ORIGINAL ARTICLE

Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma

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ABSTRACT

BACKGROUND

Alterations in fibroblast growth factor receptor 2 (*FGFR2*) have emerged as promising drug targets for intrahepatic cholangiocarcinoma, a rare cancer with a poor prognosis. Futibatinib, a next-generation, covalently binding FGFR1–4 inhibitor, has been shown to have both antitumor activity in patients with *FGFR*-altered tumors and strong preclinical activity against acquired resistance mutations associated with ATP-competitive FGFR inhibitors.

METHODS

In this multinational, open-label, single-group, phase 2 study, we enrolled patients with unresectable or metastatic *FGFR2* fusion–positive or *FGFR2* rearrangement–positive intrahepatic cholangiocarcinoma and disease progression after one or more previous lines of systemic therapy (excluding FGFR inhibitors). The patients received oral futibatinib at a dose of 20 mg once daily in a continuous regimen. The primary end point was objective response (partial or complete response), as assessed by independent central review. Secondary end points included the response duration, progression-free and overall survival, safety, and patient-reported outcomes.

RESULTS

Between April 16, 2018, and November 29, 2019, a total of 103 patients were enrolled and received futibatinib. A total of 43 of 103 patients (42%; 95% confidence interval, 32 to 52) had a response, and the median duration of response was 9.7 months. Responses were consistent across patient subgroups, including patients with heavily pretreated disease, older adults, and patients who had co-occurring *TP53* mutations. At a median follow-up of 17.1 months, the median progression-free survival was 9.0 months and overall survival was 21.7 months. Common treatment-related grade 3 adverse events were hyperphosphatemia (in 30% of the patients), an increased aspartate aminotransferase level (in 7%), stomatitis (in 6%), and fatigue (in 6%). Treatment-related adverse events led to permanent discontinuation of futibatinib in 2% of the patients. No treatment-related deaths occurred. Quality of life was maintained throughout treatment.

CONCLUSIONS

In previously treated patients with *FGFR2* fusion or rearrangement–positive intrahepatic cholangiocarcinoma, the use of futibatinib, a covalent FGFR inhibitor, led to measurable clinical benefit. (Funded by Taiho Oncology and Taiho Pharmaceutical; FOENIX-CCA2 ClinicalTrials.gov number, NCT02052778.)

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THE INCIDENCE OF INTRAHEPATIC CHOLangiocarcinoma, an aggressive cancer of the intrahepatic bile ducts, is increasing worldwide.[1-3] Surgery is the main curative option, but up to two thirds of patients have disease recurrence.[4] Patients with intrahepatic cholangiocarcinoma have a 5-year overall survival rate of less than 8%, and among those with advanced disease, the median overall survival is approximately 1 year.[5,6] After failure of first-line gemcitabine–cisplatin, FOLFOX (fluorouracil, leucovorin, and oxaliplatin) is the established second-line standard of care[1]; however, efficacy is modest, with an objective response of 5% and a median overall survival of 6.2 months.[7]

Fibroblast growth factor receptor 2 (*FGFR2*) fusions or rearrangements occur in up to 14% of patients with intrahepatic cholangiocarcinoma.[8-10] Two selective FGFR1–3 inhibitors, pemigatinib and infigratinib, have received accelerated Food and Drug Administration approval for the treatment of advanced, refractory, metastatic cholangiocarcinoma with confirmed *FGFR2* fusions or rearrangements; the responses with these agents have been reported to be 35.5% and 23.1%, respectively.[11-13] These FGFR inhibitors are ATP-competitive, binding reversibly to the ATP-binding pocket in the FGFR kinase domain (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Their efficacy has been shown to be limited by the development of acquired resistance mutations affecting amino acid residues in the kinase domain. These mutations interfere sterically with drug binding, lead to increased receptor activity, or both.[14-22]

Futibatinib (TAS-120) is a highly selective, irreversible inhibitor of FGFR1–4. Unlike reversible ATP-competitive inhibitors, it forms a covalent adduct with a conserved cysteine residue in the FGFR kinase domain P-loop structure. The irreversible nature of binding and its distinct binding site[23,24] make futibatinib less susceptible to on-target resistance mutations than pemigatinib and infigratinib.[24] In preclinical experiments, futibatinib showed stronger activity against a wider spectrum of FGFR2 kinase domain mutations, including mutations in gatekeeper and molecular brake residues (a triad of residues in the hinge region that is autoinhibitory), than other FGFR inhibitors (Fig. 1).[24,25] Furthermore, fewer

A Quick Take is available at NEJM.org

FGFR2 Mutation	Kinase Domain Region	Factor Change in IC_{50} vs. Wild-Type *FGFR2*			
		Futibatinib	Pemigatinib	Infigratinib	Erdafitinib
Wild-type	—	1	1	1	1
N550D	Regulatory triad	2	102	81	10
N550K	Regulatory triad	8	164	68	13
V563L	—	3	5	14	1
V565I	Gatekeeper	4	42	>236	1
V565L	Gatekeeper	44	335	>236	23
E566A	Regulatory triad	3	8	12	1
E566G	Regulatory triad	2	6	10	1
K642I	Regulatory triad	2	20	15	22
K642R	Regulatory triad	2	7	16	1
K660M	Activation loop	5	23	63	19

Figure 1. Inhibitory Activity of Futibatinib, Pemigatinib, Infigratinib, and Erdafitinib against Acquired Resistance Mutations in the FGFR2 Kinase Domain.

