

# Futibatinib, an Irreversible FGFR1–4 Inhibitor, in Patients with Advanced Solid Tumors Harboring *FGF/FGFR* Aberrations: A Phase I Dose-Expansion Study



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## ABSTRACT

Futibatinib, a highly selective, irreversible FGFR1–4 inhibitor, was evaluated in a large multihistology phase I dose-expansion trial that enrolled 197 patients with advanced solid tumors. Futibatinib demonstrated an objective response rate (ORR) of 13.7%, with responses in a broad spectrum of tumors (cholangiocarcinoma and gastric, urothelial, central nervous system, head and neck, and breast cancer) bearing both known and previously uncharacterized *FGFR1–3* aberrations. The greatest activity was observed in *FGFR2* fusion/rearrangement-positive intrahepatic cholangiocarcinoma (ORR, 25.4%). Some patients with acquired resistance to a prior FGFR inhibitor also experienced responses with futibatinib. Futibatinib demonstrated a manageable safety profile. The most common treatment-emergent adverse events were hyperphosphatemia (81.2%), diarrhea (33.5%), and nausea (30.4%). These results formed the basis for ongoing futibatinib phase II/III trials and demonstrate the potential of genomically selected early-phase trials to help identify molecular subsets likely to benefit from targeted therapy.

**SIGNIFICANCE:** This phase I dose-expansion trial demonstrated clinical activity and tolerability of the irreversible FGFR1–4 inhibitor futibatinib across a broad spectrum of *FGFR*-aberrant tumors. These results formed the rationale for ongoing phase II/III futibatinib trials in cholangiocarcinoma, breast cancer, gastroesophageal cancer, and a genomically selected disease-agnostic population.

## INTRODUCTION

Deregulation of the FGFR signaling pathway is known to drive oncogenesis in cancers harboring *FGFR* aberrations such as fusions, point mutations, insertion-deletion mutations, or amplifications (1). The frequency and oncogenic potential of these aberrations appear to vary across tumors (2, 3), as do their sensitivity to FGFR inhibition. Selective FGFR inhibitors are currently under clinical investigation in a variety of *FGFR*-aberrant cancers (4–11), and the promising clinical benefit observed in these tumors has led to the approvals of the FGFR inhibitors erdafitinib in patients with *FGFR*-aberrant urothelial carcinoma and pemigatinib and

infigratinib in patients with *FGFR2* fusion/rearrangement-positive cholangiocarcinoma (CCA; refs. 4, 7–9).

Most FGFR inhibitors being evaluated in the clinic are reversible ATP-competitive inhibitors (12), and the activity of these agents is mainly seen in select tumor types harboring specific *FGFR* aberrations (4, 6, 9, 13). In addition, the efficacy of ATP-competitive inhibitors has been limited by the development of resistance due to acquired mutations, mostly in the kinase domain (14–17). Potent FGFR inhibitors that show efficacy across a broader spectrum of *FGFR* aberrations and tumor types and also have a lower risk of development of acquired resistance mutations are needed.

Futibatinib is a highly potent selective FGFR1–4 inhibitor, which, unlike ATP-competitive FGFR inhibitors, binds covalently and irreversibly to a conserved cysteine in the P-loop of the FGFR kinase domain (18, 19). In preclinical experiments, futibatinib demonstrated antiproliferative activity against tumor cell lines from diverse tissue origins (including gastric, bladder, lung, endometrial, and breast) harboring various *FGFR* genomic aberrations (19). Futibatinib treatment resulted in the emergence of fewer drug-resistant clones than ATP-competitive FGFR inhibitor treatment. In addition, futibatinib showed robust inhibition of *FGFR2* gatekeeper mutants and a number of other *FGFR2* kinase mutations that conferred resistance to ATP-competitive inhibitors such as erdafitinib, pemigatinib, infigratinib, and AZD4547.

A first-in-human phase I study was initiated to investigate the safety and efficacy of futibatinib in patients with advanced solid tumors (NCT02052778). The dose-finding portion evaluated intermittent and once-daily continuous dosing of futibatinib. The MTD and recommended phase II dose (RP2D) were determined to be futibatinib 20 mg once daily, based on safety, pharmacokinetic, and pharmacodynamic data observed in this study (20). Futibatinib had

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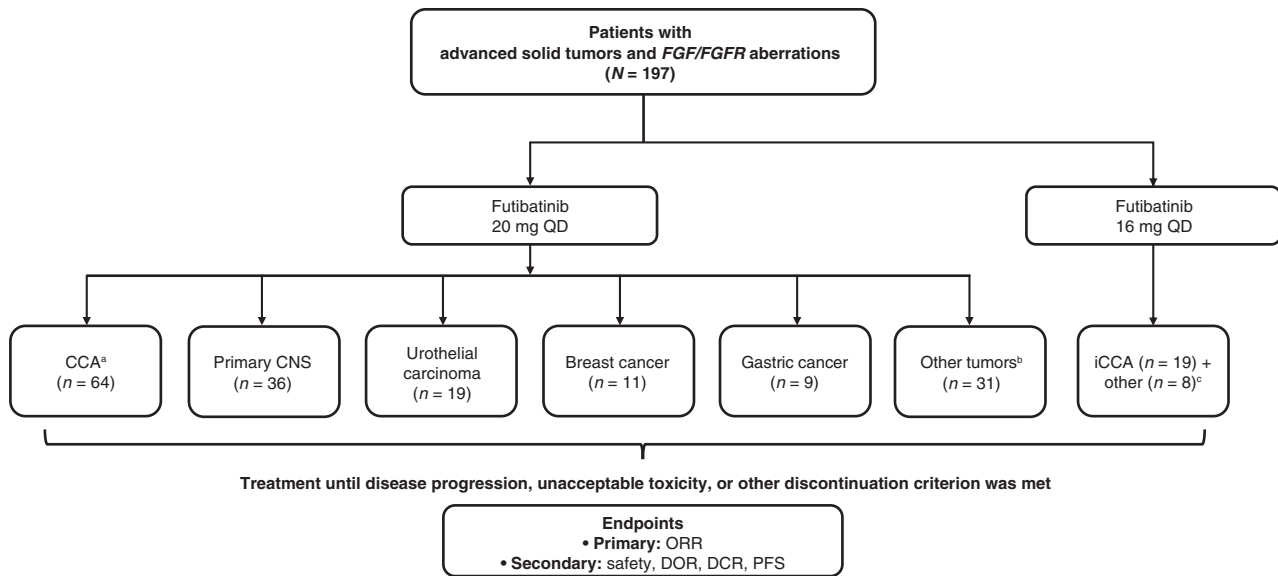
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**Figure 1.** Phase I expansion study design. <sup>a</sup>Intrahepatic ( $n = 61$ ) and extrahepatic ( $n = 3$ ) CCA. <sup>b</sup>Sarcoma ( $n = 6$ ); colorectal cancer ( $n = 5$ ); endometrial cancer ( $n = 3$ ); esophageal cancer ( $n = 3$ ); gallbladder cancer ( $n = 3$ ); head and neck cancer ( $n = 2$ ); adrenal cortical cancer, lung cancer, mesothelioma, ovarian cancer, pancreatic cancer, and thyroid cancer ( $n = 1$  each); and primary unknown ( $n = 3$ ). <sup>c</sup>Breast cancer, gallbladder cancer, primary CNS cancer, sarcoma, urothelial cancer, and thyroid cancer ( $n = 1$  each), and primary unknown ( $n = 2$ ). iCCA, intrahepatic CCA; QD, once daily.

a manageable safety profile, and objective responses were observed in patients with intrahepatic CCA and primary central nervous system (CNS) tumors.

These data informed the dose-expansion portion of this phase I study, the results of which are reported here. The phase I dose expansion evaluated futibatinib in patients with a variety of tumor types, including CCA, CNS tumors, breast cancer, gastric cancer, and others harboring *FGF/FGFR* alterations (Fig. 1). The primary objective was to evaluate the safety and antitumor activity of futibatinib.

