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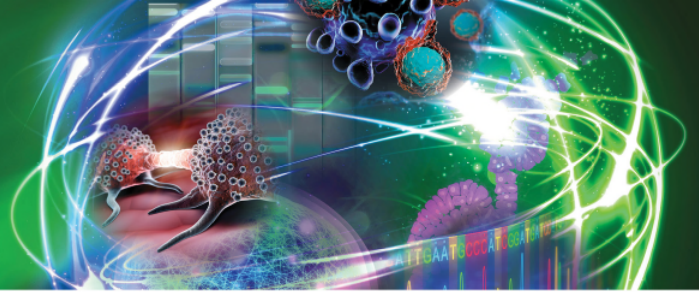

Primary Results of Phase 2 FOENIX-CCA2: the Irreversible FGFR1–4 Inhibitor Futibatinib in Intrahepatic Cholangiocarcinoma With *FGFR2* Fusions/Rearrangements

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Presentation CT010

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Lipika Goyal

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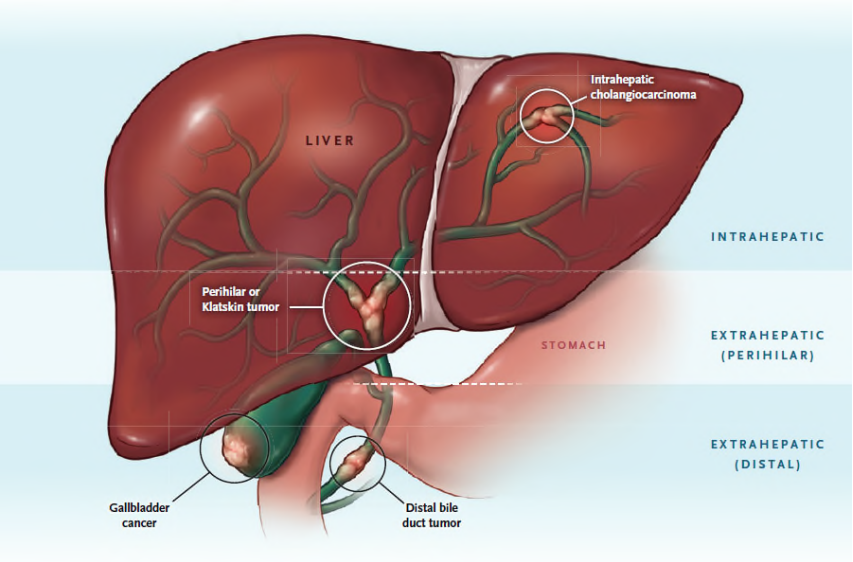
Intrahepatic Cholangiocarcinoma

Classification of biliary tract cancer



From *The New England Journal of Medicine*, Goyal L, et al. Case 8-2021: A 34-Year-Old Woman with Cholangiocarcinoma. Vol 384 Pg 1054–64 Copyright © 2021 Massachusetts Medical Society. Reproduced with permission.

Intrahepatic cholangiocarcinoma (iCCA) is:

- An aggressive malignancy with poor survival outcomes[1]
  - With first-line gemcitabine–cisplatin: median OS, ≈1 year[2]
  - With second-line FOLFOX: median OS, 6.2 mo; ORR, 5%[3]
- A molecularly heterogeneous disease
  - 40-50% of iCCA tumors harbor actionable alterations[1,4]
  - 13–14% of patients with iCCA harbor *FGFR2* fusions[5–7]

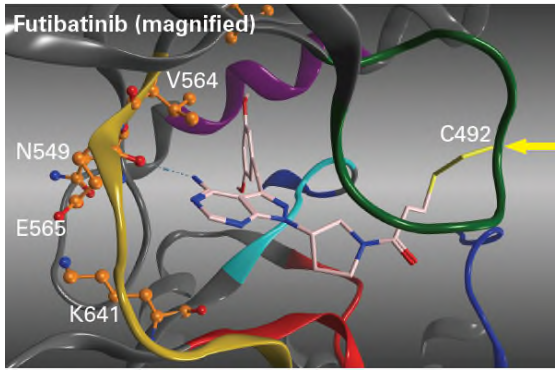
Several FGFR inhibitors are being investigated in iCCA[8–11]

- Pemigatinib (an ATP-competitive, reversible FGFR1–3 inhibitor) was approved in April 2020 for advanced, refractory CCA with *FGFR2* fusions/rearrangements based on a phase 2 study showing an ORR of 35.5%[8]
  - Co-alterations in certain tumor suppressor genes (eg, *TP53*) were associated with reduced benefit from pemigatinib in exploratory analyses[12]

CCA, cholangiocarcinoma; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ORR, objective response rate; OS, overall survival.