Shown are the results of preclinical experiments in murine Ba/F3 cells in which the activity of four agents against acquired secondary fibroblast growth factor receptor 2 (FGFR2) kinase domain mutations was investigated.[25] Regulatory triad refers to a triad of autoinhibitory residues in the hinge region. Random mutagenesis was used to generate FGFR2 kinase domain mutants, which were transfected as fusions with the leukemia-associated *TEL* gene (also called *ETV6*) into Ba/F3 cells, which are dependent on FGFR2 signaling for growth. FGFR inhibition was assessed by means of growth suppression of these cells.[25] Green, orange, and red represent changes in attenuation by a factor of less than 5, 5 to 10, and greater than 10, respectively, in half-maximal inhibitory concentration (IC_{50}) as compared with inhibition of wild-type *FGFR2* (futibatinib IC_{50}, 2 nmol per liter; pemigatinib IC_{50}, 2 nmol per liter; infigratinib IC_{50}, 4 nmol per liter; and erdafitinib IC_{50}, 3 nmol per liter). Amino acids are numbered according to the *FGFR2-IIIb* splice isoform (National Center for Biotechnology Information reference sequence, NM_001144913.1) because *FGFR2* fusions in intrahepatic cholangiocarcinoma are expressed in this context.[18]

drug-resistant clones emerged with futibatinib treatment.[24] Clinical data from a phase 1 study and case series provided support for these findings and showed sustained clinical benefit with futibatinib in patients with *FGFR*-altered cholangiocarcinoma who had had disease progression after previous FGFR inhibitor therapy.[21,22,26]

Data from the dose-escalation portion of a multinational phase 1–2 study[27] and a Japanese phase 1 study[28] established 20 mg of oral futibatinib once daily as the recommended dose for the phase 2 study. Futibatinib showed antitumor activity and generally low-grade toxic effects in heavily pretreated patients with advanced, *FGFR*-altered tumors.[26-28] In the multinational, phase 1, dose-expansion part of the study, activity was pronounced in patients with intrahepatic cholangiocarcinoma harboring *FGFR2* fusions or rearrangements, and 25.4% of the patients had a response.[26]

In FOENIX-CCA2, a multinational phase 2 study, we investigated the efficacy and safety of futibatinib in patients with intrahepatic cholangiocarcinoma harboring *FGFR2* fusions or other rearrangements after one or more lines of systemic therapy. Correlative research was also performed to assess the use of circulating tumor DNA (ctDNA) profiling of plasma samples for the detection of *FGFR2* fusions and rearrangements.

METHODS

PATIENTS

Eligible patients were at least 18 years of age and had unresectable or metastatic intrahepatic cholangiocarcinoma harboring an *FGFR2* fusion or rearrangement that had been prospectively identified by local testing of tumor tissue or ctDNA or by testing of tumor tissue at a central or local laboratory with the use of a 324-gene-panel assay (FoundationOne CDx assay, Foundation Medicine). The patients had radiologically measurable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[29]; disease progression after systemic therapy (including ≥1 previous regimen of gemcitabine plus platinum-based chemotherapy and no previous treatment with an FGFR inhibitor); adequate organ function; and a performance-status score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, which ranges from 0 (no disability) to 5 (death). Patients with a history of or current clinically significant retinal disorder or altered non–tumor-related calcium–phosphorus homeostasis were excluded. Complete eligibility criteria are provided in the Supplementary Methods section in the Supplementary Appendix and in the protocol, available at NEJM.org.

STUDY DESIGN AND OVERSIGHT

This open-label, single-group, phase 2 study was conducted at 47 sites across 13 countries (Supplementary Appendix). The study was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, local laws, and applicable regulatory requirements. All the patients provided written informed consent.

The study was designed by the sponsors (Taiho Oncology and Taiho Pharmaceutical) in collaboration with the authors. A data review committee performed study oversight. Agreements requiring the authors to maintain data confidentiality were in place between the authors and Taiho Oncology. All the authors participated in the collection, analysis, or interpretation of the data. The first and last authors prepared the first draft of the manuscript with professional writing and editorial assistance funded by Taiho Oncology. All the authors had access to the data and vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol.