## RESULTS

### Patients

A total of 284 patients were screened across 37 sites in 8 countries between July 2014 and May 2019; 83 patients were ineligible, and 201 patients were enrolled. Of these, 197 patients received at least one dose of futibatinib. Four patients did not receive treatment, as 3 patients fell out of eligibility prior to the first dose and 1 patient died prior to the first futibatinib dose. Of 197 treated patients, 170 patients received futibatinib 20 mg once daily, the RP2D, and 27 patients who had been enrolled prior to the confirmation of the RP2D received futibatinib 16 mg once daily.

Among the 170 patients receiving futibatinib 20 mg once daily, CCA was the most common tumor type represented (37.6%), followed by primary CNS tumors (21.2%), urothelial cancer (11.2%), breast cancer (6.5%), and gastric cancer (5.3%); 18.2% of patients had other tumors (Table 1). In the CCA cohort, most patients (61/64; 95.3%) had intrahepatic CCA. *FGF/FGFR* aberrations were analyzed in tumor tissue in 168 of 170 patients; in 2 patients, circulating tumor DNA (ctDNA) analysis was used. Tumors harboring *FGFR*

fusions/rearrangements were most frequently represented (85/170; 50.0%), followed by those with *FGFR* mutations (51/170; 30.0%), *FGFR* amplifications (24/170; 14.1%), and *FGF1/3/4/19* ligand amplifications (23/170; 13.5%). Fourteen (8%) patients had more than one type of *FGF* or *FGFR* alteration. The most common type of *FGFR* aberration was *FGFR2* fusion/rearrangement (28.2%; most commonly in CCA), followed by *FGFR3* fusion/rearrangement (18.8%; mostly primary CNS tumors), *FGFR2* mutation (13.5%), and *FGF1* and *FGF19* amplification (12.9% each; Table 2). Patients were heavily pretreated, with most (75.3%) having received two or more prior regimens, and 27.1% of patients having received at least four prior regimens. Thirty-three patients (19.4%), including 22 with intrahepatic CCA and 8 with urothelial cancer, had previously received *FGFR* inhibitors.

At the data cutoff on June 30, 2019, 149 of 170 patients (87.6%) had discontinued treatment, primarily because of disease progression (72.9% of patients). Ninety-four patients (55.3%) received poststudy anticancer treatment.

Among the 27 patients who received futibatinib 16 mg once daily, 19 patients (70.3%) had intrahepatic CCA, 17 (63.0%) had *FGFR2* fusions/rearrangements, and 15 (55.6%) had received at least two prior regimens, with 7 patients (25.9%) having previously received *FGFR* inhibitors (Supplementary Table S1). At data cutoff, 92.6% of patients had discontinued treatment, primarily because of disease progression.

### Antitumor Activity

Across cohorts, tumor response was assessed per investigator review using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). For CNS tumors, Response Assessment in Neuro-oncology (RANO) criteria were used. For intrahepatic CCA harboring an *FGFR2* fusion

**Table 1. Baseline characteristics and prior therapy in patients receiving futibatinib 20 mg once daily**

Characteristic	20-mg cohort (N = 170)
Age, years	
Mean (SD)	56.0 (13.1)
Sex, n (%)	
Female	95 (55.9)
Male	75 (44.1)
Race, n (%)	
White	100 (58.8)
Asian	21 (12.4)
Black or African American	4 (2.4)
Native Hawaiian or other Pacific Islander	1 (0.6)
Unknown	44 (25.9)
ECOG PS, n (%)	
0	51 (30.0)
1	119 (70.0)
<i>FGF/FGFR</i> alteration, <sup>a</sup> n (%)	
<i>FGFR1</i>	
Fusions/rearrangement	5 (2.9)
Mutation	10 (5.9)
Amplification	2 (1.2)
<i>FGFR2</i>	
Fusions/rearrangement	48 (28.2)
Mutation	23 (13.5)
Amplification	21 (12.4)
<i>FGFR3</i>	
Fusions/rearrangement	32 (18.8)
Mutation	15 (8.8)
Amplification	3 (1.8)
<i>FGFR4</i> mutation	3 (1.8)
<i>FGF1/3/4/19</i> amplification	23 (13.5)
Cancer type, n (%)	
Cholangiocarcinoma	64 (37.6)
Intrahepatic	61 (35.9)
Extrahepatic	3 (1.8)
Primary CNS	36 (21.2)
Urothelial	19 (11.2)
Breast	11 (6.5)
Gastric	9 (5.3)
Other solid tumors <sup>b</sup>	31 (18.2)
Type of prior therapy, n (%)	
Chemotherapy	161 (94.7)
Targeted therapy	58 (34.1)
<i>FGFR</i> inhibitor	33 (19.4)
Immunotherapy	31 (18.2)
Hormonal therapy	7 (4.1)
Other	16 (9.4)
Number of prior regimens, n (%)	
1	35 (20.6)
2	43 (25.3)
3	39 (22.9)
4	18 (10.6)
≥5	28 (16.5)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; *FGF*, fibroblast growth factor.

<sup>a</sup>Fourteen patients had more than one type of *FGF/FGFR* aberration.

<sup>b</sup>Sarcoma (*n* = 6); colorectal cancer (*n* = 5); endometrial, esophageal, and gallbladder cancer (*n* = 3 each); head and neck cancer (*n* = 2); adrenal cortical cancer, lung cancer, mesothelioma, ovarian cancer, pancreatic cancer, and thyroid cancer (*n* = 1 each); and primary unknown (*n* = 3).

or rearrangement, tumor response per independent central review (ICR) was reported in addition to investigator-assessed response. Across the 20- and 16-mg cohorts, 27 of 197 patients (13.7%) experienced a confirmed best overall response of partial response (PR) and 74 patients (37.6%) experienced stable disease (SD). More than half of all treated patients (103/197; 52.3%) experienced shrinkage in target lesions (Fig. 2; Supplementary Fig. S1).

Among the 170 patients who received futibatinib 20 mg once daily, 10.6% experienced PRs, and 38.2% experienced SD. Patients with PRs included 10 patients with CCA (intrahepatic CCA, *n* = 9; extrahepatic CCA, *n* = 1), 3 patients with urothelial cancer, 2 patients with gastric cancer, and 1 patient each with a CNS tumor, head and neck cancer, or an unknown primary tumor (Supplementary Table S2). When stratified by tumor type (Fig. 2; Supplementary Table S3), the most pronounced target-lesion shrinkage and responses were observed in patients with CCA, followed by gastric cancer, urothelial carcinoma, CNS tumors, and other tumors (i.e., breast cancer, head and neck cancer, endometrial cancer, colorectal cancer, and tumors of unknown primary origin). Responses to futibatinib were not restricted to a specific *FGFR* isoform or aberration and were observed in tumors harboring *FGFR1*, 2, or 3 aberrations, including fusions, rearrangements, mutations, and amplifications (Fig. 3; Supplementary Table S3). Target-lesion shrinkage and responses were most evident in tumors harboring *FGFR2* fusions/rearrangements (nearly all CCA), followed by tumors with *FGFR2* mutations (mostly CCA but also in other tumor types), *FGFR3* mutations (urothelial), and *FGFR3* fusions/rearrangements (mostly CNS tumors). In addition, patients with tumors harboring *FGFR2* amplifications (gastric and breast cancer), *FGFR1* fusions/rearrangements (primary CNS and head and neck cancer), and *FGFR1* mutations (urothelial cancer) also had target-lesion shrinkage (Fig. 2).

Among 27 patients who received futibatinib 16 mg once daily, the objective response rate (ORR) was 33.3%. Eight of 9 responders had intrahepatic CCA and an *FGFR2* fusion (*n* = 5), *FGFR2* rearrangement (*n* = 2), or *FGFR2* amplification and *FGFR2* rearrangement (*n* = 1). The remaining responder had triple-negative breast cancer harboring an *FGFR2* amplification (Supplementary Fig. S1).