Futibatinib: A Highly Selective Irreversible FGFR1–4 Inhibitor

Futibatinib in the ATP-binding pocket of the FGFR2 kinase domain[15]



Inhibitory activity against *FGFR2* kinase domain mutations[15]

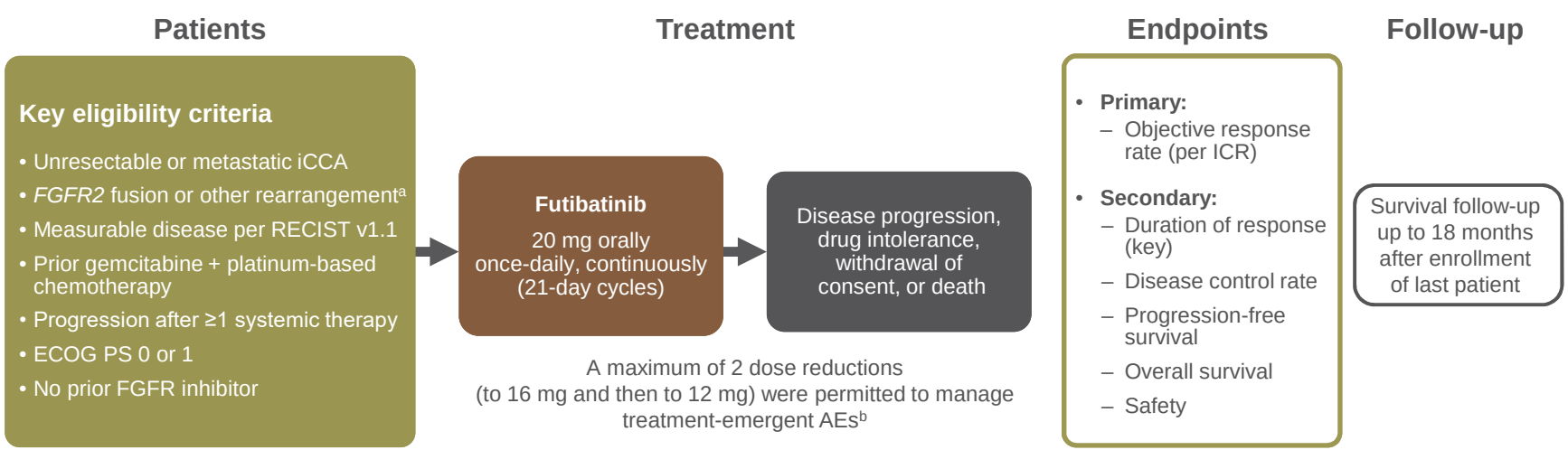
FGFR2 WT or mutants	Fold difference in IC_{50} vs WT FGFR2		
	Futibatinib	Erdafitinib	Pemigatinib
WT	1	1	1
N549D	2	10	102
N549K	8	13	164
V564I	4	1	42
V564L	44	23	335
E565A	3	1	8

Values in cells with yellow and red shading represent 5–15-fold and >15-fold attenuation with respect to wild-type inhibition, respectively.

- In contrast to other FGFR inhibitors, futibatinib demonstrates:
  - Covalent irreversible binding to a conserved cysteine in the FGFR kinase domain P-loop[13]
  - Robust inhibition of FGFR2 kinase domain mutants resistant to reversible ATP-competitive inhibitors[13–15]
- Futibatinib shows activity against tumors of diverse tissue origins harboring various *FGFR* aberrations[13,16]
- In a phase 1 study, futibatinib demonstrated tolerability and antitumor activity in patients with advanced *FGFR*-aberrant tumors, including *FGFR2*-rearranged iCCA[16,17]
- These data formed the basis for the pivotal phase 2 FOENIX-CCA2 study

FGFR, fibroblast growth factor receptor; IC_{50}, half-maximal inhibitory concentration; iCCA, intrahepatic cholangiocarcinoma; WT, wild-type.

FOENIX-CCA2: Phase 2 Global Study of Futibatinib in *FGFR2* Fusion or Rearrangement-Positive Intrahepatic CCA



- 103 patients enrolled across 36 international sites[c]
- At data cutoff (October 1, 2020), all patients had ≥6 months follow-up; median follow-up was 17.1 months

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central radiology review; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1.
[a]Identified centrally in tumor tissue by Foundation Medicine (FMI) or by local laboratory testing of tumor tissue or circulating tumor DNA; [b]Treatment was discontinued if treatment-emergent AEs did not resolve after 2 dose modifications or if the next cycle of treatment was delayed >21 days; [c]Between April 2018 and November 2019.

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Patient Baseline Demographics

Baseline characteristic	Category	All patients (N=103)
Age (range), years	Median	58.0 (22–79)
Sex, n (%)	Female	58 (56)
ECOG PS, n (%)	0	48 (47)
	1	55 (53)
Region, n (%)	North America	47 (46)
	Europe	28 (27)
	Japan	14 (14)
	Asia Pacific	14 (14)
Number of prior regimens, n (%)	1	48 (47)
	2	31 (30)
	≥3	24 (23)
***FGFR2* aberration,[a] n (%)**	Fusions	80 (78)
	Rearrangements	23 (22)

Data cutoff: October 1, 2020.
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor.
[a]Determined by Foundation Medicine Central (n=68), Foundation Medicine Local reports (n=25), or by local testing (n=10); 2 patients had *FGFR2* mutations in addition to fusions.