TREATMENT

The patients received oral futibatinib at a dose of 20 mg once daily (five 4-mg tablets) in a continuous regimen over a 21-day cycle. Treatment continued until the occurrence of imaging-based or clinical disease progression or unacceptable toxic effects or until any other discontinuation criterion was met. For patients with continued clinical benefit, treatment after disease progression was permitted after discussion between the investigators and one of the sponsors (Taiho Oncology). Dose modifications were implemented in patients with adverse events (Table S1); in patients with hyperphosphatemia, dose modifications and phosphate-lowering therapies were initiated after the detection of a serum phosphate level of 5.5 mg per deciliter or more (1.8 mmol per liter) (Table S2). Treatment was discontinued if toxic effects did not resolve after two dose reductions (to 16 mg, then to 12 mg) or if the toxic effects caused treatment-cycle delays of more than 21 days.

ASSESSMENTS

Tumor response was assessed by means of computed tomography, magnetic resonance imaging, or both in accordance with RECIST, version 1.1, every 6 weeks for the first four cycles and every 9 weeks thereafter. Plasma samples were obtained from the patients in accordance with the protocol for blinded exploratory ctDNA analysis (Fig. S2). The samples were assessed for *FGFR2* fusions or rearrangements with the use of the TruSight Oncology 500 (Illumina) ctDNA sequencing assay. Additional details regarding the ctDNA and genomic profiling analyses are provided in the Supplementary Appendix.

Safety was assessed from the time of the first dose of futibatinib until 30 days after the last dose or until the initiation of a new agent, whichever occurred earlier. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03; hyperphosphatemia was graded on the basis of serum phosphate levels. Serum phosphate levels were measured on days 1, 4, 8, and 15 of cycle 1 and on day 1 of every cycle thereafter. Schedules for ophthalmologic examinations and other evaluations are provided in the protocol and the Supplementary Appendix.

Data on patient-reported outcomes were collected with the use of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 (EORTC QLQ-C30), the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), and the EuroQol visual-analogue scale (EQ VAS). Details regarding these assessment measures are provided in the Supplementary Appendix.

END POINTS

The primary end point was objective response (partial or complete response), as assessed by independent central review. Secondary end points were response duration, disease control, progression-free survival, overall survival, safety, and patient-reported outcomes (Supplementary Appendix).

STATISTICAL ANALYSIS

This study was designed to enroll and treat approximately 100 patients. Sample-size considerations were based on the results of the phase 1 study[26,27] and the historical response in this population.[7] The study had a power of 81% to reject the null hypothesis that the response rate was 10% or less[7] (target, 20%), at a two-sided alpha level of 5%. We estimated that with a sample of 100 patients, if the observed response was 17.0% (95% confidence interval [CI], 10.2 to 25.8), the lower boundary of the 95% confidence interval would exclude 10% (the null hypothesis).

Planned interim analyses included safety reviews approximately every 3 months. A formal interim efficacy analysis was performed when 67% of all the patients who received futibatinib had at least 6 months of follow-up (Supplementary Appendix). The primary analysis was planned when at least 50% of the patients with an objective response had at least 6 months of follow-up from the onset of response.

The safety and efficacy populations included all the patients who received at least one dose of futibatinib. The patient-reported outcome population included all patients who received futibatinib and completed EORTC QLQ-C30 or EQ-5D assessments at baseline and at at least one subsequent visit.

For the analysis of the primary end point, all the patients who did not have postbaseline assessments or who had insufficient tumor data were considered to have not had a response, and the numbers of those patients were included in the denominator for calculation of the percentage of patients with an objective response. Confidence intervals for binomial proportions, response, and disease control were determined with the use of the exact two-sided Clopper–Pearson method. Time-to-event distributions (response duration, progression-free survival, overall survival, and time to response) were estimated with the use of Kaplan–Meier techniques, and associated 95% confidence intervals were estimated with the use of the Brookmeyer–Crowley method (Supplementary Methods section in the Supplementary Appendix).

The consistency of treatment effects was determined by summarizing responses in various subgroups of patients. This subgroup analysis was exploratory in nature; no multiplicity adjustment was used and no inferential conclusions were drawn. Additional methods, including data-handling rules, are described in the Supplementary Appendix.

RESULTS

PATIENTS

Between April 16, 2018, and November 29, 2019, a total of 783 patients underwent screening, and

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=103)
Age — yr	
Median	58
Range	22–79
Sex — no. (%)	
Female	58 (56)
Male	45 (44)
ECOG performance-status score — no. (%)†	
0	48 (47)
1	55 (53)
Race or ethnic group — no. (%)‡	
White	51 (50)
Asian	30 (29)
Black	8 (8)
Native Hawaiian or Pacific Islander	1 (1)
Unknown	13 (13)
Geographic region — no. (%)	
North America	47 (46)
Europe	28 (27)
Japan	14 (14)
Asia Pacific, excluding Japan	14 (14)
FGFR2 alteration — no. (%)§	
Fusion	80 (78)
Rearrangement	23 (22)
Previous therapy — no. (%)	
Anticancer therapy	103 (100)
Radiotherapy	28 (27)
Anticancer surgery	41 (40)
No. of previous lines of systemic therapy — no. (%)¶	
1	48 (47)
2	31 (30)
≥3	24 (23)
Median time from previous anticancer therapy to first dose of futibatinib (interquartile range) — mo	1.5 (1.0–3.4)