### Antitumor Activity in CCA

Futibatinib showed higher response rates in CCA than in any other tumor type. A total of 83 patients with CCA were treated in this phase I expansion: 64 patients at 20 mg and 19 patients at 16 mg. Most patient tumors harbored an *FGFR2* fusion or rearrangement (59/83; 71.1%), followed by *FGFR2* mutations (15/83; 18.1%), with 3 of 83 (3.6%) harboring both an *FGFR2* fusion and an *FGFR2* mutation. Patients with CCA were heavily pretreated, with 73.4% in the 20-mg cohort and 68.4% in the 16-mg cohort having received at least two prior regimens, and 37.5% and 52.6%, respectively, at least three prior regimens. Twenty-eight patients (33.7%) were previously treated with another *FGFR* inhibitor.

Among patients with CCA who received futibatinib 20 mg once daily (*n* = 64), the ORR per investigator assessment was 15.6% [95% confidence interval (CI), 7.8%–26.9%] and the disease control rate (DCR) was 71.9% (Fig. 2; Supplementary



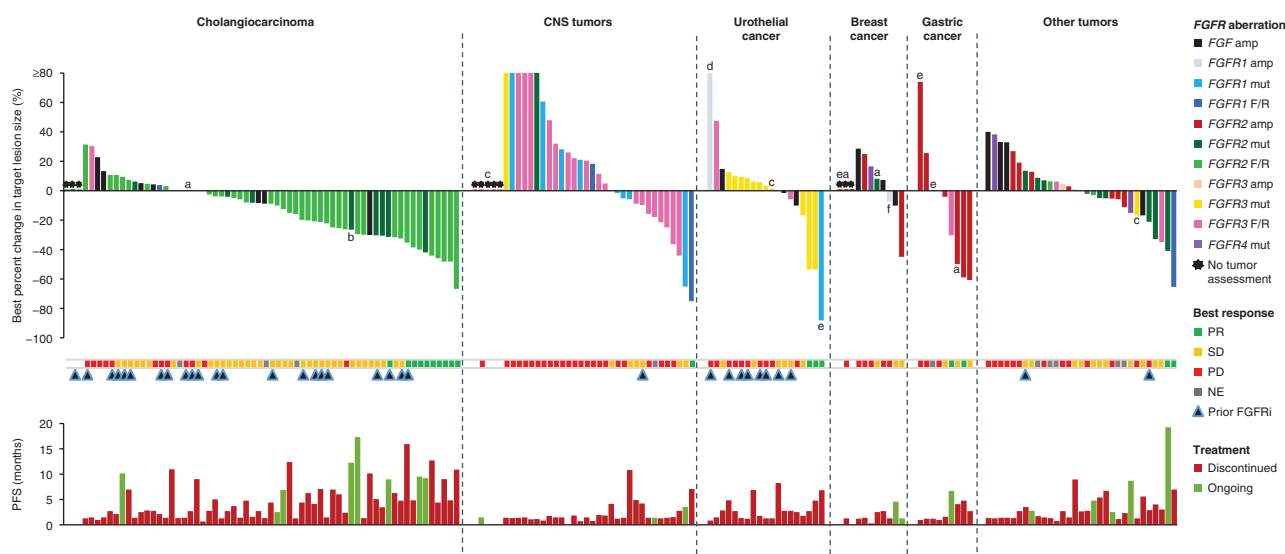
**Table 2. FGFR aberrations by tumor type in patients receiving futibatinib 20 mg once daily**

Tumor type	Gene	Fusions/rearrangements, n (%)	Mutation, n (%)	Amplification, n (%)
Cholangiocarcinoma (n = 64) <sup>a</sup>	<i>FGFR1</i>	1 (1.6)	0	0
	<i>FGFR2</i>	43 (67.2)	13 (20.3)	0
	<i>FGFR3</i>	1 (1.6)	0	0
	<i>FGF1</i>	0	0	7 (10.9)
	<i>FGF3</i>	0	0	6 (9.4)
	<i>FGF4</i>	0	0	5 (7.8)
	<i>FGF19</i>	0	0	8 (12.5)
Primary CNS (n = 36)	<i>FGFR1</i>	2 (5.6)	9 (25.0)	0
	<i>FGFR2</i>	0	1 (2.8)	0
	<i>FGFR3</i>	23 (63.9)	1 (2.8)	1 (2.8)
Urothelial cancer (n = 19)	<i>FGFR1</i>	0	1 (5.3)	1 (5.3)
	<i>FGFR3</i>	3 (15.8)	13 (68.4)	0
	<i>FGF1</i>	0	0	4 (21.1)
	<i>FGF3</i>	0	0	4 (21.1)
	<i>FGF4</i>	0	0	2 (10.5)
	<i>FGF19</i>	0	0	4 (21.1)
Breast (n = 11)	<i>FGFR1</i>	0	0	1 (9.1)
	<i>FGFR2</i>	2 (18.2)	1 (9.1)	5 (45.5)
	<i>FGFR3</i>	0	0	1 (9.1)
	<i>FGFR4</i>	0	1 (9.1)	0
	<i>FGF1</i>	0	0	5 (45.5)
	<i>FGF3</i>	0	0	4 (36.4)
	<i>FGF4</i>	0	0	3 (27.3)
	<i>FGF19</i>	0	0	5 (45.5)
Gastric (n = 9)	<i>FGFR2</i>	1 (11.1)	0	8 (88.9)
	<i>FGFR3</i>	1 (11.1)	0	0
	<i>FGF1</i>	0	0	2 (22.2)
	<i>FGF3</i>	0	0	2 (22.2)
	<i>FGF4</i>	0	0	1 (11.1)
	<i>FGF19</i>	0	0	2 (22.2)
Other (n = 31)	<i>FGFR1</i>	2 (6.5)	0	0
	<i>FGFR2</i>	2 (6.5)	8 (25.8)	8 (25.8)
	<i>FGFR3</i>	4 (12.9)	1 (3.2)	1 (3.2)
	<i>FGFR4</i>	0	2 (6.5)	0
	<i>FGF1</i>	0	0	3 (9.7)
	<i>FGF3</i>	0	0	2 (6.5)
	<i>FGF4</i>	0	0	1 (3.2)
	<i>FGF19</i>	0	0	3 (9.7)

<sup>a</sup>Sixty-one patients had intrahepatic CCA, and 3 patients had extrahepatic CCA harboring *FGFR2* fusions/rearrangements (n = 1), *FGF19* amplification (n = 1), and *FGFR2* mutation (n = 1).

Table S3). Responses observed were durable: the median duration of response (mDOR) was 5.3 months (range, 1.9–9.9 months), and 5 of 10 responders (50%) had responses lasting at least 6 months (Fig. 4; Supplementary Table S2). The responders included one patient with extrahepatic CCA harboring an *FGFR2*–*POC1B* fusion (mDOR, 3.5 months) and 9 patients with intrahepatic CCA harboring an *FGFR2* fusion (n = 5) or *FGFR2* rearrangement (n = 2), *FGFR2* p.C383R mutation (n = 1), or an *FGFR2* p.W290C mutation (n = 1; Supplementary Table S2). Within the subgroup of patients with intrahepatic CCA harboring *FGFR2* fusions or rearrangements (n = 42), the investigator-assessed ORR was 16.7%

(95% CI, 7.0%–31.4%), with an mDOR of 6.9 months and a DCR of 78.6% (95% CI, 63.2%–89.7%); there were three unconfirmed PRs among patients with SD. Per ICR, the ORR in these 42 patients was 14.3% (95% CI, 5.4%–28.5%) and the DCR was 61.9% (95% CI, 45.6%–76.4%). Median progression-free survival (PFS) in the 20-mg CCA cohort (n = 64) was 5.1 months (95% CI, 3.7–9.0 months), and the 6-month PFS rate was 46.0% (95% CI, 31.6%–59.3%). Among patients with intrahepatic CCA and *FGFR2* fusions or rearrangements (n = 42), median PFS was 6.0 months (95% CI, 3.7–9.0 months). The PFS values of the patients with the *FGFR2* p.C383R and p.W290C mutations were 9.2 and 8.9 months, respectively.