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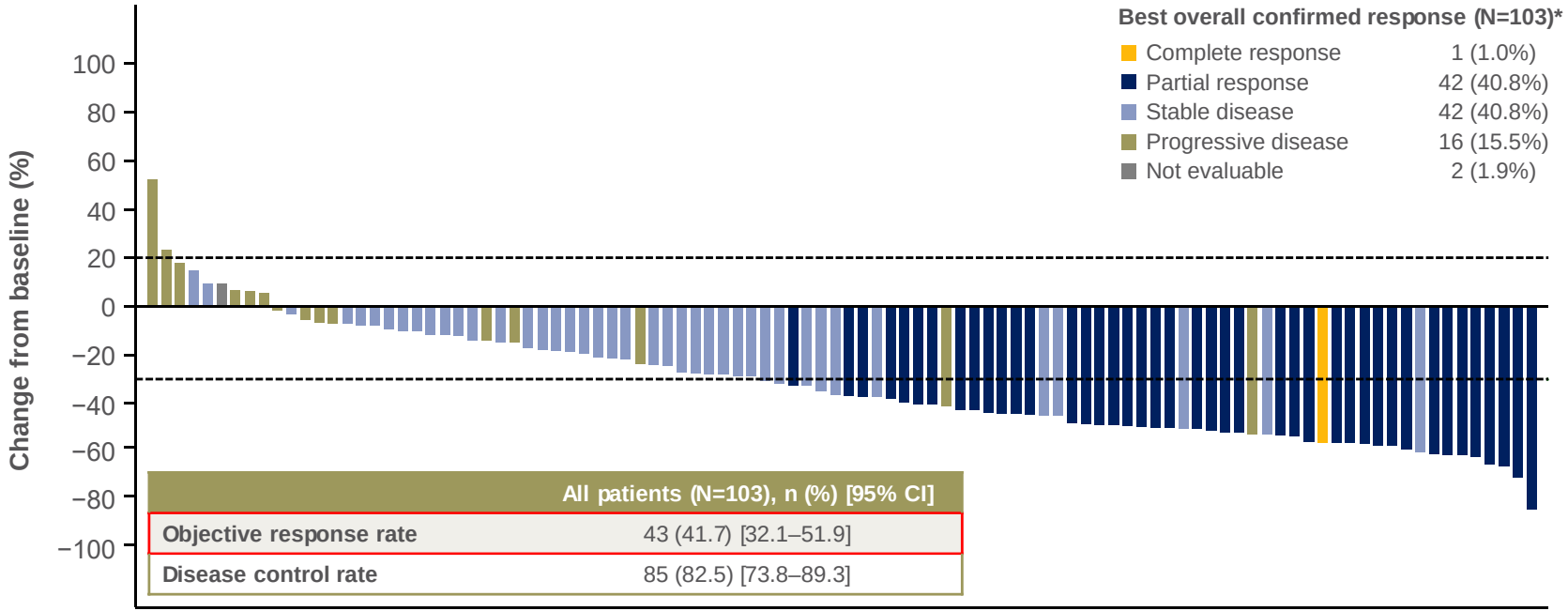
Futibatinib in iCCA: Best Percent Change in Target Lesion Size

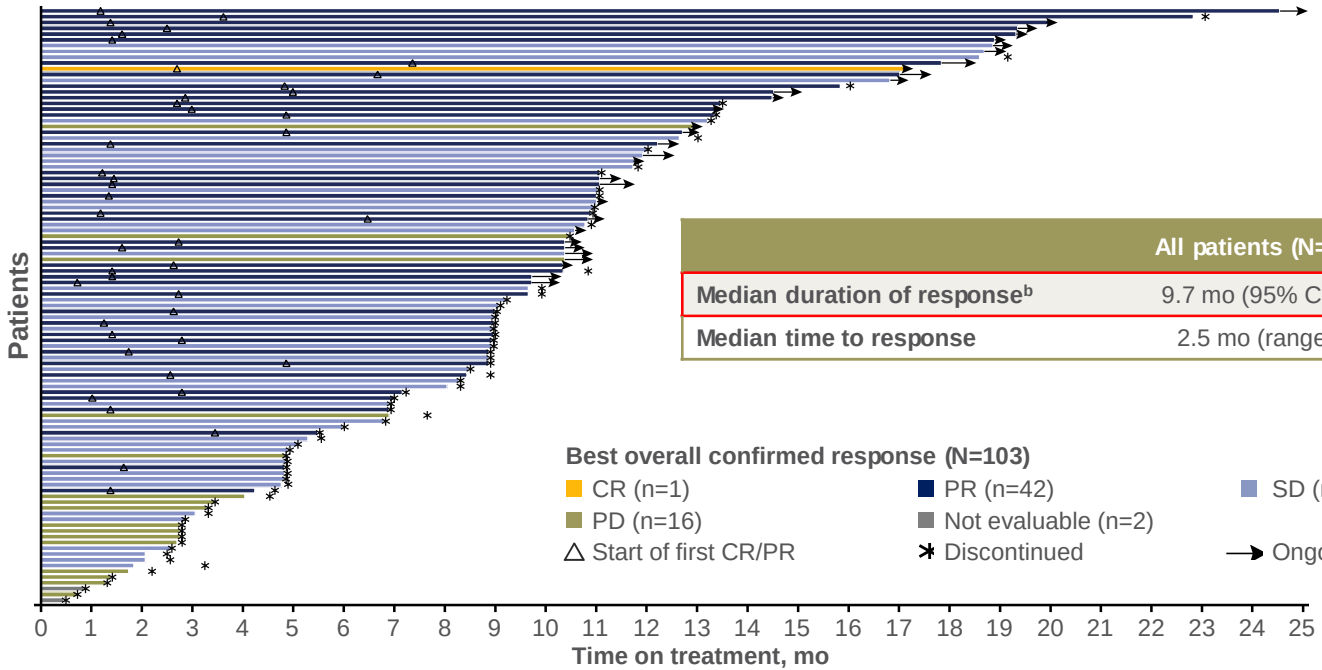


	All patients (N=103), n (%) [95% CI]
Objective response rate	43 (41.7) [32.1–51.9]
Disease control rate	85 (82.5) [73.8–89.3]