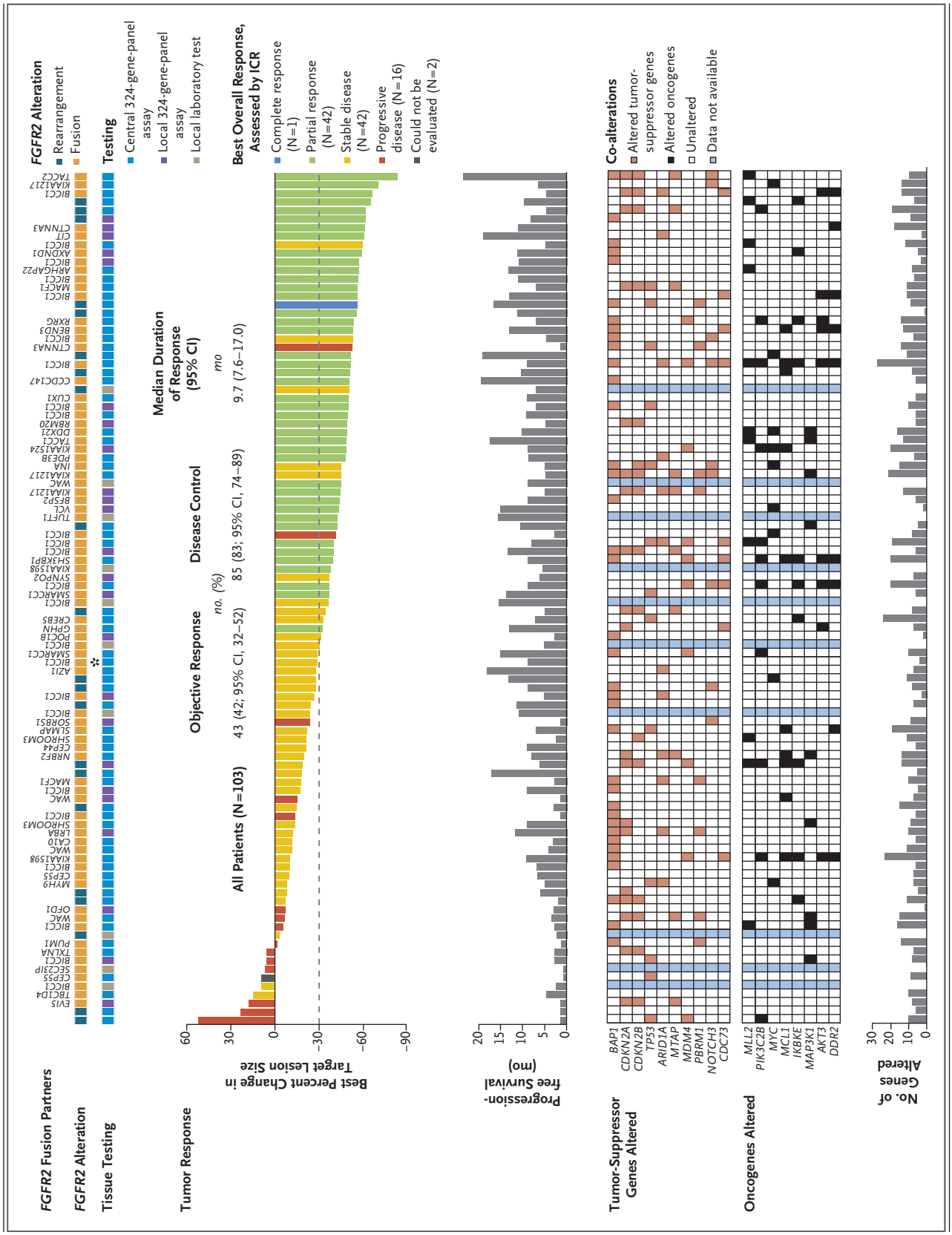
* Percentages may not total 100 owing to rounding. FGFR2 denotes fibroblast growth factor receptor 2.
† Scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 (no disability) to 5 (death).
‡ Race or ethnic group was reported by the patient.
§ Rearrangements were categorized as fusions only if the fusion gene partner was identified (Supplementary Methods section in the Supplementary Appendix).
¶ A total of 101 patients (98%) received previous systemic therapy for unresectable or metastatic intrahepatic cholangiocarcinoma.

Figure 2 (facing page). Antitumor Activity of Futibatinib and Molecular Profiles of Individual Patients in the Study.

