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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Supplementary Methods

Additional eligibility criteria

Patients aged 18 years or older with histologically or cytologically confirmed locally advanced or metastatic cancer and measurable disease per RECIST v1.1 or RANO criteria (for CNS tumors) were enrolled. Patients had to have adequate organ function, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN) or ALT and AST ≤ 5 × ULN if there is underlying liver metastases, total bilirubin ≤1.5 × ULN, international normalized ratio <1.3, absolute neutrophil count ≥1000/mm^3, platelet count ≥75,000/mm^3, hemoglobin ≥9.0 g/dL, phosphorus ≤ ULN. In addition, patients had to have a creatinine clearance of ≥40 mL/min. Additional exclusion criteria were history or current evidence of clinically significant ectopic mineralization or calcification, clinically significant retinal disorder, evidence of serious uncontrolled ventricular arrhythmias, any major surgery, extended field radiotherapy locoregional therapy within 2–4 weeks of starting futibatinib, serious illness of medical conditions, or history of another primary malignancy.

Additional statistical considerations

For primary CNS tumors with *FGFR* fusions or *FGFR1* activating mutations, sample size considerations were based on a multinomial 2-stage design, which would differentiate between poor activity (ORR ≤10% and early progression <50%) and promising activity (ORR ≥10% and early progression ≤30%) at an approximate 5% 1-sided significance level and 80% power. Fifteen tumor response-evaluable patients were planned to be enrolled at each of the 2 stages. For urothelial carcinoma with *FGFR3* gene fusions or FGFR3-activating mutations, approximately 28 patients were planned to be enrolled to reach a target of 25 tumor response-evaluable patients and sample size considerations were based on a minimax 2-stage design differentiating between a poor ORR of 10% vs a promising ORR of 30% at an approximate 5% 1-sided significance level and 80% power. Patients with *FGFR2*-amplified tumors were subdivided into subgroups of ovarian cancer, gastric/esophageal/gastroesophageal junction cancer, or other tumor types. The first 2 subgroups were enrolled based on a Simon's 2-stage design (differentiating between an ORR of 10% vs ORR of 30% at an approximate 10% 1-sided significance level and 80% power), and up to 20 patients were planned for enrollment into the 3rd subgroup. For tumor types with *FGFR* gene fusions or activating mutations, 15 patients were planned to be enrolled across the different tumor types with no single tumor type exceeding 10 patients.

Supplementary Table S1. Baseline characteristics and prior therapy in patients receiving futibatinib 16 mg QD

	16-mg cohort (*n* = 27)
Age, years	
Median (range)	56.0 (34–74)
Sex, *n* (%)	
Female	21 (77.8)
Male	6 (22.2)
Race, *n* (%)	
White	23 (85.2)
Black or African American	1 (3.7)
Asian	1 (3.7)
Unknown	2 (7.4)
ECOG PS, *n* (%)	
0	13 (48.1)
1	14 (51.9)
***FGF/FGFR* alteration,** *n* (%)	
FGFR1 amplification	1 (3.7)
FGFR2 fusions/rearrangement	17 (63.0)
FGFR2 mutation	3 (11.1)
FGFR2 amplification	4 (14.8)
FGFR3 fusions/rearrangement	3 (11.1)
FGFR3 mutation	2 (7.4)
FGFR3 amplification	1 (3.7)
Cancer type, *n* (%)	
Cholangiocarcinoma	19 (70.4)
Intrahepatic	19 (70.4)
Extrahepatic	0
Breast	1 (3.7)
Primary CNS	1 (3.7)
Urothelial carcinoma	1 (3.7)
Sarcoma	1 (3.7)
Gall bladder	1 (3.7)
Thyroid	1 (3.7)
Primary unknown	2 (7.4)
Number of prior regimens, *n* (%)	
1	11 (40.7)
2	3 (11.1)
3	4 (14.8)
4	5 (18.5)
≥5	3 (11.1)
Type of prior therapy, *n* (%)	
Chemotherapy	9 (33.3)
FGFR inhibitor	7 (25.9)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; QD, once daily; SD, standard deviation.