*Assessed by Independent Central Review

Data cutoff: October 1, 2020. Dotted horizontal lines represent partial response (≥30% reduction in lesion size) and progressive disease (≥20% increase) per RECIST v1.1.
CI, confidence interval; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central review; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Duration of Futibatinib Response in iCCA



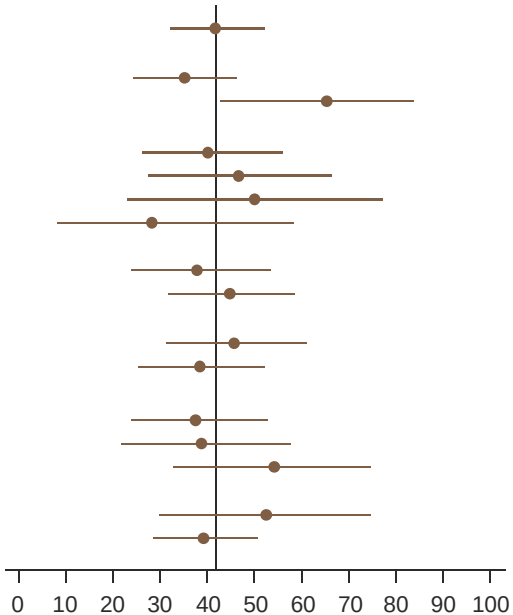
	All patients (N=103), n (%)
Median duration of response[b]	9.7 mo (95% CI, 7.6–17.0)
Median time to response	2.5 mo (range, 0.7–7.4)

- In 72% of responders, responses lasted ≥6 mo, and in 14%, ≥12 mo
- At data cutoff, treatment was ongoing for nearly a third (30%) of patients

Data cutoff: October 1, 2020.
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]Calculated as (last dose date – first dose date) +1; [b]Calculated using the Kaplan–Meier method; responses were based on independent central review per RECIST v1.1.

Prespecified Subgroup Analysis of ORR of Futibatinib in iCCA

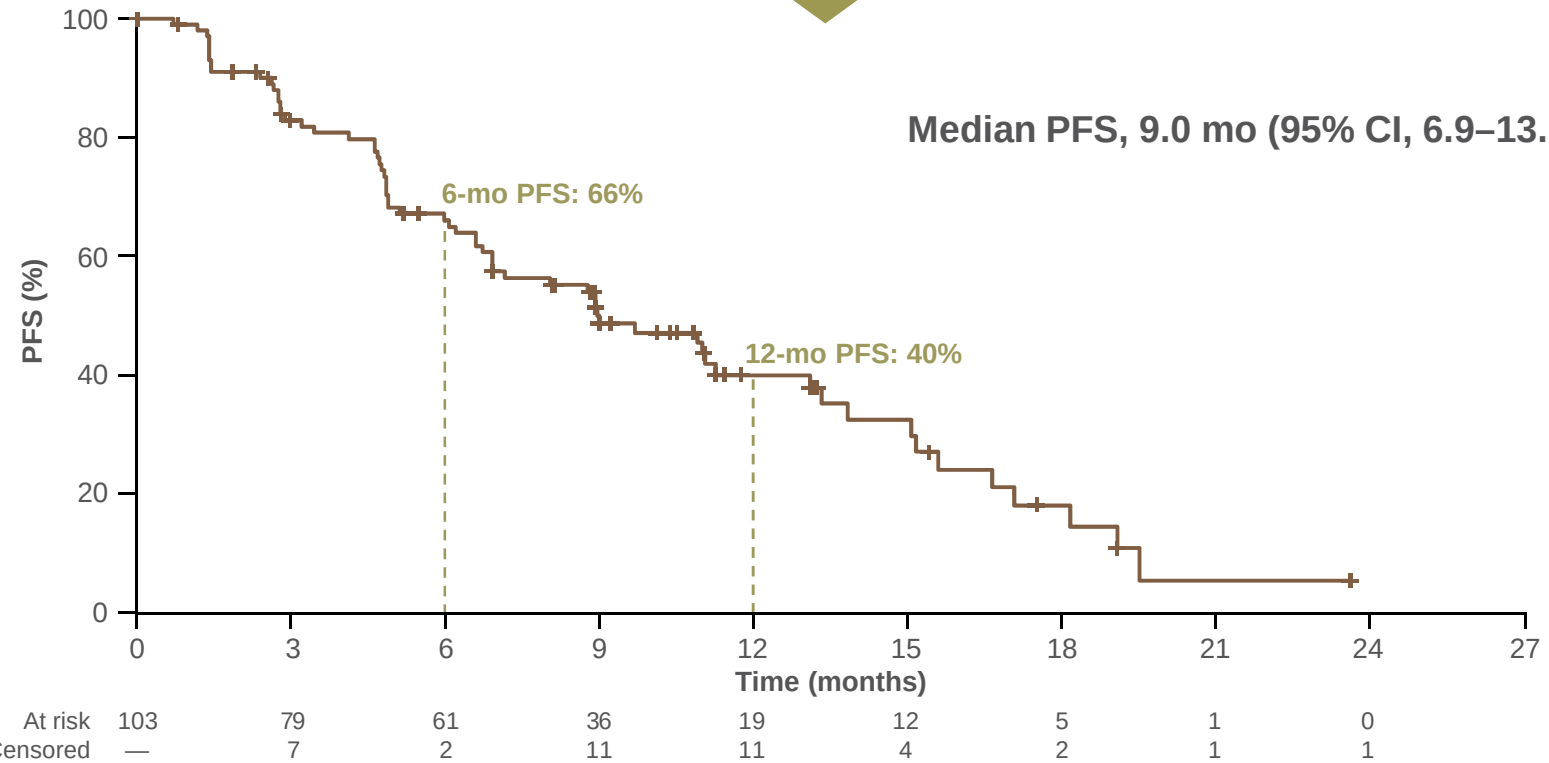
Subgroup	Patients with response n/N (%)	ORR (95% CI), %
All patients	43/103 (41.7)	41.7 (32.1–51.9)
Age		
<65 years	28/80 (35.0)	35.0 (24.7–46.5)
≥65 years	15/23 (65.2)	65.2 (42.7–83.6)
Region		
North America	19/47 (40.4)	40.4 (26.4–55.7)
Europe	13/28 (46.4)	46.4 (27.5–66.1)
Asia Pacific	7/14 (50.0)	50.0 (23.0–77.0)
Japan	4/14 (28.6)	28.6 (8.4–58.1)
Sex		
Male	17/45 (37.8)	37.8 (23.8–53.5)
Female	26/58 (44.8)	44.8 (31.7–58.5)
Baseline ECOG PS		
0	22/48 (45.8)	45.8 (31.4–60.8)
1	21/55 (38.2)	38.2 (25.4–52.3)
Prior systemic therapy		
1	18/48 (37.5)	37.5 (24.0–52.6)
2	12/31 (38.7)	38.7 (21.8–57.8)
≥3	13/24 (54.2)	54.2 (32.8–74.4)
Prior surgical resection		
Yes	11/21 (52.4)	52.4 (29.8–74.3)
No	32/82 (39.0)	39.0 (28.4–50.4)