FGFR2 alterations were assessed by testing tumor tissue in local laboratories or with the use of a 324-gene-panel assay in central or local laboratories. The *FGFR2* alteration (fusion or rearrangement) in each patient is indicated, along with the fusion partner, if one was identified. One patient had an *FGFR2* S799fs*22 mutation in addition to an *FGFR2* fusion (asterisk). The best percent change from baseline in the target lesion size in individual patients is shown in a waterfall plot. The bar graph below the waterfall plot shows progression-free survival among the individual patients. Co-occurring genomic alterations were assessed with the use of the 324-gene-panel assay. The most frequently co-altered genes in at least nine patients are shown. The *MDM4* gene may also be classified as an oncogene. The bar graph at the bottom of the figure shows the total number of altered genes (identified with the use of the panel) in each patient. Data on three patients were not included because they were missing tumor assessments (one did not have a postbaseline assessment, and two did not have any target lesions available, according to independent central review [ICR]). The widths of the confidence intervals have not been adjusted for multiplicity; thus, the confidence intervals should not be used to reject or not reject treatment effects.

103 were enrolled and received futibatinib at a 20-mg once-daily starting dose (Fig. S3). At the data-cutoff date for the primary analysis on October 1, 2020, the median follow-up was 17.1 months (range, 10.1 to 29.6) and the median duration of treatment was 9.1 months (Table S3). A total of 72 of 103 patients (70%) discontinued treatment, predominantly because of imaging-based or clinical disease progression (in 62%) and less commonly because of adverse events (in 5%). Thirteen patients (13%) received futibatinib after imaging-based disease progression because of continued clinical benefit. A total of 26 of 72 patients (36%) received subsequent anticancer treatment, most commonly chemotherapy (Table S4).

The 103 patients in the study were representative of the worldwide population of patients with intrahepatic cholangiocarcinoma who have disease progression after previous therapy (Table S5). The median age of the patients in the study was 58 years (range, 22 to 79), 56% of the patients were women, and 53% had received at least two previous lines of systemic therapy (Table 1 and Table S6). Tumors in these patients were genetically profiled with the use a 324-gene-panel assay at a central laboratory (in 66% of the patients), a 324-gene-panel assay at a local laboratory (in 24%), other local testing of tumor tissue (in 7%), or ctDNA testing (in 3%). A total of 80 of 103 patients (78%) had *FGFR2* fusions to known partner genes; the remainder of the patients had rearrangements (with unidentified partner genes) (Table 1). The distribution of



