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ORIGINAL ARTICLE

Phase I study of the irreversible fibroblast growth factor receptor 1–4 inhibitor futibatinib in Japanese patients with advanced solid tumors

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Abstract

This phase I study was designed to: (1) determine the maximum tolerated dose (MTD) and recommended dose (RD) of the fibroblast growth factor receptor (FGFR) inhibitor futibatinib in Japanese patients with advanced solid tumors, and (2) examine the antitumor activity of the RD in patients with gastric cancer (GC) or other advanced solid tumors who have *FGFR* or *FGF/FGFR* abnormalities, respectively. In the dose-escalation phase, patients were assigned to 21-day cycles of oral futibatinib 8–160 mg three times a week (TIW) or 16 or 20 mg once daily (QD). In the expansion phase, patients received oral futibatinib 56, 80, or 120 mg TIW, or 16 or 20 mg QD. Eighty-three patients received futibatinib TIW (n = 40) or QD (n = 43). No dose-limiting toxicities were observed according to the final study protocol definition, and the MTD was not reached. The most common adverse events with both regimens were hyperphosphatemia (TIW, 82.5%; QD, 100.0%) and decreased appetite (TIW, 40.0%; QD,

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AUC, area under the concentration–time curve; CI, confidence interval; C_{max}, maximal plasma concentration; CN, copy number; DCR, disease control rate; DEP, dose escalation phase; DLT, dose-limiting toxicity; EP, expansion phase; FAS, full analysis set; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GC, gastric cancer; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; MTD, maximum tolerated dose; ORR, overall response rate; Pi, phosphorus; PR, partial response; QD, once daily; RD, recommended dose; SD, stable disease; Std Dev, standard deviation; TIW, three times a week.

Clinical trial registry number: Japan Pharmaceutical Information Center, JapicCTI-142552

58.1%). Hyperphosphatemia was asymptomatic, not leading to futibatinib discontinuation. The overall response rate (ORR) was 11.5% in patients with *FGF/FGFR* abnormalities. Notably, in GC patients harboring *FGFR2* copy number (CN) ≥10, the ORR was 36.4% versus 0 in patients with CN <10. Therefore, futibatinib had a generally predictable and manageable safety profile in patients with advanced solid tumors. Antitumor activity was seen in patients with *FGF/FGFR* abnormalities, particularly those with GC and high *FGFR2* CNs. Thus, futibatinib 20 mg QD was chosen as the RD for phase II studies.

KEYWORDS
FGFR, futibatinib, gastric cancer, phase 1, TAS-120

1 | INTRODUCTION

The FGF signaling axis plays an essential role in organ development, metabolism, and homeostasis.[1] Activating *FGFR* gene abnormalities are reported in various tumor types, and genetic modifications or overexpression of FGFRs are associated with tumorigenesis and progression in breast, lung, gastric, bladder, hematologic, and other malignancies.[2–9] The most common type of abnormalities are gene amplifications, primarily affecting *FGFR1* and *FGFR4*, but gene fusions are also common, particularly a fusion with the *TACC3* gene, and mainly affect *FGFR2* and *FGFR3*.[10–12]

The involvement of these abnormalities in cancer pathogenesis has led to growing interest in the FGF/FGFR axis as a therapeutic target, particularly in GC, for which few targeted therapies exist. A relatively high proportion of GC patients express *FGFR* abnormalities, which are predictive of a poor outcome.[13–16] In the last several years, reversible FGFR inhibitors have been approved for the treatment of FGFR-driven cholangiocarcinoma (infigratinib and pemigatinib) or bladder cancer (erdafitinib).