- ORRs were consistent across patient subgroups
- Dosing modifications did not affect futibatinib response (40.0% ORR in patients with dosing interruptions/reductions [n=90])

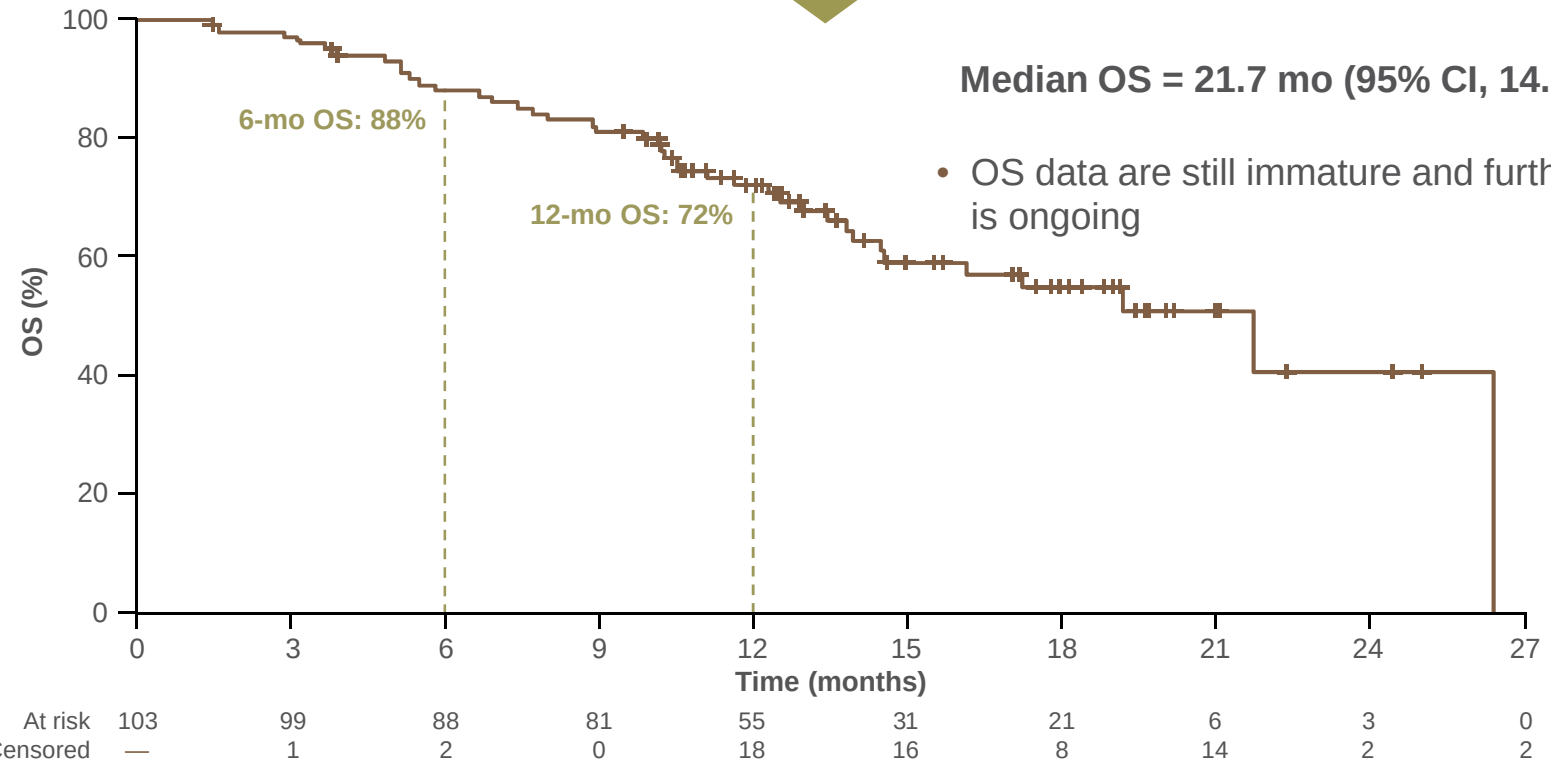
Data cutoff: October 1, 2020. The solid vertical line in the plot indicates the ORR in the overall efficacy population.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate.