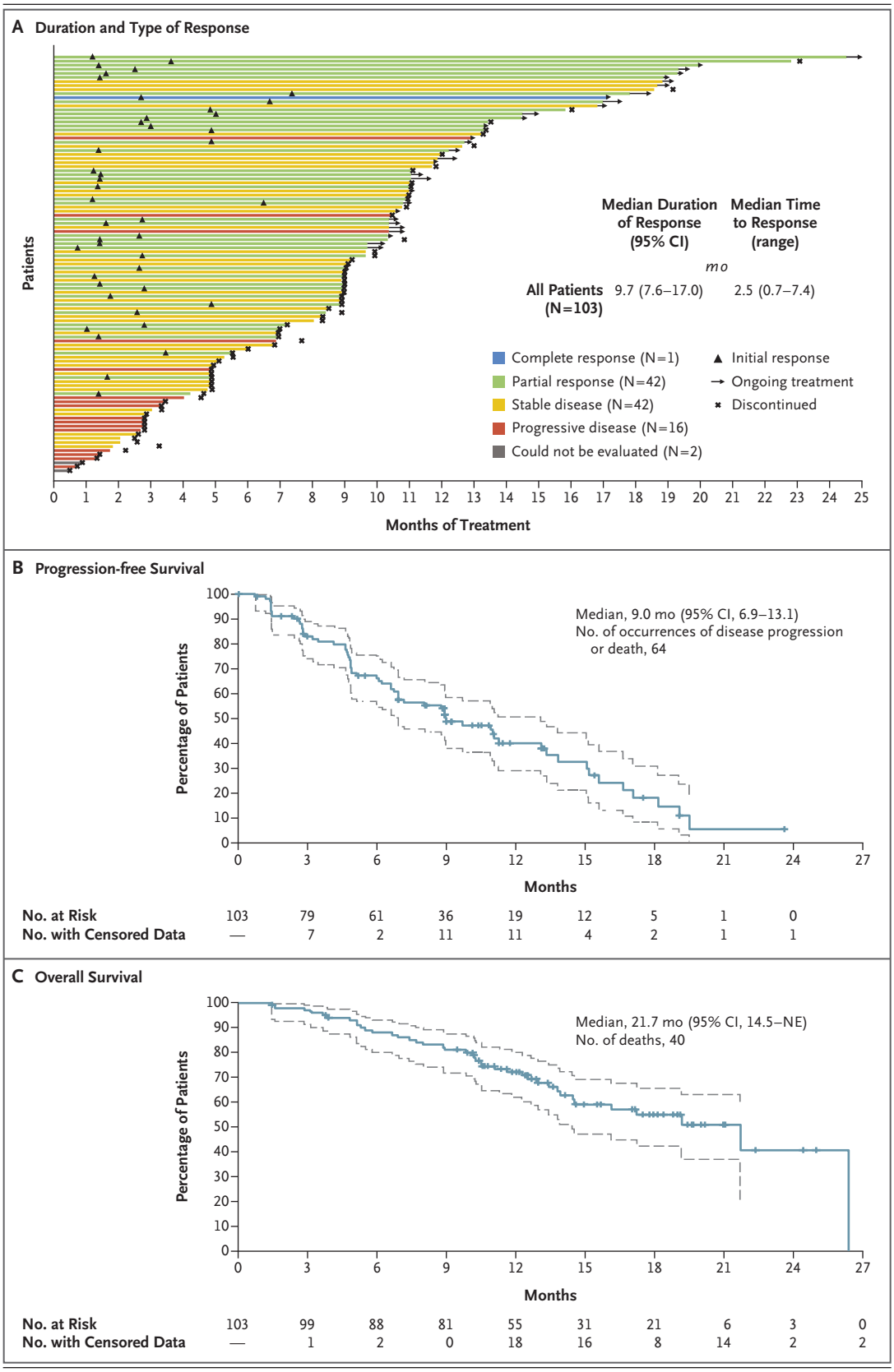


Figure 3 (facing page). Duration and Type of Response, Progression-free Survival, and Overall Survival among Patients Who Received Futibatinib.

Panel A shows the duration and type of response in 103 patients. The median duration of response was calculated with the use of the Kaplan–Meier method; responses were based on independent central review in accordance with Response Evaluation Criteria in Solid Tumors, version 1.1. Panel B shows Kaplan–Meier estimates of progression-free survival, and Panel C shows Kaplan–Meier estimates of overall survival. In Panels B and C, the gray dashed lines denote the upper and lower boundaries of the 95% confidence intervals. In Panel B, tick marks represent data censored at the time of the last tumor assessment in patients who were alive and without disease progression. In Panel C, tick marks represent data censored at the date of the last follow-up (or data-cutoff date, whichever was earlier) in patients who were alive or whose death was not confirmed. In all three panels, the widths of the confidence intervals have not been adjusted for multiplicity; thus, the confidence intervals should not be used to reject or not reject treatment effects. NE denotes not evaluable.

baseline characteristics according to geographic region is provided in Table S7.

EFFICACY

Among the 103 patients in the efficacy population, 43 (42%; 95% CI, 32 to 52) had a response, as assessed by independent central review (Fig. 2), including 1 patient who had a complete response. A total of 85 of 103 patients (83%; 95% CI, 74 to 89) had disease control. The median duration of response was 9.7 months (95% CI, 7.6 to 17.0) (Fig. 3A). Among the 43 patients with a response, 31 (72%) had responses lasting at least 6 months and 6 (14%) had responses lasting at least 12 months. In a time-to-event analysis of response in all 103 patients who received futibatinib, the median time to response, calculated with the use of the Kaplan–Meier method, was not reached; the Kaplan–Meier cumulative response was 34% at 4 months and 42% at 8 months after the start of treatment (Fig. S4). Among patients with a response, the median time to response was 2.5 months (range, 0.7 to 7.4). At the time of data cutoff, response was ongoing in 21 of 43 patients who had a response. Objective responses were observed across all protocol-specified subgroups, including in patients who were at least 65 years of age and those with one, two, or three or more previous lines of treatment (Fig. S5).

The median progression-free survival was 9.0 months (95% CI, 6.9 to 13.1) (Fig. 3B), with 6- and 12-month progression-free survival of 66% (95% CI, 56 to 75) and 40% (95% CI, 29 to 51), respectively. The median overall survival was 21.7 months (95% CI, 14.5 to not reached) (Fig. 3C); the 12-month overall survival rate was 72% (95% CI, 62 to 80). During the study, 40 patients (39%) died after treatment discontinuation; the majority (90%) died from disease progression. During the study treatment period, no deaths were reported among the patients who received futibatinib. Similar data on response and survival were documented at extended follow-up, 8 months after the primary analysis (Supplementary Results section in the Supplementary Appendix).

GENOMIC PROFILING ANALYSIS

Analysis of the molecular profile of the tumors in the 103 patients in the efficacy population indicated that responses did not correlate with *FGFR2* fusion-partner status or co-occurring alterations in tumor-suppressor genes or oncogenes (Fig. 2). Overall, 46 unique *FGFR2* fusion partners were identified in this patient population. *BICC1* was the most common (in 24 patients), followed by *KIAA1217* and *WAC* (each in 3 patients). Responses occurred in 10 of 24 patients (42%) with *BICC1* fusions and in 25 of 56 patients (45%) with non-*BICC1* fusions. In 93 patients with available results of the 324-gene-panel assay, *BAP1* was identified as the most frequently co-altered gene (in 43% of the patients), followed by *CDKN2A* (in 22%), *CDKN2B* (in 17%), and *TP53* (in 14%) (Table S8). Responses occurred in 35% to 49% of patients with or without *BAP1*, *TP53*, *CDKN2A*, or *CDKN2B* alterations.