Futibatinib (TAS-120) is a novel, highly selective, covalent inhibitor of all four subtypes of FGFR, and differs from the currently available FGFR inhibitors by irreversibly binding to the FGFR. Futibatinib showed potent in vitro activity against a range of cancer cell lines harboring various *FGFR* gene abnormalities, including cells with mutations that were resistant to other ATP-competitive FGFR inhibitors, and showed a low susceptibility to resistance development.[17] In vivo studies showed that futibatinib had strong antitumor activity in animal models of tumors with various *FGFR* gene abnormalities (*FGFR1* or *FGFR2* amplification and *FGFR3* translocation).[17]

The global phase I study in patients with advanced solid tumors in the United States, Europe, and Australia showed that futibatinib had anticancer activity and a manageable safety profile.[18,19] As expected for this class of drugs, serum Pi levels and FGF23 increased during treatment.[18]

The aim of the current phase I study was to determine the MTD and RD of futibatinib in Japanese patients with advanced solid tumors, and to examine the antitumor activity of the RD in patients with GC and other advanced solid tumors harboring *FGFR* or *FGF/FGFR* abnormalities.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an open-label, nonrandomized, phase I study (JapicCTI-142552), undertaken at four sites in Japan. The study had two parts: a dose escalation phase (DEP) and an expansion phase (EP). This study was designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki, and was conducted only after institutional review board approval at all participating study sites. Written informed consent was obtained from all patients prior to any study procedures being undertaken.

2.2 | Study objectives

The primary objective of the DEP was to investigate the safety profile of futibatinib, and identify the MTD and the RD of futibatinib in patients with advanced solid tumors, for whom there are no remaining standard treatments available. The secondary objectives of the DEP were to investigate the pharmacokinetics, pharmacodynamics, and antitumor activity of futibatinib in patients with advanced solid tumors.

The primary objective of the EP was to investigate the antitumor activity of the RD(s) and regimen(s) of futibatinib in patients with GC who were positive for any *FGFR* abnormality and in patients with other advanced solid tumor(s) who were positive for any *FGF/FGFR* abnormalities. The secondary objectives of this phase were to investigate the safety profile of the RD(s) and regimen(s) of futibatinib in patients with advanced solid tumors who were positive for any *FGF/FGFR* abnormalities and to categorize the population of GC patients with any *FGFR* abnormality who

responded to futibatinib by assessing their *FGFR* abnormalities using IHC score or CN.

A post hoc analysis evaluated whether phosphate-binding therapy for the treatment of hyperphosphatemia affected the efficacy and safety of futibatinib QD in the 43 patients receiving 16 or 20 mg/day in the DEP or EP.

2.3 | Study patient cohort

Patients were eligible for either phase of the study if they were aged 20 years or older, had a histologically or cytologically confirmed advanced or metastatic solid tumor for which no standard treatments remained available, and had an ECOG performance status of 0 or 1 at study entry with adequate organ function (see Table S1 for complete inclusion/exclusion criteria). In addition to these criteria, patients in the EP were required to have tumors harboring *FGF/FGFR* abnormalities, based on positive assessments carried out by the central or other laboratories. Patients who had previously received treatment with other FGFR inhibitors were eligible. Key exclusion criteria were a history and/or current evidence of ectopic mineralization/calcification, excluding calcified lymph nodes or asymptomatic coronary calcification, evidence of corneal disorder/keratopathy confirmed by ophthalmologic examination, and hypercalcemia of grade 2 or higher or hyperphosphatemia of 5 mg/dl or more.

2.4 | Study treatment

The DEP followed an accelerated titration and 3+3 design in which three to six patients were sequentially enrolled into one of 10 dose-level cohorts to determine the MTD (Figure S1). Eight cohorts received oral futibatinib 8, 16, 24, 36, 56, 80, 120, or 160 mg TIW on Monday, Wednesday, and Friday. Two cohorts received futibatinib 16 or 20 mg QD. Enrollment of patients into the next dose-level cohort only commenced if none or one of three patients developed a DLT during cycle 1.

During the EP, patients were assigned to one of five regimens of oral futibatinib: 56, 80, or 120 mg TIW, or 16 or 20 mg QD. Futibatinib had to be taken on an empty stomach and was taken in 21-day treatment cycles until disease progression, unacceptable toxicity, or patient/physician decision.