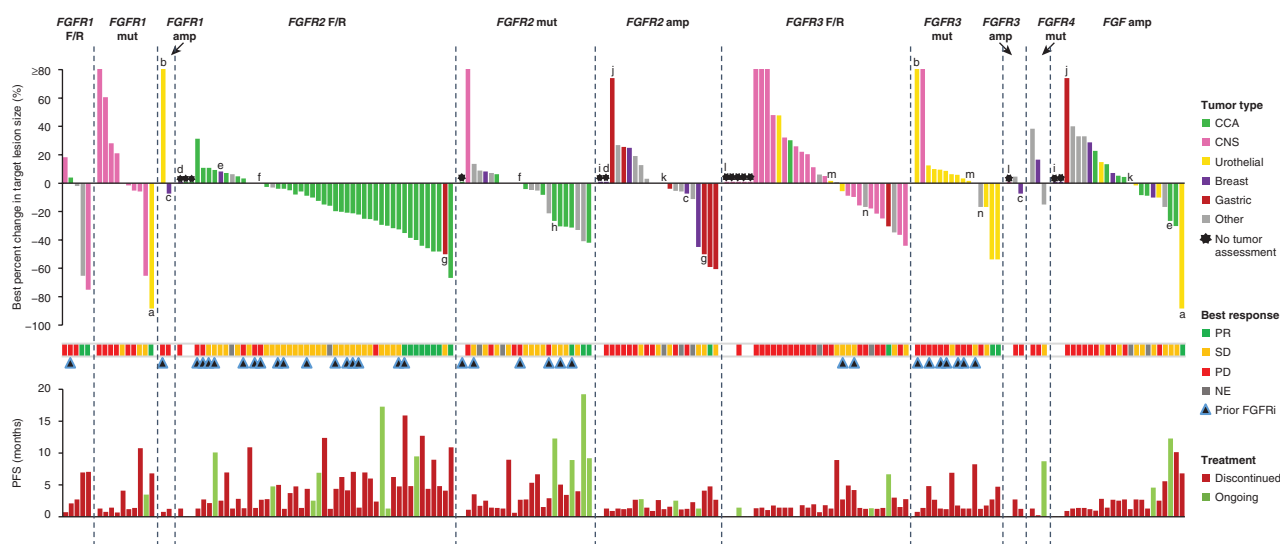


**Figure 2.** Individual response and treatment outcome by tumor type in patients who received futibatinib 20 mg once daily. This figure shows individual treatment outcomes organized by tumor type, color coded for *FGFR* aberration in patients who received futibatinib 20 mg once daily ( $n = 170$ ). RECIST v1.1 criteria were used for tumor response assessment for all tumor types except CNS tumors, for which RANO criteria were used to assess tumor response. Several patients ( $n = 14$ ; indicated with a-f) had more than one type of *FGF/FGFR* aberration. In addition to the *FGF/FGFR* aberration indicated by the color-coded bars, patients had (a) *FGFR2* F/R, (b) *FGF3/4/19* amp, (c) *FGFR3* F/R, (d) *FGFR3* mut, (e) *FGF3/19* amp, or (f) *FGFR2/3* amp. amp, amplification; *FGFRi*, *FGFR* inhibitor; F/R, fusion/rearrangement; mut, point mutation; NE, not evaluable; PD, progressive disease.

In the 16-mg cohort, 8 of 19 patients (42.1%) with intrahepatic CCA experienced PRs, as described above. Patients achieved durable responses, with DORs ranging from 3.5 to 20.4 months (Fig. 4; Supplementary Table S2).

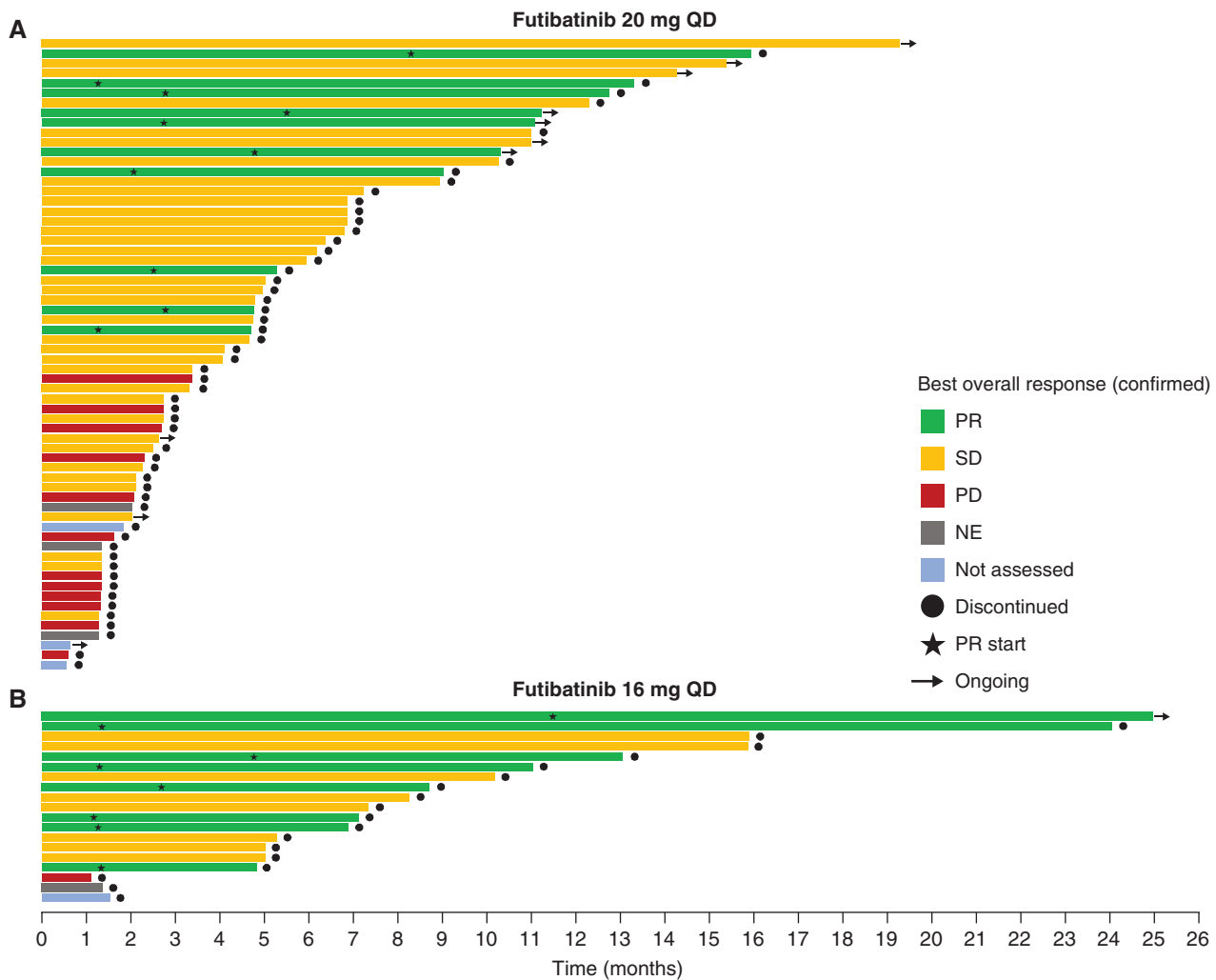
Efficacy among patients with CCA previously treated with an *FGFR* inhibitor was also evaluated. Overall, 22 of 61 (36.0%) patients with intrahepatic CCA in the 20-mg cohort and 6 of

19 (31.6%) patients with intrahepatic CCA in the 16-mg cohort had previously received *FGFR* inhibitors, mostly ATP-competitive inhibitors. Of these 28 patients, 17.9% experienced objective responses with futibatinib: 2 received futibatinib 20 mg once daily and 3 received futibatinib 16 mg once daily (Fig. 2; Supplementary Fig. S1; Supplementary Table S2). Among these 5 responders, 3 had *FGFR2* fusions, 1 had an *FGFR2*



**Figure 3.** Individual response and treatment outcome by *FGFR* aberration in patients who received futibatinib 20 mg once daily. The figure shows individual treatment outcomes organized by *FGFR* aberration type, color coded for tumor type in patients who received futibatinib 20 mg once daily. RECIST v1.1 criteria were used for tumor response assessment for all tumor types except for CNS tumors, for which RANO criteria were used. Several patients ( $n = 14$ ) had more than one type of *FGF/FGFR* aberration and are represented in each relevant *FGFR* aberration category. These patients are indicated with the letters a-n, with each letter representing an individual patient.