Median progression-free survival was similar among patients with and those without *BAP1* alterations (9.0 months and 8.0 months, respectively), as it was among patients with and those without *TP53* alterations (7.0 months and 9.0 months). Numerical differences were noted with respect to median progression-free survival between patients with and those without *CDKN2A* (4.9 months and 9.7 months, respectively) and those with and those without *CDKN2B* alterations (4.8 months and 11.0 months). Exploratory ctDNA analysis identified *FGFR2* fusions or rearrangements in 83 of the 95 patients (87%) evaluated, including 78 of 90 with a baseline

Table 2. Treatment-Related Adverse Events Reported in at Least 10% of the Patients.*

Event	All Patients (N=103)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
		number of patients (percent)			
Any adverse event	102 (99)	8 (8)	35 (34)	58 (56)	1 (1)
Hyperphosphatemia	88 (85)	10 (10)	47 (46)	31 (30)	0
Alopecia	34 (33)	26 (25)	8 (8)	0	0
Dry mouth	31 (30)	28 (27)	3 (3)	0	0
Diarrhea	29 (28)	21 (20)	8 (8)	0	0
Dry skin	28 (27)	22 (21)	6 (6)	0	0
Fatigue	26 (25)	15 (15)	5 (5)	6 (6)	0
Palmar–plantar erythrodysesthesia syndrome	22 (21)	3 (3)	14 (14)	5 (5)	0
Stomatitis	21 (20)	10 (10)	5 (5)	6 (6)	0
Dysgeusia	19 (18)	12 (12)	7 (7)	0	0
Increased aspartate aminotransferase level	19 (18)	11 (11)	1 (1)	7 (7)	0
Dry eye	18 (17)	14 (14)	3 (3)	1 (1)	0
Constipation	17 (17)	12 (12)	5 (5)	0	0
Nail disorder	16 (16)	9 (9)	7 (7)	0	0
Onycholysis	16 (16)	8 (8)	8 (8)	0	0
Increased alanine aminotransferase level	15 (15)	5 (5)	5 (5)	4 (4)	1 (1)
Nail discoloration	14 (14)	12 (12)	2 (2)	0	0
Onychomadesis	14 (14)	6 (6)	7 (7)	1 (1)	0
Decreased appetite	13 (13)	6 (6)	7 (7)	0	0
Myalgia	12 (12)	9 (9)	3 (3)	0	0
Nausea	12 (12)	7 (7)	3 (3)	2 (2)	0
Arthralgia	10 (10)	9 (9)	1 (1)	0	0
Muscle spasms	10 (10)	8 (8)	1 (1)	1 (1)	0

* No grade 5 treatment-related adverse events were reported.

sample and 5 of 5 with an on-treatment sample (Supplementary Results section in the Supplementary Appendix).

SAFETY

All the patients had at least one adverse event of any cause (Table S9). The most frequent treatment-related adverse events of any grade (in ≥25% of patients) were hyperphosphatemia (in 85%), alopecia (in 33%), dry mouth (in 30%), diarrhea (in 28%), dry skin (in 27%), and fatigue (in 25%) (Table 2). The most common grade 3 treatment-related adverse event was hyperphosphatemia (in 30% of the patients), defined as a serum phosphate level of 7 mg per deciliter or more, followed by an increased aspartate aminotransferase level (in 7%), stomatitis (in 6%), and fatigue (in 6%). Serious treatment-related adverse events were reported in 10 patients (10%) (Table S10).

The onset of hyperphosphatemia was early (median, 5 days) and was manageable with phosphate-lowering therapy in 78% of the patients, with dose interruptions in 17%, and with dose reductions in 20%; all cases of grade 3 hyperphosphatemia resolved in a median of 7 days (range, 2 to 26). None of the patients discontinued treatment because of hyperphosphatemia.

Other adverse events commonly reported in patients who receive FGFR inhibitors were generally mild, including nail toxic effects (any

grade, in 47% of the patients; grade ≥3, in 2%) and retinal disorders (any grade, in 8%; grade ≥3, in 0%). Overall, treatment-related adverse events led to dose interruptions in 52 patients (50%) and dose reductions in 56 patients (54%). Two patients (2%) permanently discontinued futibatinib; 1 patient had grade 2 stomatitis, grade 3 oral dysesthesia, and grade 2 pharyngeal inflammation, and the other patient had grade 3 esophagitis. No new safety concerns were reported in the extended follow-up.