Supplementary Table S2. Characteristics of patients with confirmed partial responses per investigator review

Patient	Dose received	Cancer type	Prior FGFRi	*FGFR* alteration	PFS, months	Duration of response, months
1	20 mg	Extrahepatic CCA	No	*FGFR2-POC1B* fusion	4.8	3.5
2	20 mg	Intrahepatic CCA	No	*FGFR2-DBP* fusion	10.9	9.6
3	20 mg	Intrahepatic CCA	Yes	*FGFR2-BICC1* fusion	15.9	7.6
4	20 mg	Intrahepatic CCA	No	*FGFR2-BICC1* fusion	4.4	1.9[a]
5	20 mg	Intrahepatic CCA	No	*FGFR2-FILIP1* fusion	4.8	2.0[a]
6	20 mg	Intrahepatic CCA	No	*FGFR2* p.C383R mutation	9.2	6.5[a]
7	20 mg	Intrahepatic CCA	No	*FGFR2* rearrangement	9.5	4.0[a]
8	20 mg	Intrahepatic CCA	Yes	*FGFR2 p.*W290C mutation	8.9	4.1[a]
9	20 mg	Intrahepatic CCA	No	*FGFR2-BICC1* fusion	12.7	9.9
10	20 mg	Intrahepatic CCA	No	*FGFR2* rearrangement	9.0	6.9
11	20 mg	Primary CNS tumor/glioblastoma	No	*FGFR1-TACC1* fusion	7.0	5.8
12	20 mg	Urothelial carcinoma	No	*FGFR3* p.S249C mutation	2.7	1.4[a]
13	20 mg	Urothelial carcinoma	No	*FGFR3* p.S249C mutation	4.7	3.4
14	20 mg	Urothelial carcinoma	No	*FGFR1* p.M563T mutation, *FGF3/FGF19* amplification	6.8	5.6
15	20 mg	Gastric cancer/adenocarcinoma	No	*FGFR2* amplification	4.8	3.5
16	20 mg	Gastric cancer/adenocarcinoma	No	*FGFR3-TACC3* fusion	6.7	5.4[a]
17	20 mg	Head and neck cancer	No	*FGFR1-PLAG1* fusion	6.9	5.6[a]
18	20 mg	Primary unknown	No	*FGFR2* p.Y375C mutation	19.2	10.3[a]
19	16 mg	Intrahepatic CCA	Yes	*FGFR2-NRAP* fusion	21.7	20.4

Patient	Dose received	Cancer type	Prior FGFRi	*FGFR* alteration	PFS, months	Duration of response, months
20	16 mg	Intrahepatic CCA	No	*FGFR2* rearrangement	7.1	6.0
21	16 mg	Intrahepatic CCA	Yes	*FGFR2* amplification/*FGFR2* rearrangement	4.8	3.5[a]
22	16 mg	Intrahepatic CCA	No	*FGFR2-WAC* rearrangement	6.9	4.2
23	16 mg	Intrahepatic CCA	No	*FGFR2-TNS1* fusion	11.0	9.7
24	16 mg	Intrahepatic CCA	No	*FGFR2-TTC28* fusion	24.1	12.7[a]
25	16 mg	Intrahepatic CCA	Yes	*FGFR2-CCDC6* fusion	6.8	8.8[a]
26	16 mg	Intrahepatic CCA	No	*FGFR2-KIAA1217* fusion	6.8	5.6
27	16 mg	Breast cancer/TNBC	No	*FGFR2* amplification	22.1	20.8[a]

Abbreviations: CCA, cholangiocarcinoma; CNS, central nervous system; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor; PFS, progression-free survival; TNBC, triple-negative breast cancer.
[a]Response was ongoing at the time of data cutoff.