**Figure 4.** Time on treatment by best response in patients with CCA who received (A) futibatinib 20 mg once daily or (B) futibatinib 16 mg once daily. Time on treatment (color coded by best overall response) of each patient with CCA who received futibatinib at (A) 20 mg once daily ( $n = 64$ ) or (B) 16 mg once daily ( $n = 19$ ). NE, not evaluable; PD, progressive disease; QD, once daily.

p.W290C mutation, and 1 had an *FGFR2* rearrangement and *FGFR2* amplification. These 5 patients had previously been treated with the ATP-competitive reversible FGFR inhibitor infigratinib ( $n = 3$ ) or pemigatinib followed by infigratinib ( $n = 1$ ) or with the irreversible FGFR inhibitor PRN1371 ( $n = 1$ ). On the prior ATP-competitive inhibitor, 2 patients had a PR and 3 patients had SD, and all patients had discontinued FGFR inhibitor treatment because of disease progression. As an immediate pretreatment tumor or liquid biopsy was not required for study enrollment, mechanisms of acquired resistance to prior FGFR inhibitors were not captured in this study.

### Antitumor Activity in Other Tumor Types

Although responses were noted with futibatinib 20 mg once daily in tumor types other than CCA, ORR was greater than 10% only in the urothelial and gastric cancer cohorts. In the urothelial carcinoma cohort, the ORR was 15.8% (95% CI, 3.4%–39.6%); 3 of 19 patients had confirmed PRs, 2 of whom

had tumors harboring activating *FGFR3* p.S249C mutations (DOR, 1.4 and 3.4 months), and 1 patient had both an *FGFR1* p.M563T mutation and *FGF3/19* amplifications (DOR, 5.6 months). Six patients had SD, leading to a DCR of 47.4% (95% CI, 24.4%–71.1%). Of note, the urothelial cohort was a heavily pretreated population, with 57.9% of patients having received three or more prior regimens; 8 patients (42.1%) previously received FGFR inhibitors, none of whom experienced responses with futibatinib (Fig. 2).

In the gastric cancer cohort, the ORR was 22.2% (95% CI, 2.8%–60.0%): PRs were seen in 2 of 9 patients, 1 with an *FGFR2* amplification (DOR, 3.5 months) and the other with an *FGFR3–TACC3* fusion (DOR, 5.4 months). Three patients experienced SD (including 2 patients with unconfirmed PRs), and the DCR was 55.6% (95% CI, 21.2%–86.3%).

Among patients with primary CNS tumors ( $n = 36$ ), 1 patient with glioblastoma harboring an *FGFR1–TACC1* fusion experienced a PR lasting 5.8 months, and 6 patients experienced SD (DCR, 19.4%). Tumor shrinkage was seen in 13 of

**Table 3. AEs in patients receiving futibatinib 20 mg once daily**

Characteristics	20-mg cohort (N = 170), n (%)					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any TEAE	168 (98.8)	12 (7.1)	34 (20.0)	97 (57.1)	9 (5.3)	16 (9.4) <sup>a</sup>
Any serious TEAE	82 (48.2)	1 (0.6)	10 (5.9)	49 (28.8)	6 (3.5)	16 (9.4)
Any treatment-related AE	162 (95.3)	27 (15.9)	62 (36.5)	72 (42.4)	1 (0.6)	0
Action taken because of TEAE						
Dosing interruption	83 (48.8)	5 (2.9)	17 (10.0)	57 (33.5)	4 (2.4)	0
Dose reduction	44 (25.9)	4 (2.4)	12 (7.1)	28 (16.5)	0	0
Treatment discontinuation	18 (10.6)	0	4 (2.4)	14 (8.2)	0	0
TEAEs <sup>b</sup> in ≥10% of patients						
Hyperphosphatemia	138 (81.2)	26 (15.3)	74 (43.5)	38 (22.4)	0	0
Diarrhea	56 (32.9)	42 (24.7)	13 (7.6)	1 (0.6)	0	0
Constipation	54 (31.8) <sup>b</sup>	39 (22.9)	12 (7.1)	2 (1.2)	0	0
Nausea	48 (28.2)	32 (18.8)	16 (9.4)	0	0	0
Fatigue	43 (25.3)	20 (11.8)	14 (8.2)	9 (5.3)	0	0
Vomiting	43 (25.3)	30 (17.6)	11 (6.5)	2 (1.2)	0	0
AST increased	41 (24.1)	19 (11.2)	13 (7.6)	9 (5.3)	0	0
ALT increased	40 (23.5)	13 (7.6)	10 (5.9)	16 (9.4)	1 (0.6)	0
Abdominal pain	33 (19.4)	16 (9.4)	12 (7.1)	5 (2.9)	0	0
Alopecia	33 (19.4)	27 (15.9)	6 (3.5)	0	0	0
Decreased appetite	32 (18.8)	18 (10.6)	11 (6.5)	3 (1.8)	0	0
Dry mouth	30 (17.6)	26 (15.3)	4 (2.4)	0	0	0
Asthenia	27 (15.9)	12 (7.1)	8 (4.7)	7 (4.1)	0	0
Stomatitis	26 (15.3)	13 (7.6)	8 (4.7)	5 (2.9)	0	0
Anemia	23 (13.5)	7 (4.1)	7 (4.1)	9 (5.3)	0	0
Dry skin	22 (12.9)	21 (12.4)	1 (0.6)	0	0	0
Palmar-plantar erythrodysesthesia	22 (12.9)	11 (6.5)	5 (2.9)	6 (3.5)	0	0
Increased blood creatinine	20 (11.8)	13 (7.6)	7 (4.1)	0	0	0
Arthralgia	19 (11.2)	14 (8.2)	5 (2.9)	0	0	0
Hypercalcemia	19 (11.2)	14 (8.2)	3 (1.8)	2 (1.2)	0	0
Dysgeusia	18 (10.6)	13 (7.6)	5 (2.9)	0	0	0
Decreased weight	17 (10.0)	10 (5.9)	6 (3.5)	1 (0.6)	0	0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.  
<sup>a</sup>None of these TEAEs were considered to be treatment-related.  
<sup>b</sup>Grade was missing for 1 patient.

36 patients (36.1%) in this primary CNS tumor cohort. In addition, PRs were observed in a patient with head and neck cancer harboring an *FGFR1-PLAG1* fusion (DOR, 5.6 months) and another patient with an *FGFR2* p.Y375C mutation (DOR, 10.3 months) whose primary tumor was unknown. Although no responses were reported in patients with breast cancer in the 20-mg cohort, 3 of 11 patients experienced tumor shrinkage (Fig. 2). As previously mentioned, 1 patient with *FGFR2*-amplified triple-negative breast cancer in the 16-mg cohort experienced a PR that lasted 20.8 months (Supplementary Table S2). This patient, who was diagnosed nearly 5 years prior to starting futibatinib treatment, had experienced disease progression on two prior chemotherapy regimens for advanced disease.