2.5 | Safety and tolerability

Adverse events (AEs) were investigated by predefined laboratory tests during the study visits (Appendix S1).

Ocular AEs, including any diagnosed ocular diseases, such as cataracts or corneal or retinal disorders, were defined as AEs of special interest. The MTD was defined as the highest dose level at which less than 33% of patients experienced a DLT during cycle 1. For QD treatment, two dose levels were used: 16 mg and 20 mg. These were determined on the basis of tolerability outcomes from the study with futibatinib undertaken in Europe and the United States.[18] A complete list of DLT definitions is included in Table S2. Key nonhematologic DLTs were: (1) hyperphosphatemia (serum Pi ≥9 mg/dl or ≥7 mg/dl lasting for ≥7 days despite phosphate-binding therapy for 7 days); (2) a corneal disorder worsening by ≥1 grade (initially), which was changed to grade ≥1 corneal disorder due to calcification after a protocol amendment; (3) creatinine increase to >1.5× upper limit of normal lasting for ≥7 days associated with serum Pi >5.5 mg/dl despite phosphate-binding therapy for 7 days and/or corrected calcium × Pi >55 mg/dl despite phosphate-binding therapy for 7 days; (4) hypercalcemia of grade ≥3 or grade 2 for >7 days; and (5) ectopic de novo calcification in soft tissues, as determined by the investigator.

2.6 | Pharmacokinetics and pharmacodynamics

Urine and blood samples were collected for pharmacokinetic and pharmacodynamic analyses in both TIW and QD dose groups according to a predefined schedule (Appendix S1).

2.7 | Genomic analysis

The analysis of protein expression level, gene CN, mutation, and translocation of *FGF/FGFR* was undertaken only in consenting patients in both study phases (Appendix S1).

2.8 | Tumor response

Objective tumor response was defined according to the revised RECIST guideline (version 1.1) based on investigator assessment (Appendix S1).

2.9 | Post hoc hyperphosphatemia assessment

Hyperphosphatemia is a known on-target class effect of FGFR inhibitors and a frequently reported treatment-related AE.[20–24] Therefore, we also conducted a post hoc analysis to evaluate the efficacy and safety of phosphate-binding therapy for futibatinib-induced hyperphosphatemia in patients receiving a QD regimen (Appendix S1).

2.10 | Statistical analysis

A formal statistical sample size calculation was not carried out, but the aim was to enroll a maximum of 72 patients in the DEP, and 70 patients for the FAS in the EP, in accordance with Japanese guidelines.[25] The FAS is defined in Table S3. Most data were analyzed with descriptive statistics, including the number of patients and frequency for categorical variables, and mean ± Std Dev or median for continuous variables. Best overall response was calculated with 95% CI.

3 | RESULTS

3.1 | Patients

Between July 1, 2014, and April 6, 2020, 83 patients were enrolled into eight TIW groups ($n = 40$) and two QD dosing groups ($n = 43$). Baseline characteristics are summarized in Table 1. Overall, 39 patients entered the DEP; 29 received futibatinib 8–160 mg TIW and 10 received futibatinib 16 or 20 mg QD. Of these, 35 were evaluable for DLTs, including 26/29 (89.7%) of those receiving a TIW regimen and 9/10 (90.0%) of those receiving a QD regimen.

Forty-four patients received treatment in the EP; 11 received futibatinib 56–120 mg TIW and 33 received 16 or 20 mg QD. Forty-three of these patients (TIW, $n = 10$; QD, $n = 33$) were evaluable for tumor response.

The most common cancer types were gastric ($n = 22$; 26.5%), colorectal ($n = 11$; 13.3%), esophageal ($n = 10$; 12.0%), biliary tract or intrahepatic bile duct ($n = 7$; 8.4%), and bladder cancer ($n = 6$; 7.2%).