Supplementary Table S3. Treatment response by tumor type and *FGFR* aberration among patients who received futibatinib 20 mg QD[a]

Category	Objective response *n*/*N* (%)	Stable disease *n*/*N* (%)	Disease control *n*/*N* (%)
By tumor type			
Cholangiocarcinoma	10/64 (15.6)	36/64 (56.3)	46/64 (71.9)
Primary CNS tumor	1/36 (2.8)	6/36 (16.7)	7/36 (19.4)
Urothelial cancer	3/19 (15.8)	6/19 (31.6)	9/19 (47.4)
Breast cancer	0/11 (0)	3/11 (27.3)	3/11 (27.3)
Gastric cancer	2/9 (22.2)	3/9 (33.3)	5/9 (55.6)
Other tumor types	2/31 (6.5)	11/31 (35.5)	13/31 (41.9)
By specific *FGF*/*FGFR* aberration[b]			
FGFR1 mutation	1/10 (10.0)	3/10 (30.0)	4/10 (40.0)
FGFR2 fusion/rearrangement	8/48 (16.7)	29/48 (60.4)	37/48 (77.1)
FGFR2 mutation	3/23 (13.0)	12/23 (52.2)	15/23 (65.2)
FGFR2 amplification	1/21 (4.8)	6/21 (28.6)	7/21(33.3)
FGFR3 fusion/rearrangement	1/32 (3.1)	6/32 (18.8)	7/32 (21.9)
FGFR3 mutation	2/15 (13.3)	3/15 (20.0)	5/15 (33.3)
FGF amplification	1/23 (4.3)	8/23 (34.8)	9/23 (39.1)
By *FGFR* isoform[c]			
FGFR1	3/17 (17.6)	3/17 (17.6)	6/17 (35.3)
FGFR2	12/88 (13.6)	45/88 (51.1)	57/88 (64.8)
FGFR3	3/47 (6.4)	9/47 (19.1)	12/47 (25.5)
By type of *FGFR* aberration			
Fusion/rearrangement	11/85 (12.9)	35/85 (41.2)	46/85 (54.1)
Mutation	6/51 (11.8)	19/51 (37.3)	25/51 (49.0)
Amplification	1/24 (4.2)	6/24 (25.0)	7/24 (29.2)

Abbreviations: CNS, central nervous system; FGF, fibroblast growth factor; FGFR, FGF receptor; RANO, Response Assessment in Neuro-oncology; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; QD, once daily.

[a]Table shows investigator-assessed response per RANO (for CNS tumors) or RECIST v1.1 (all other tumor types); only categories with ≥9 patients are included.

[b]Patients who had >1 type of *FGFR* aberration are represented in each relevant category.

[c]Three patients had *FGFR4* mutations, of whom 1 patient had stable disease and 2 patients had disease progression.

Supplementary Table S4. TRAEs in patients receiving futibatinib 20 mg QD

	20-mg cohort (*N* = 170) *n* (%)					
	Any grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Any TRAE	162 (95.3)	27 (15.9)	62 (36.5)	72 (42.4)	1 (0.6)	0
Any serious TRAE	11 (6.5)	0	3 (1.8)	8 (4.7)	0	0
Action taken because of TRAE						
Dosing modification	75 (44.1)	2 (1.2)	13 (7.6)	60 (35.3)	0	0
Treatment discontinuation	6 (3.5)	0	3 (1.8)	3 (1.8)	0	0
TRAEs in ≥10% of patients						
Hyperphosphatemia	137 (80.6)	26 (15.3)	73 (42.9)	38 (22.4)	0	0
Diarrhea	41 (24.1)	29 (17.1)	11 (6.5)	1 (0.6)	0	0
ALT increased	35 (20.6)	13 (7.6)	8 (4.7)	14 (8.2)	0	0
Alopecia	32 (18.8)	26 (15.3)	6 (3.5)	0	0	0
AST increased	32 (18.8)	14 (8.2)	11 (6.5)	7 (4.1)	0	0
Fatigue	26 (15.3)	12 (7.1)	11 (6.5)	3 (1.8)	0	0
Nausea	25 (14.7)	20 (11.8)	5 (2.9)	0	0	0
Dry mouth	22 (12.9)	18 (10.6)	4 (2.4)	0	0	0
Dry skin	22 (12.9)	21 (12.4)	1 (0.6)	0	0	0
Stomatitis	22 (12.9)	9 (5.3)	8 (4.7)	5 (2.9)	0	0
Palmar–plantar erythrodysesthesia	21 (12.4)	10 (5.9)	5 (2.9)	6 (3.5)	0	0
Decreased appetite	18 (10.6)	11 (6.5)	7 (4.1)	0	0	0
Asthenia	17 (10.0)	8 (4.7)	6 (3.5)	3 (1.8)	0	0
Constipation	17 (10.0)	14 (8.2)	3 (1.8)	0	0	0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; QD, once daily; TRAE, treatment-related adverse event.