## Safety

Among 170 patients who received futibatinib 20 mg once daily, the median duration of treatment was 10.7 weeks

(range, 1–86.9 weeks), with a median of four cycles (range, 1–29 cycles) completed. Overall, 168 patients (98.8%) experienced treatment-emergent adverse events (TEAE) of any cause and grade (Table 3). The most common any-grade TEAEs were hyperphosphatemia (81.2%), diarrhea (32.9%), constipation (31.8%), nausea (28.2%), fatigue (25.3%), and vomiting (25.3%). Grade 3 TEAEs were reported in 97 patients (57.1%) and treatment-related grade 3 AEs in 42.4% of patients (Table 3; Supplementary Table S4). Grade 3 TEAEs occurring in 5% or more of patients were hyperphosphatemia (22.4%, defined as a serum phosphate >7.0 mg/dL and ≤10.0 mg/dL), increased alanine transaminase (9.4%), increased aspartate transaminase (5.3%), anemia (5.3%), and fatigue (5.3%). Grade 4 TEAEs were reported in 9 patients (5.3%), and only one event (increased  $\gamma$ -glutamyltransferase) was considered treatment-related (Supplementary Table S4). No grade 5 treatment-related AEs were reported. Grade 5 events unrelated to study treatment occurred in 16 patients within 30 days



of treatment; those TEAEs reported in more than 1 patient included death due to disease progression or malignant neoplasm progression ( $n = 6$ ), hepatic failure ( $n = 2$ ), and gastrointestinal or small intestinal hemorrhage ( $n = 2$ ).

Hyperphosphatemia, the most common TEAE with futibatinib, was managed using phosphate binders (in 74.7% of patients in the 20-mg cohort), futibatinib dosing interruptions (20.0%), and dose reductions (8.2%). At the time of database lock, grade 3 hyperphosphatemia had resolved in 38 of 40 patients (95%); the remaining 2 patients discontinued the study for other reasons (disease progression and withdrawal of consent), and follow-up could not be obtained. No patients in the study discontinued because of hyperphosphatemia.

In the 20-mg cohort, 82 patients (48.2%) experienced serious AEs, and in 11 patients (6.5%), these serious AEs were considered related to treatment (Table 3; Supplementary Table S4). Treatment-related serious AEs included grade 3 intestinal obstruction ( $n = 2$ ); grade 3 upper abdominal pain, stomatitis, anemia, pharyngitis, myalgia, and increased blood bilirubin ( $n = 1$  each); and grade 2 retinal detachment, transient ischemic attack, and hydronephrosis ( $n = 1$  each).

TEAEs were managed with dosing interruptions and/or dose reductions in 58.2% of patients in the 20-mg cohort. The most common AE leading to dose reduction was hyperphosphatemia (in 8% of patients), followed by increased alanine aminotransferase (6%) and palmar-plantar erythrodysesthesia (5%). Overall, 10.6% of patients discontinued because of TEAEs (Table 3) and 3.5% because of treatment-related AEs (Supplementary Table S4). The latter included 3 patients with gastrointestinal-related events [grade 3 oral mucositis ( $n = 1$ ), grade 3 vomiting and grade 1 diarrhea and nausea ( $n = 1$ ), and grade 2 diarrhea, fatigue, and anorexia, and grade 2 nail detachment ( $n = 1$ )], 2 patients with eye disorders [grade 2 retinal detachment ( $n = 1$ ) and grade 3 cataract ( $n = 1$ )], and 1 patient with skin-related toxicities (grade 2 eczema).

Eye toxicities and nail toxicities, AEs of special interest for FGFR inhibitors, were reported in 44 patients (25.9%) and 34 patients (20%), respectively, in the 20-mg cohort. The most common eye toxicities were dry eye (9.4%) and blurred vision (6.5%; Supplementary Table S5). Central serous retinopathy occurred in 7 patients (4.1%; all grade 1 or 2 in severity). Grade  $\geq 3$  eye-related AEs were reported in 2 patients. One patient had a grade 3 cataract that was considered related to treatment. Another patient had grade 3 macular fibrosis and grade 4 ocular ischemic syndrome; both events were considered unrelated to treatment by the investigator and local ophthalmologist because this patient had underlying eye disorders. The most common nail-related AEs were onycholysis (5.9%) and nail disorders (5.3%), the latter of which included nail changes, nail hardening, nail dryness, onychodysplasia, and onychopathy. All nail toxicities were grade 1 or 2 in severity, except for one case of treatment-related grade 3 onychalgia.

In the 16-mg cohort ( $n = 27$ ), the most common any-grade TEAEs were similar to those seen at the 20-mg dose level: hyperphosphatemia (81.5%), nausea (44.4%), and diarrhea (37.0%; Supplementary Table S6). Overall, 48.1% of patients experienced grade 3 or higher TEAEs, and grade 3 hyperphosphatemia was reported in 14.8% of patients. TEAEs were managed with dosing modifications in 51.9%

of patients receiving futibatinib 16 mg once daily, and 1 patient (3.7%) discontinued because of grade 2 asthenia.

## DISCUSSION

This large phase I expansion study of nearly 200 patients demonstrated that the irreversible FGFR inhibitor futibatinib has antitumor activity in a broad range of cancers and against a broad variety of *FGFR* aberrations. CCA constituted the largest tumor cohort, likely because of early efficacy signals in this disease (20), followed by CNS and urothelial carcinoma. Objective responses were seen in 14% of patients, and tumor shrinkage was observed in more than 50% of all patients across cohorts. Notably, responses were observed in tumors harboring *FGFR* aberrations not previously characterized as being sensitive to FGFR inhibition (5, 21–24). This finding demonstrates the potential of biomarker-driven oncology trials to guide biological discovery in the clinic in a manner previously thought possible only in the laboratory.

As seen in multihistology basket tumor studies with other targeted agents (25–30), tissue context as well as gene aberration type affected drug activity in this study. The greatest degree of activity was observed in patients with advanced intrahepatic CCA, a difficult-to-treat tumor type with a poor prognosis (31). Consistent with prior observations (20), patients with intrahepatic CCA harboring *FGFR2* fusions or rearrangements experienced the most benefit. However, a notable outcome was that objective responses were seen in 2 patients with *FGFR*-mutated CCA; in two other trials of selective FGFR inhibitors, no objective responses were noted in this patient population (4, 7). Of the 2 patients with objective responses, one had an *FGFR2* p.W290C mutation and the other had an *FGFR2* p.C383R mutation (also known as a p.C382R mutation in an alternative transcript; ref. 17). These mutations, in the extracellular domain (p.W290C) and in the transmembrane domain (p.C383R), have been classified as pathogenic or activating in the ClinVar database and have been shown to be sensitive to FGFR inhibitors in preclinical experiments (32–35). Notably, in the phase II trial of pemigatinib, 3 of 4 patients with tumors harboring p.C382R mutations achieved tumor stability with PFS ranging from 4.0 to 9.0 months (17), also suggesting the potential actionability of these alterations.

This study also confirmed the findings of a prior proof-of-concept study (36) in which futibatinib treatment was associated with antitumor activity in patients with intrahepatic CCA who developed resistance to a prior FGFR inhibitor. The development of acquired resistance through secondary mutations in the kinase domain has been reported with reversible ATP-competitive FGFR inhibitors, including infigratinib, pemigatinib, and Debio1347 (14, 15, 17, 36). In preclinical experiments, several of these mutations conferred lower resistance to futibatinib than to reversible ATP-competitive inhibitors, and futibatinib also demonstrated robust activity against most of these mutations (19, 36, 37). Data from the current study showing durable responses in 5 patients with intrahepatic CCA after progression on FGFR inhibitors support these initial findings and demonstrate the unique mechanism of action of futibatinib.

This genotype-driven multihistology study also led to the identification of novel driver mutations that were not

previously reported to be sensitive to *FGFR* inhibition to our knowledge. One patient with treatment-refractory urothelial cancer harboring an *FGFR1* p.M563T mutation concurrently with *FGF3/19* amplifications had 88% tumor shrinkage and a PFS of 6.8 months. The *FGFR1* p.M563T mutation, residing within the kinase domain hinge region (12, 38), has not been previously characterized with respect to either *in vitro* kinase activity or *FGFR* inhibitor sensitivity. Although erdafitinib is currently approved in patients with metastatic urothelial cancer harboring susceptible *FGFR2/3* alterations (39), neither this *FGFR1* mutation nor *FGF* amplifications were included in the eligibility criteria of the trial that led to drug approval (9). In addition, 1 patient with an *FGFR1-PLAG1* fusion-positive treatment-refractory head and neck cancer had 65% tumor shrinkage and a PFS of 6.9 months. Although the *FGFR* gene is frequently altered in head and neck cancers (3%–9% with *FGFR1* amplifications/mutations; 2%, *FGFR2* amplifications/mutations; 3%, *FGFR3* amplifications/mutations/fusions; refs. 40–43), *FGFR1* fusions occur rarely and have not been functionally characterized in this tumor type. Thus, tumor-agnostic biomarker-driven studies may uncover these rare patients who benefit clinically, providing proof of concept for the actionability of targets prior to biological characterization. This type of approach may become increasingly relevant as wide-scale genomic profiling techniques identify additional rare molecular subgroups across tumor types.