Progression-free Survival With Futibatinib in iCCA



Data cutoff: October 1, 2020. Median follow-up 17.1 mo (range, 10.1–29.6).
CI, confidence interval; PFS, progression-free survival.

Overall Survival With Futibatinib in iCCA



Median OS = 21.7 mo (95% CI, 14.5–NR)

- OS data are still immature and further follow-up is ongoing

Data cutoff: October 1, 2020. Median follow-up 17.1 mo (range, 10.1–29.6).
CI, confidence interval; iCCA, intrahepatic cholangiocarcinoma; NR, not reached; OS, overall survival.

Futibatinib Safety Summary

	Safety population (N=103), n (%)	
	Any grade	Grade ≥3
AEs of any cause	103 (100)	79 (77)
Treatment-related AEs	102 (99)	59 (57)[a]
Serious treatment-related AEs	10 (10)	7 (7)
Actions taken because of treatment-related AEs		
Dosing interruption	52 (50)	
Dose reduction	56 (54)	
Drug discontinuation	2 (2)[b]	
Treatment-related AEs with outcome of death	0	

Data cutoff: October 1, 2020.
AE, adverse event.
[a]Except for 1 event of grade 4 increased alanine aminotransferase, all events were grade 3 in severity; [b]Of these 2 patients, 1 patient had grade 2 stomatitis, grade2 pharyngeal inflammation and grade 3 oral dysesthesia, and the other patient had grade 3 esophagitis

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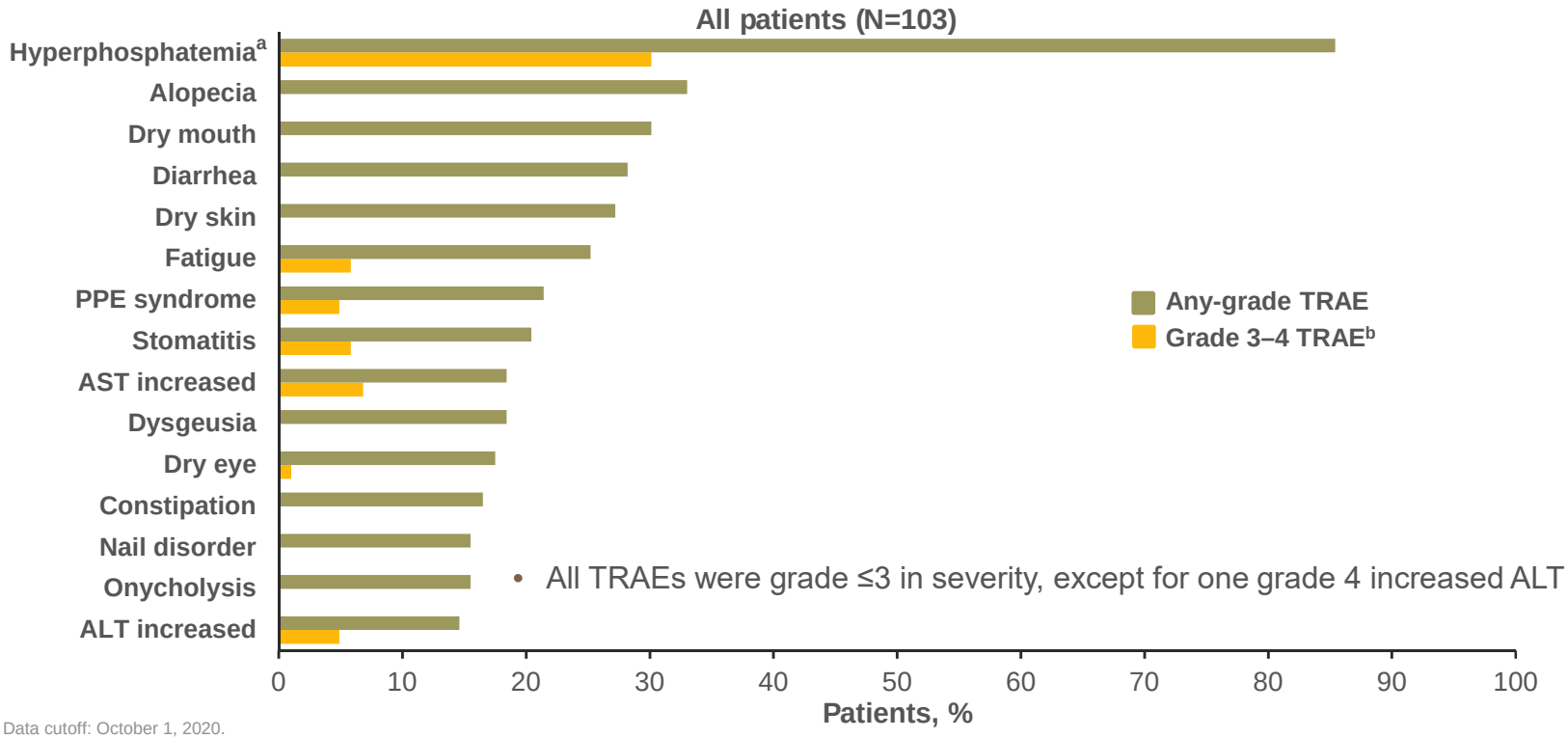
Most Common (≥15%) Treatment-Related AEs With Futibatinib



- All TRAEs were grade ≤3 in severity, except for one grade 4 increased ALT

Data cutoff: October 1, 2020.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; PPE, palmar–plantar erythrodysesthesia; TRAE, treatment-related adverse event.
[a]Graded by serum phosphate levels; [b]Only 1 grade 4 event of increased ALT was reported, and no grade 5 TRAEs occurred.

