
Any TRAE, n (%)	379 (98.4)	116 (100)
Any CTCAE Grade ≥3 TRAE, n (%)	167 (43.4)	67 (57.8)
Any TRAE Leading to Study Drug Dose Reduction, n (%)	213 (55.3)	88 (75.9)
Any TRAE Leading to Study Drug Interruption, n (%)	262 (68.1)	96 (82.8)
Any TRAE Leading to Study Treatment Discontinuation, n (%)	10 (2.6)	5 (4.3)
Any TRAE Leading to Death, n (%)	0	0

CCA, cholangiocarcinoma; CP, chemotherapy pretreated; CTCAE, Common Terminology Criteria for Adverse Events; FN, fibroblast growth factor receptor inhibitor treatment naïve; f/r, fusion/rearrangement; QD, once daily on a continuous dosing schedule; TRAE, treatment-related adverse event.

Summary of On-Target TEAEs (Safety Analysis Set)

	All Solid Tumors (70 mg QD Safety Population; N=385)		CCA f/r FN CP (Pivotal Safety Population; N=116)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Stomatitis[a], n (%)	263 (68.3)	47 (12.2)	91 (78.4)	14 (12.1)
Palmar-plantar erythrodysesthesia syndrome, n (%)	255 (66.2)	77 (20.0)	95 (81.9)	38 (32.8)
Nail toxicities[b], n (%)	282 (73.2)	31 (8.1)	102 (87.9)	14 (12.1)
Retinal pigment epithelial detachment[c], n (%)	113 (29.4)	7 (1.8)	43 (37.1)	2 (1.7)

CCA, cholangiocarcinoma; CP, chemotherapy pretreated; FN, fibroblast growth factor receptor inhibitor treatment naïve; f/r, fusion/rearrangement; QD, once daily on a continuous dosing schedule; RPED, retinal pigment epithelial detachment; TEAE, treatment-emergent adverse event.

[a]Includes preferred terms of lip ulceration, mouth ulceration, and stomatitis.

[b]Nail toxicities is an umbrella term and included preferred terms of nail aplasia, nail atrophy, nail avulsion, nail bed bleeding, nail bed disorder, nail bed inflammation, nail bed tenderness, nail cuticle fissure, nail discoloration, nail discomfort, nail disorder, nail dystrophy, nail fold inflammation, nail growth abnormal, nail hypertrophy, nail injury, nail pigmentation, nail pitting, nail ridging, nail toxicity, onychalgia, onychoclasis, onychogryphosis, onycholysis, onychomadesis, onychomalacia, and paronychia.

[c]RPED is an umbrella term and included preferred terms of acquired pigmented retinopathy, central serous chorioretinopathy, chorioretinal disorder, chorioretinal scar, chorioretinitis, chorioretinopathy, cystoid macular edema, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, exudative retinopathy, macular detachment, outer retinal tubulation, maculopathy, retinal detachment, retinal disorder, retinal pigment epithelial tear, retinal pigment epitheliopathy, retinal scar,

Summary of Most Common TRAEs Leading to Dose Interruption and Study Discontinuation (Safety Analysis Set)

	All Solid Tumors (70 mg QD Safety Population; N=385)	CCA f/r FN CP (Pivotal Safety Population; N=116)
TRAEs Leading to Dose Interruption (>10%), n (%)		
Stomatitis	80 (20.8)	25 (21.6)
Palmar-plantar erythrodysesthesia syndrome	138 (35.8)	63 (54.3)
TRAEs Leading to Study Discontinuation, n (%)		
Stomatitis	3 (0.8)	1 (0.9)
Anaphylactic reaction	1 (0.3)	1 (0.9)
Drug hypersensitivity	1 (0.3)	0
Palmar-plantar erythrodysesthesia syndrome	4 (1.0)	3 (2.6)
Nail disorder	1 (0.3)	0

CCA, cholangiocarcinoma; CP, chemotherapy pretreated; FN, fibroblast growth factor receptor inhibitor treatment naïve; f/r, fusion/rearrangement; QD, once daily dosing schedule; TRAE, treatment-related adverse event.

Summary of Off-Isoform Toxicity TEAEs (Safety Analysis Set)

	All Solid Tumors (70 mg QD Safety Population; N=385)		CCA f/r FN CP (Pivotal Safety Population; N=116)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hyperphosphatemia[a], n (%)	79 (20.5)	0	24 (20.7)	0
Diarrhea, n (%)	72 (18.7)	3 (0.8)	25 (21.6)	1 (0.9)

CCA, cholangiocarcinoma; CP, chemotherapy pretreated; FGFRi, fibroblast growth factor receptor inhibitor; FN, FGFRi treatment naïve; f/r, fusion/rearrangement; QD, once daily on a continuous dosing schedule; TEAE, treatment-emergent adverse event.

[a]Hyperphosphatemia did not require dose reductions or discontinuations; 1 patient (0.3%) experienced a dose interruption, and no phosphate binder interventions were needed.

Conclusions

- Lirafugratinib at the proposed dosage regimen of 70 mg QD demonstrated positive antitumor activity in patients with previously treated, unresectable, locally advanced or metastatic CCA harboring *FGFR2*-f/r.
  - ORR assessed by IRC was 46.5% (95% CI: 37.1, 56.1) with a median DOR of 11.8 months (95% CI: 7.5, 13.0).
- The safety profile of lirafugratinib is consistent with FGFR2 inhibition and is predictable and manageable.
  - The most common adverse events (eg, stomatitis and palmar-plantar erythrodysesthesia syndrome) are on-target and reversible.
- Overall, lirafugratinib is a valuable therapeutic option for patients with *FGFR2* fusion/rearrangement CCA who have progressed on standard therapies.

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