This trial was among the first *FGFR* inhibitor trials to enroll patients with primary CNS tumors, a decision that was based on preclinical evidence in glioblastoma mouse models (data on file) and initial activity noted in the phase I dose-escalation portion of this study (20). Success of *FGFR* inhibitors in primary CNS tumors depends on both the ability of a drug to penetrate the blood-brain barrier and the extent of target representation in this molecularly heterogeneous tumor type (44). Among 36 patients with primary CNS tumors in this study, 1 patient with a glioblastoma harboring an *FGFR1-TACCI* fusion had an objective response, 6 patients had SD (DCR, 19%), and 36% of patients had some degree of tumor shrinkage. These data warrant further investigation of futibatinib and other *FGFR* inhibitors in patients with *FGFR*-altered primary CNS tumors, a patient population that lacks alternative therapeutic options.

In addition to benefiting patients with intrahepatic CCA and CNS primary tumors, futibatinib led to an objective response in 1 patient with gastric cancer and 1 patient with breast cancer harboring *FGFR2* amplifications. Both patients, who had advanced disease and had received two or more prior treatments, experienced durable responses with futibatinib. In prior studies with other *FGFR* inhibitors, antitumor activity was rather disappointing among *FGFR*-amplified tumors, highlighting the weakness of copy-number alterations as predictive biomarkers for *FGFR* inhibitors (5, 21, 22). Of note, a phase II proof-of-concept trial of AZD4547 in *FGFR*-amplified breast and gastric cancers demonstrated that efficacy might be limited to patients harboring high clonal amplification (translating to high *FGFR* mRNA levels; ref. 11). Although copy-number alteration or transcriptomic data were not available for the *FGFR*-amplified cancers reported here, the efficacy of futibatinib in *FGFR*-amplified cancers confirms the finding seen in other trials that select patients

with *FGFR*-amplified tumors may benefit from *FGFR* inhibitors (5, 21, 22, 24, 45).

Futibatinib demonstrated activity in urothelial carcinoma (with responses in patients harboring *FGFR3* or *FGFR1* mutations), showing an ORR of 16% and DCR of 47%, but the response rate in this small urothelial carcinoma cohort ( $n = 19$ ) was numerically lower than that reported with other selective *FGFR* inhibitors in this disease type (9, 22). This result may in part be attributed to the fact that in this study, 42% had previously received *FGFR* inhibitors and nearly 60% had received three or more prior regimens, making it a heavily pretreated population. In the phase II pivotal study of erdafitinib in *FGFR2*- and *FGFR3*-altered urothelial cancer, in which the ORR was 40%, no prior treatment with *FGFR* inhibitor was allowed, and fewer than 20% of patients had received three or more prior regimens (9). Of note, unlike in intrahepatic CCA, futibatinib treatment was not associated with responses in the 8 patients with urothelial carcinoma after prior *FGFR* inhibitor treatment. The reasons for the lack of responses with futibatinib remain unclear at present and could be attributed to upregulation in bypass signaling pathways, such as EGFR, PI3K, and ERBB2/3 (46–48). Future studies in larger patient populations will help clarify the activity of futibatinib in urothelial cancer, including in patients previously treated with *FGFR* inhibitors.

The RP2D of futibatinib is 20 mg once daily based on clinical safety and pharmacokinetic data (20). However, anti-tumor activity was also seen in the cohort starting at 16 mg once daily, in which the ORR was 42% among patients with CCA. This clinical activity at 16 mg once daily is reassuring, as this is the first reduced dose level recommended in cases of toxicity at 20 mg once daily. The higher ORR in the 16-mg cohort compared with the 20-mg cohort (where the ORR was 16%), although not completely understood, may partly be explained by unintentional molecular selection: 84% (16/19) of patients with CCA in the 16-mg cohort had intrahepatic CCA harboring *FGFR2* fusions or rearrangements compared with 66% (42/64) of patients with CCA in the 20-mg cohort. No differences in safety, including dosing modification rates, were noted between the two dose cohorts, and the small population size in the 16-mg cohort precluded a comparative analysis of antitumor activity between the cohorts.

Within the subpopulation of patients with *FGFR2* fusion/rearrangement-positive intrahepatic CCA ( $n = 42$ ), the ORR of 17% with futibatinib 20 mg once daily was numerically lower than that reported in the phase II study of futibatinib at the same dose (ORR, 42%; ref. 49) and was also lower than that reported with pemigatinib (36%) or infigratinib (23%) in the respective phase II studies (4, 8). This difference in the ORR may be attributed to the low sample size in the current phase I expansion study compared with the other phase II studies (which each enrolled more than 100 patients) and to the proportion of patients with prior *FGFR* treatment (which was 40% in the current study vs. 0% in all three phase II studies).

The safety profile of futibatinib was consistent with previous observations in the dose-escalation portion of this phase I study (20) and with the safety profile of other *FGFR* inhibitors (4, 5, 7, 10, 21). The incidence of treatment-related serious AEs was low, and no treatment-related deaths occurred.



Hyperphosphatemia, an on-target off-tumor effect due to inhibition of FGFR1 (50), was the most common TEAE, occurring in 81% of patients, with 22% being grade 3 in severity. The somewhat higher incidence of grade 3 hyperphosphatemia compared with other FGFR inhibitors (4, 7, 9) may result from different definitions of grade 3 hyperphosphatemia across studies, given that hyperphosphatemia was not a defined term in the NCI Common Criteria for Adverse Events (NCI-CTCAE) version 4.03. Grade 3 hyperphosphatemia was defined as a laboratory value alone (serum phosphate  $>7.0$ – $\leq 10$  mg/dL) in this study, whereas it was dependent on clinical severity in other FGFR inhibitor studies (4). Differences in dosing schedules between futibatinib and other FGFR inhibitors may have also contributed to the different rates of hyperphosphatemia. Futibatinib is administered on a continuous once-daily dosing schedule with safety assessments conducted while on treatment; in contrast, infigratinib and pemigatinib have a 1-week treatment break prior to hyperphosphatemia assessment on the first day of each cycle. It should be noted, however, that all hyperphosphatemia events in this study were managed using concomitant medications and dosing modifications, and no patients discontinued because of hyperphosphatemia. Nail and eye toxicities, also class effects of FGFR inhibitors, were almost all grade 1 or 2 in severity. Overall, AEs were well managed, and few patients discontinued due to treatment-related AEs.

A limitation of this study was the reliance on local genomic testing for patient enrollment, which allowed for rapid accrual, but posed challenges for thorough molecular characterization of tumors. Some patients identified as harboring *FGFR2* rearrangements likely had fusions with a novel partner gene that was predicted to be out of strand or out of frame with *FGFR2*, making the fusion partner undetectable in certain assays. Computations have been shown to affect FGFR inhibitor sensitivity in certain contexts (17); however, data on co-occurring genetic alterations were not available in this study. These data are expected to be available in later-phase studies requiring central biomarker testing. In addition, detailed genotyping analyses, including copy number of amplified genes, clonality, and transcriptomic data, were not available. Finally, an immediate pretreatment biopsy and postprogression biopsy were not required in this study, so information on acquired resistance mechanisms to prior FGFR inhibitors and futibatinib was not captured. Later-phase futibatinib studies require serial liquid biopsies, and molecular characterization of these serial samples will provide insight into predictors of futibatinib sensitivity and resistance.