TABLE 1 Demographics and other baseline characteristics of patients with advanced solid tumors treated with futibatinib ($n = 83$)

	TIW dosing ($n = 40$)	QD dosing ($n = 43$)	Total ($n = 83$)
Sex, *n* (%)			
Male	29 (72.5)	32 (74.4)	61 (73.5)
Female	11 (27.5)	11 (25.6)	22 (26.5)
Age (years)			
Mean (Std Dev)	61.5 (12.3)	62.4 (11.6)	62.0 (11.9)
Median (range)	64.5 (27–79)	64.0 (32–77)	64.0 (27–79)
ECOG performance status, *n* (%)			
0	26 (65.0)	33 (76.7)	59 (71.1)
1	14 (35.0)	10 (23.3)	24 (28.9)
Cancer type, *n* (%)			
Gastric	3 (7.5)	19 (44.2)	22 (26.5)
Biliary tract + IHBD	4 (10.0)	3 (7.0)	7 (8.4)
Bladder	6 (15.0)	0 (0.0)	6 (7.2)
Breast	0 (0.0)	1 (2.3)	1 (1.2)
Colorectum	8 (20.0)	3 (7.0)	11 (13.3)
GIST	2 (5.0)	1 (2.3)	3 (3.6)
Lung	2 (5.0)	2 (4.7)	4 (4.8)
Pancreas	3 (7.5)	0 (0.0)	3 (3.6)
Esophagus	3 (7.5)	7 (16.3)	10 (12.0)
Other	9 (22.5)	7 (16.3)	16 (19.3)
All *FGF/FGFR* abnormal, *n* (%)			
No/not tested	25 (62.5)	5 (11.6)	30 (36.1)
Yes	15 (37.5)	38 (88.4)	53 (63.9)

Abbreviations: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; IHBD, intrahepatic bile duct; QD, once daily; Std Dev, standard deviation; TIW, three times a week.

FGF/FGFR abnormalities were present in 9/35 patients in the DEP and in all patients in the EP, for a total of 53/83 patients (63.9%). Of the 22 patients with GC (Table S4), two patients in the DEP and one in the EP received a TIW regimen, while the other 19 patients in the EP received futibatinib QD. Nineteen patients with GC had FGFR2 overexpression, and 14 patients had *FGFR2* amplification.

The most common reason for treatment discontinuation was disease progression in 63/83 patients (75.9%).

3.2 | Tolerability and MTD in the dose-escalation phase

No DLTs were observed with either TIW or QD dosing regimens according to the final study protocol definition, and therefore a MTD was not reached for either regimen. Two out of six patients receiving futibatinib 80 mg TIW experienced grade 1 corneal opacity, which constituted a DLT according to the original protocol definition (a corneal disorder worsening by ≥1 grade). Following a safety review, this DLT criterion was amended to "grade ≥1 corneal disorder due to calcification," and dose escalation continued without any further DLTs up to 160 mg TIW.

3.3 | Safety

Adverse events reported with an incidence of at least 10% are shown in Table 2. The most common AEs were hyperphosphatemia, decreased appetite, nausea, constipation, pyrexia, and diarrhea in the TIW regimen, and hyperphosphatemia, decreased appetite, constipation, diarrhea, nausea, and vomiting in the QD regimen. While the incidence of alanine aminotransferase increase was 20.9% in the QD regimen, it was 7.5% in the TIW regimen. Adverse events of grade 3 or higher that developed in at least 10% of patients were grade 3 anemia and hypophosphatemia and grade 5 disease progression in those receiving futibatinib TIW, and grade 3 anemia in those receiving futibatinib QD.

Serious AEs developed in 18/40 patients in the combined TIW groups and in 13/43 in the combined QD groups. However, only three of these events were considered to be futibatinib-related: stomatitis in one patient receiving futibatinib 160 mg TIW, and decreased appetite and hyponatremia in one patient receiving 20 mg QD.