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Adverse Events of Special Interest

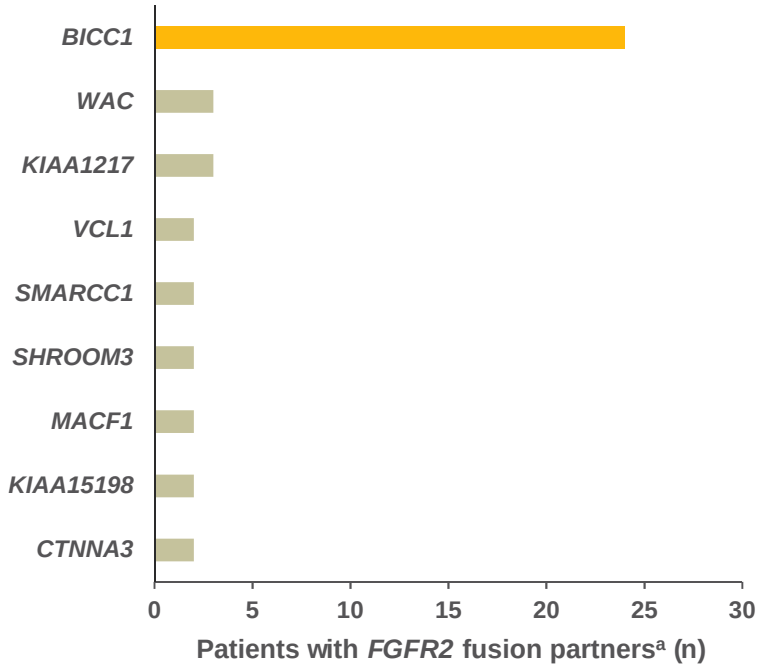
AE of special interest by group term	Safety population (N=103), n (%)		
	Any grade[a]	Grade 3	Grade 4
Hyperphosphatemia[b]	94 (91)	32 (31)	0
Nail toxicities[c]	48 (47)	2 (2)	0
Increased ALT and AST[d]	28 (27)	12 (12)	1 (1)
Palmar–plantar erythrodysesthesia syndrome	22 (21)	5 (5)	0
Rash[e]	9 (9)	0	0
Retinal disorders[f]	8 (8)	0	0

- No AEs of special interest led to treatment discontinuations
  - Hyperphosphatemia was managed with phosphate binders (78%) or dosing reductions/interruptions (20%/17%)
  - All grade 3–4 AEs of special interest resolved (median time to resolution, 4.0–7.0 days)

Data cutoff: October 1, 2020.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase.
[a]No grade 5 events of special interest were reported; [b]Includes increased blood phosphorus; [c]Includes nail discoloration, disorder, dystrophy, hypertrophy, infection, pigmentation, or toxicity, and onychalgia, onycholasis, onycholysis, onychomadesis, onychomycosis, and paronychia; [d]Also includes 2 events of increased GGT; [e]Includes macular, maculopapular, or papular rash; [f]Includes chorioretinopathy, detachment of retinal pigment epithelium, maculopathy, serous retinal detachment, and subretinal fluid.

Futibatinib Activity: *FGFR2* Fusions and Other Rearrangements

FGFR2 fusion partner frequency (≥2 patients)



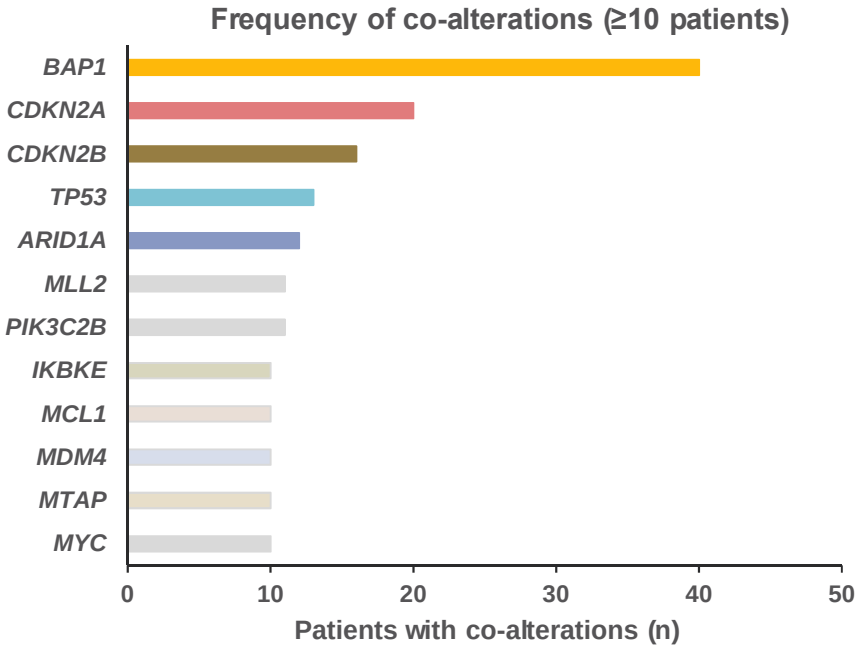
Outcomes by *FGFR2* fusions/rearrangements