In conclusion, futibatinib demonstrated clinical activity and a tolerable safety profile in heavily pretreated patients with advanced tumors in this phase I dose-expansion study. The broad range of antitumor activity across *FGFR* aberrations helped identify novel genomic alterations as potential FGFR inhibitor targets that have not been functionally characterized in the laboratory. This study also succeeded in the mission of preliminary signal finding to identify populations to further evaluate futibatinib in phase II and III trials. The signal was most robust in patients with intrahepatic CCA harboring an *FGFR2* fusion or rearrangement, and this activity was confirmed in the follow-on FOENIX-CCA2 study, a phase II trial in the same population showing an ORR of 42%

(NCT02052778; ref. 49). The activity in CCA in this phase I study also led to the recently initiated phase III trial of first-line futibatinib versus gemcitabine-cisplatin in the same molecular subgroup (FOENIX-CCA3; NCT04093362). On the basis of the data in other tumor types, two phase II trials of futibatinib have been initiated. The first is a three-arm trial enrolling patients with *FGFR1–4* rearrangement-positive advanced solid tumors (arm 1), *FGFR2*-amplified gastroesophageal junction tumors (arm 2), and *FGFR1* rearrangement-positive myeloid and lymphoid malignancies (arm 3; NCT04185445). The second phase II trial is evaluating futibatinib alone or combined with fulvestrant in patients with metastatic breast cancer harboring *FGFR1* or *FGFR2* amplifications (NCT04024436). Futibatinib is also being explored in combination with pembrolizumab in patients with urothelial cancer in another phase II trial (NCT04601857). Results of these studies will build on the hypotheses generated in the current phase I study and help clarify the role of futibatinib both in a variety of tumor types and as a disease-agnostic option for patients with *FGFR* rearrangement-positive advanced solid tumors.

## METHODS

### Study Design and Patients

This first-in-human phase I two-part dose-escalation and dose-expansion study was conducted at 37 sites across eight countries. The study was designed and conducted in compliance with the ethical principles of Good Clinical Practice and in accordance with the Declaration of Helsinki. The study protocol was approved by all the institutional review boards/independent ethics committees at participating centers, and written informed consent was obtained from all patients at enrollment.

The design and results of the dose-escalation portion have been reported separately (20). Briefly, the dose-escalation portion of the study enrolled patients with advanced solid tumors with or without *FGF/FGFR* aberrations and assessed futibatinib dosing on an intermittent schedule (doses ranging from 8 to 200 mg) and on a continuous, once-daily schedule (doses ranging from 4 to 24 mg). The MTD and RP2D were determined to be 20 mg once daily.

On the basis of antitumor activity observed in the dose-escalation portion, the dose-expansion portion of the study was initiated to evaluate futibatinib efficacy and safety at the RP2D (20 mg once daily). Some patients, who were enrolled in the phase I dose expansion prior to the final confirmation of the RP2D, received 16 mg once daily.

Patients enrolled into the phase I dose expansion were 18 years or older, with histologically or cytologically confirmed local, advanced, or metastatic cancer, and an Eastern Cooperative Oncology Group performance status of 0 or 1 with adequate organ function (see Supplementary Methods). Enrollment was based on both tumor type and *FGFR* aberration. *FGF/FGFR* aberrations were assessed by local laboratory testing of archived formalin-fixed, paraffin-embedded tumor tissue samples. A later amendment allowed for inclusion of patients with *FGFR* aberrations based on ctDNA analysis. Per the protocol, patients with any of the following tumors and *FGFR* aberrations were enrolled: (i) intrahepatic or extrahepatic CCA harboring *FGFR2* gene fusions or rearrangements regardless of prior therapy, including those who received prior FGFR inhibitors; (ii) intrahepatic or extrahepatic CCA harboring *FGFR* aberrations other than *FGFR2* fusions or rearrangements; (iii) primary CNS tumors harboring *FGFR* gene fusions or *FGFR1*-activating mutations; (iv) advanced urothelial carcinoma harboring *FGFR3* gene fusions or *FGFR3*-activating

mutations; (v) any other tumor type with *FGFR2* amplifications; or (vi) any other tumor type with *FGFR* gene fusions or activating mutations. Of note, to focus on biological and clinical relevance, efficacy was analyzed by tumor type and *FGFR* aberration instead of the originally proposed patient cohorts.

All patients had disease progression following standard therapies or were intolerant of prior standard therapies (including prior *FGFR* inhibitors). Patients with a history or current evidence of clinically significant calcium-phosphorus alterations or ectopic calcification were excluded. Additional exclusion criteria are detailed in the Supplementary Appendix.

## Procedures

Futibatinib was administered at 20 mg or 16 mg once daily with a glass of water on an empty stomach (fasting  $\geq 2$  hours before and 1 hour after administration) on a continuous 21-day cycle. In cases of toxicity, a maximum of two dose reductions (to 16 mg and 12 mg) was permitted for patients who received futibatinib 20 mg once daily, and one reduction (to 12 mg) was allowed for patients who received futibatinib 16 mg once daily. Treatment continued until RECIST v1.1–defined disease progression, clinical progression, unacceptable toxicity, patient request, physician decision, and/or pregnancy.

Tumor assessments were performed up to 28 days prior to cycle 1 initiation, at the end of cycles 2 and 4, and every three cycles thereafter. If a patient had a response, response confirmation was obtained through tumor assessments or scans 4 to 6 weeks after the first documentation of response. Tumor response was assessed per RECIST v1.1 for all tumor types except primary brain tumors, which were assessed per RANO criteria. Tumor response was assessed by ICR for intrahepatic CCA but not other tumor types; investigator-assessed efficacy data are presented here for all tumor types except intrahepatic CCA, for which both investigator-assessed and ICR efficacy data are included.

Safety was monitored from the first dose of futibatinib until 30 days after the last dose or initiation of another anticancer therapy, whichever occurred first. AEs were graded using NCI-CTCAE v4.03, and hyperphosphatemia was graded on the basis of serum phosphorus levels (grade 1,  $>$ upper limit of normal but  $< 5.5$  mg/dL; grade 2,  $\geq 5.5$ – $\leq 7.0$  mg/dL; grade 3,  $> 7.0$ – $\leq 10.0$  mg/dL; grade 4,  $> 10.0$  mg/dL). At the start of the trial, serum phosphate levels were monitored 7 and 14 days after the first dose; however, following an amendment to the protocol on August 29, 2017, serum phosphate levels were monitored 4 days after the first dose to initiate early intervention for hyperphosphatemia. Phosphate-lowering therapy was mandated within 24 hours of observing phosphorus elevation ( $\geq 5.5$  mg/dL). Management of hyperphosphatemia included phosphate-binding agents (sevelamer, acetazolamide, lanthanum, or a combination) and a low-phosphate diet.

## Endpoints

The primary endpoint of the dose expansion was to evaluate the ORR in each treatment group. Secondary endpoints included safety, DCR, DOR, and PFS.

## Statistical Analysis

Approximately 185 patients were planned to be enrolled among the different tumor types, based on ORR considerations. Sample size considerations were exploratory and based on a common assumption of a target ORR of 30% versus a null hypothesis ORR of 10% or less, although the exact method and assumptions for sample size differed by group based on historical control data for each patient population. For CCA, the sample size was determined on the basis of the 95% CI of the ORR necessary to exclude an ORR of 10% or less if the overall ORR was 30% or higher. Detailed sample size considerations for the remaining groups are specified in the Supplementary Appendix.

All patients who received one or more doses of study drug were included in the safety and efficacy analysis. Efficacy was analyzed by tumor type and by *FGFR* aberration type, whereas safety was analyzed by dose cohort (i.e., 16 mg and 20 mg once-daily cohorts). Time-to-event distributions (e.g., PFS and DOR) were estimated using the Kaplan–Meier method. CIs for binomial proportions, ORR, and DCR were derived using the Clopper–Pearson method.

## Data Sharing

Data generated or analyzed during this study are on file with Taiho Oncology, Inc. and Taiho Pharmaceuticals Co., Ltd. and are not publicly available. Inquiries about data access should be sent to th-datasharing@taiho.co.jp.

## Authors' Disclosures

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### Authors' Contributions

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