A total of 92 patients (89%) completed at least one EORTC QLQ-C30 or EQ-5D at baseline and at one or more follow-up assessments. Patient-reported outcome data were evaluated through the cycle 13 visit (in 48 patients) because this was the last visit before data were missing for more than 50% of the patients in the patient-reported outcome population. During these 9.0 months of treatment, EORTC QLQ-C30 scores were stable and global health status was well maintained, except for constipation, which worsened by the minimal threshold of 10.0 points only at cycle 4 (Fig. S6 and Table S11). The status across all EQ-5D-3L dimensions remained the same or improved in the majority of patients (Fig. S7). Mean (±SD) EQ VAS scores were sustained from baseline (71.7±20.3) to cycle 13 (75.6±21.6) (Fig. S8). ECOG performance status was also maintained or improved relative to baseline in most patients with available data (in 95% of the patients at cycle 2 and in 81% of those at cycle 13) (Fig. S9).

EXPLORATORY PHARMACOKINETIC ANALYSES

Within the range of futibatinib exposures (area under the concentration-time curve at steady state) at a dose of 20 mg once daily (the recommended dose used in this study), no significant associations were observed between futibatinib exposure and any of the efficacy end points (Fig. S10). However, the numerically lowest response duration and progression-free survival values were observed at the lowest exposure quartile.

DISCUSSION

Small-molecule inhibitors of tyrosine kinases have transformed the landscape of treatment for several oncogene-addicted tumors, such as *EGFR*-mutant and *ALK* fusion–positive lung cancers.[30-32] *FGFR2* fusion or rearrangement–positive intrahepatic cholangiocarcinoma has been proposed as another pathway-addicted cancer.[8,11-13,26,33,34] Data from our FOENIX-CCA2 study suggest that molecularly targeted agents will substantially improve outcomes in this molecularly defined subgroup. In our study, 42% of the patients who received futibatinib had a response, as determined by independent central review. The use of futibatinib resulted in durable responses and survival that surpassed those indicated by historical data with chemotherapy in patients with refractory intrahepatic cholangiocarcinoma,[7,35-37] findings that led to an accelerated approval by the Food and Drug Administration for the use of this agent in patients with *FGFR2* fusion or rearrangement–positive intrahepatic cholangiocarcinoma. Futibatinib-related adverse events were common and consistent with those associated with other FGFR inhibitors.[11-13,33] Serious events occurred in 10% of the patients, but treatment discontinuation owing to treatment-related adverse events was rare. We evaluated patient-reported outcomes as a secondary end point and found that quality of life was stable over 9.0 months of futibatinib treatment. Combined with results of other trials of FGFR inhibitors (Table S12),[11-13,33] these data support *FGFR2* fusions or rearrangements as a molecular target for intrahepatic cholangiocarcinoma.

A major strength of the current study is the correlative biomarker analysis. The exploratory analysis of primary resistance yielded the clinically interesting observation that responses with futibatinib were observed regardless of *TP53* genomic status. The mechanisms underlying this observation remain unclear.

FGFR2 fusions and rearrangements are important actionable alterations in cholangiocarcinoma, so a practical, high-performance method for identifying these therapeutic targets will materially contribute to improved care of patients with this disease. The failure rate of tissue-biopsy profiling in metastatic biliary tract cancer is as high as 26.8%,[38] and ctDNA profiling offers a noninvasive alternative. Although the detection of *FGFR2* fusion by ctDNA assays has historically been low with some platforms,[39] the partner-agnostic ctDNA platform used in the correlative analyses in this study identified *FGFR2* fusions or rearrangements in 87% of the patients evaluated.

In addition, ctDNA analysis may provide an avenue for selecting patients for trials of frontline FGFR inhibitors, even before tissue-biopsy samples are obtained. Further studies are warranted to assess the clinical performance of ctDNA profiling assays in identifying patients who would benefit from treatment with FGFR inhibitors.

The limitations of the current study include the single-group design and the relatively small sample size. The lack of a comparator group precluded accurate quantification of the treatment effect of this FGFR inhibitor because estimates of the natural history of *FGFR* fusion–positive disease are variable.[8,9,40] The effect of FGFR inhibition on overall survival is currently under investigation in three phase 3, randomized trials comparing first-line FGFR2 inhibitors with chemotherapy (ClinicalTrials.gov numbers, NCT04093362, NCT03656536, and NCT03773302). However, enrollment in these trials is occurring slowly, and other research strategies may be considered for assessing benefit in the interim. Given that intrahepatic cholangiocarcinoma is an uncommon cancer, conditional regulatory and reimbursement approval on the basis of single-group study data has been granted for the use of FGFR inhibitors in patients with cholangiocarcinoma.

Clinical and translational research has shown that *FGFR2* fusion or rearrangement–positive intrahepatic cholangiocarcinoma is a treatable cancer. Data from this study establish futibatinib as having measurable clinical benefit in patients with this disease and show the value of molecular profiling in identifying tumors that are likely to respond to FGFR2 inhibition.

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APPENDIX

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