Supplementary Table S5. TEAEs of special interest in ≥5% of patients receiving futibatinib 20 mg QD

	20-mg cohort (*N* = 170) *n* (%)				
	Any grade[a]	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any TEAE of special interest	145 (85.3)	27 (15.9)	77 (45.3)	40 (23.5)	1 (0.6)
Hyperphosphatemia (including increased blood phosphorus)[b]	141 (82.9)	24 (14.1)	77 (45.3)	40 (23.5)	0
Hyperphosphatemia	138 (81.2)	26 (15.3)	74 (43.5)	38 (22.4)	0
Eye disorders[b,c]	44 (25.9)	35 (20.6)	7 (4.1)	1 (0.6)	1 (0.6)
Dry eye	16 (9.4)	16 (9.4)	0 (0)	0	0
Vision blurred	11 (6.5)	11 (6.5)	0 (0)	0	0
Nail toxicities[b]	34 (20.0)	23 (13.5)	10 (5.9)	1 (0.6)	0
Onycholysis	10 (5.9)	8 (4.7)	2 (1.2)	0	0
Nail disorder	9 (5.3)	6 (3.5)	3 (1.8)	0	0
Paronychia	6 (3.5)	3 (1.8)	3 (1.8)	0	0
Central serous retinopathy[b]	7 (4.1)	4 (2.4)	3 (1.8)	0	0

Abbreviations: QD, once daily; TEAE, treatment-emergent adverse event.
[a]No grade 5 toxicities were reported. [b]Group terms. [c]Other than central serous retinopathy.

Supplementary Table S6. AEs in patients receiving futibatinib 16 mg QD

	16-mg cohort (*n* = 27) *n* (%)	
	Any grade	**Grade ≥3**
Any TEAE	27 (100.0)	13 (48.1)
Any treatment-related AE	27 (100.0)	8 (29.6)
Any serious TEAE	4 (14.8)	1 (3.7)
Action taken because of TEAE		
Dosing modification	14 (51.9)	7 (25.9)
Treatment discontinuation	1 (3.7)	0
TEAEs in ≥20% of patients		
Hyperphosphatemia	22 (81.5)	4 (14.8)
Nausea	12 (44.4)	0
Diarrhea	10 (37.0)	0
Constipation	9 (33.3)	0
ALT increased	8 (29.6)	1 (3.7)
Stomatitis	8 (29.6)	0
Dry mouth	7 (25.9)	0
Dry skin	7 (25.9)	0
Palmar–plantar erythrodysesthesia	7 (25.9)	1 (3.7)
AST increased	7 (25.9)	1 (3.7)
Fatigue	6 (22.2)	0

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; QD, once daily; TEAE, treatment-emergent AE.

Supplementary Figure S1. Individual response and treatment outcome by tumor type in patients who received futibatinib 16 mg QD

The figure shows individual treatment outcomes organized by color coded tumor type in 27 patients who received futibatinib 16 mg QD. *FGFR* aberrations are indicated in the grid below the waterfall plot; in some cases, patients had >1 type of *FGFR* aberration, as indicated. CCA, cholangiocarcinoma; CNS, central nervous system; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease.

Supplementary Figure S1