No futibatinib-related deaths were reported. All AEs leading to death were related to the underlying tumor and included disease progression ($n = 4$), tumor hemorrhage ($n = 1$), bronchostenosis ($n = 1$), pulmonary tumor thrombotic microangiopathy ($n = 1$), malignant neoplasm progression ($n = 1$), and intestinal obstruction/cerebral infarction ($n = 1$).

The ADRs related to futibatinib are summarized in Table S5.

Six of the 40 patients receiving futibatinib TIW (15.0%) and 16/43 receiving futibatinib QD (37.2%) required dose reduction. Treatment was interrupted because of AEs in 22/40 patients receiving a TIW regimen (55.0%) and 29/43 patients receiving a QD regimen (67.4%). Two patients discontinued treatment because of an

TABLE 2 Adverse events (AEs) reported with an incidence of ≥10% in patients with advanced solid tumors treated with futibatinib ($n = 83$)

	TIW dosing ($n = 40$)				QD dosing ($n = 43$)			
Preferred term	All	Grade 1	Grade 2	≥Grade 3	All	Grade 1	Grade 2	≥Grade 3
Any AE	40 (100.0)	7 (17.5)	12 (30.0)	21 (52.5)	43 (100.0)	6 (14.0)	16 (37.2)	21 (48.8)
Hyperphosphatemia	33 (82.5)	26 (65.0)	7 (17.5)	0 (0.0)	43 (100)	21 (48.8)	20 (46.5)	2 (4.7)
Decreased appetite	16 (40.0)	4 (10.0)	10 (25.0)	2 (5.0)	25 (58.1)	8 (18.6)	15 (34.9)	2 (4.7)
Constipation	11 (27.5)	8 (20.0)	3 (7.5)	0 (0.0)	17 (39.5)	12 (27.9)	5 (11.6)	0 (0.0)
Diarrhea	10 (25.0)	10 (25.0)	0 (0.0)	0 (0.0)	13 (30.2)	11 (25.6)	2 (4.7)	0 (0.0)
Nausea	14 (35.0)	10 (25.0)	4 (10.0)	0 (0.0)	13 (30.2)	5(11.6)	8 (18.6)	0 (0.0)
Vomiting	8 (20.0)	5 (12.5)	3 (7.5)	0 (0.0)	10 (23.3)	8 (18.6)	1 (2.3)	1 (2.3)
ALT increased	3 (7.5)	2 (5.0)	0 (0.0)	1 (2.5)	9 (20.9)	5 (11.6)	4 (9.3)	0 (0.0)
AST increased	6 (15.0)	2 (5.0)	1 (2.5)	3 (7.5)	9 (20.9)	3 (7.0)	5 (11.6)	1 (2.3)
Anemia	8 (20.0)	1 (2.5)	3 (7.5)	4 (10.0)	8 (18.6)	0 (0.0)	3 (7.0)	5 (11.6)
Stomatitis	8 (20.0)	7 (17.5)	0 (0.0)	1 (2.5)	7 (16.3)	6 (14.0)	1 (2.3)	0 (0.0)
Blood creatinine increased	9 (22.5)	5 (12.5)	4 (10.0)	0 (0.0)	7 (16.3)	3 (7.0)	3 (7.0)	1 (2.3)
Hypoalbuminemia	4 (10.0)	0 (0.0)	4 (10.0)	0 (0.0)	6 (14.0)	1 (2.3)	1 (2.3)	4 (9.3)
Hyponatremia	2 (5.0)	0 (0.0)	0 (0.0)	2 (5.0)	6 (14.0)	2 (4.7)	0 (0.0)	4 (9.3)
Malaise	2 (5.0)	2 (5.0)	0 (0.0)	0 (0.0)	6 (14.0)	1 (2.3)	5 (11.6)	0 (0.0)
Edema peripheral	2 (5.0)	2 (5.0)	0 (0.0)	0 (0.0)	6 (14.0)	3 (7.0)	2 (4.7)	1 (2.3)
Dry skin	7 (17.5)	6 (15.0)	1 (2.5)	0 (0.0)	6 (14.0)	5 (11.6)	1 (2.3)	0 (0.0)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (14.0)	2 (4.7)	4 (9.3)	0 (0.0)
Tumor pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (14.0)	2 (4.7)	4 (9.3)	0 (0.0)
Weight decreased	9 (22.5)	4 (10.0)	3 (7.5)	2 (5.0)	5 (11.6)	1 (2.3)	4 (9.3)	0 (0.0)
Insomnia	7 (17.5)	6 (15.0)	1 (2.5)	0 (0.0)	5 (11.6)	5 (11.6)	0 (0.0)	0 (0.0)
Fatigue	7 (17.5)	3 (7.5)	4 (10.0)	0 (0.0)	4 (9.3)	1 (2.3)	3 (7.0)	0 (0.0)
Hypophosphatemia	5 (12.5)	0 (0.0)	1 (2.5)	4 (10.0)	3 (7.0)	1 (2.3)	0 (0.0)	2 (4.7)
Pyrexia	10 (25.0)	8 (20.0)	2 (5.0)	0 (0.0)	3 (7.0)	3 (7.0)	0 (0.0)	0 (0.0)
Serous retinal detachment	7 (17.5)	7 (17.5)	0 (0.0)	0 (0.0)	3 (7.0)	3 (7.0)	0 (0.0)	0 (0.0)
Cancer pain	7 (17.5)	4 (10.0)	3 (7.5)	0 (0.0)	3 (7.0)	1 (2.3)	1 (2.3)	1 (2.3)
Arthralgia	5 (12.5)	3 (7.5)	2 (5.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (4.7)	0 (0.0)
Hypokalemia	5 (12.5)	1 (2.5)	2 (5.0)	2 (5.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)
Dyspnea	7 (17.5)	4 (10.0)	1 (2.5)	2 (5.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)
Edema	5 (12.5)	5 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease progression	4 (10.0)	0 (0.0)	0 (0.0)	4 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; QD, once daily; TIW, three times a week.