FGFR2 alteration	No. with alteration	ORR (95% CI), %	Median PFS (95% CI), mo
FGFR2 fusions	80	43.8 (32.7–55.3)	8.9 (6.6–11.3)
FGFR2–BICC1 fusions	24	41.7 (22.1–63.4)	9.0 (4.9–11.0)
Non-*FGFR2–BICC1* fusions	56	44.6 (31.3–58.5)	8.8 (4.9–15.1)
FGFR2 rearrangements	23	34.8 (16.4–57.3)	16.7 (6.0–NR)

- 46 different fusion partners were identified in 80 patients with fusions
  - *BICC1* was the most common fusion partner (30%)
  - Unique fusion partners (n=1 each) were seen in 46% of patients

Data cutoff: October 1, 2020.
CI, confidence interval; NR, not reached; ORR, objective response rate; PFS, progression-free survival.
[a]The fusion partner was unknown in 1 patient.

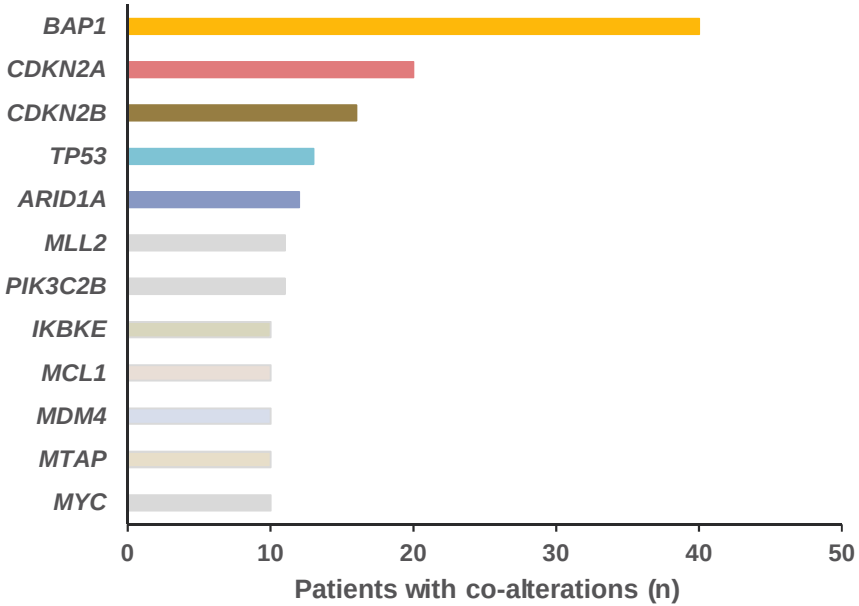
Futibatinib Activity: Co-occurring Genomic Alterations[a]



Data cutoff: October 1, 2020.
CI, confidence interval; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Analyses only included patients with available Foundation Medicine reports (n=93).

Futibatinib Activity: Co-occurring Genomic Alterations[a]

Frequency of co-alterations (≥10 patients)



Outcomes in patients[a] with the most frequent co-alterations

Gene	Molecular status (n)	ORR (95% CI), %	Median PFS (95% CI), mo
All patients (n=93)[a]	—	**43.0 (32.8–53.7)**	**8.9 (6.6–13.1)**
BAP1	Unaltered (53)	49.1 (35.1–63.2)	8.0 (4.9–13.8)
	Altered (40)	35.0 (20.6–51.7)	9.0 (5.1–13.3)
CDKN2A	Unaltered (73)	43.8 (32.2–55.9)	9.7 (6.9–13.8)
	Altered (20)	40.0 (19.1–63.9)	4.9 (3.4–13.3)
CDKN2B	Unaltered (77)	42.9 (31.6–54.6)	11.0 (7.2–15.1)
	Altered (16)	43.8 (19.8–70.1)	4.8 (3.4–4.9)
TP53	Unaltered (80)	43.8 (32.7–55.3)	9.0 (6.6–13.3)
	Altered (13)	38.5 (13.9–68.4)	7.0 (1.4–13.8)
ARID1A	Unaltered (81)	42.0 (31.1–53.5)	9.0 (6.2–13.1)
	Altered (12)	50.0 (21.1–78.9)	8.8 (4.9–18.2)

- Of 4 patients harboring both *FGFR2* and *IDH1* alterations, 2 (50%) experienced centrally confirmed PRs

Data cutoff: October 1, 2020.
CI, confidence interval; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Analyses only included patients with available Foundation Medicine reports (n=93).

Conclusions

- **Study FOENIX-CCA2 met its primary endpoint with a 41.7% ORR in previously treated patients with iCCA harboring *FGFR2* fusions/rearrangements**
  - Responses were consistent across subgroups and were durable (overall median DOR, 9.7 mo)
  - Median PFS was 9.0 mo, and median OS was 21.7 mo
- **Futibatinib had a monitorable and manageable safety profile, and treatment-related discontinuations were rare**
  - Hyperphosphatemia, the most frequent AE, was managed with phosphate binders or dose adjustments
- **Exploratory analyses showed that responses occurred in patients with *BICC1* and non-*BICC1* fusion partners and in patients with co-occurring genomic alterations, including in *TP53***

AE, adverse event; DOR, duration of response; iCCA, intrahepatic cholangiocarcinoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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Questions

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