AE, one due to grade 3 duodenal obstruction, and another due to grade 5 pulmonary tumor thrombotic microangiopathy; neither AE was futibatinib-related.

3.3.1 | Adverse events of special interest

Thirty ocular AEs (TIW, 15/40 [37.5%]; QD, 15/43 [34.9%]) were reported in 24 patients across both phases of the study.

Eighteen patients reported retinal AEs, which included serous retinal detachment (TIW, 7/40 [17.5%]; QD, 3/43 [7.0%]), subretinal fluid (TIW, 0/40; QD, 4/43 [9.3%]), detachment of retinal pigment epithelium (TIW, 1/40 [2.5%]; QD, 1/43 [2.3%]), and macular edema (TIW, 0/40; QD, 2/43 [4.7%]). All retinal AEs were grade 1 and considered to be treatment-related. The main corneal AE was corneal opacity (TIW, 2/40 [5.0%]; QD, 0/43) and was considered to be treatment related.

Overall, 26 ocular AEs were considered to be ADRs, including the 10 serous retinal detachment events, all of which were grade 1 or 2 and none of which required treatment. Seventeen of the 30 ocular AEs (including 6/10 of the grade 1 serous retinal detachments) were "resolved" or "resolving" and 13 (including 4/10 grade 1 serous retinal detachments) were "not resolved". In all patients with "not

TABLE 3 Best overall response with futibatinib in subgroups of patients with advanced solid tumors ($n = 83$)

	Futibatinib regimen			FGF/FGFR abnormality status		FGFR-abnormal patients with GC		
	TIW ($n = 39$)	QD ($n = 43$)	Total ($n = 82$)	With FGF/FGFR abnormalities ($n = 52$)	Without FGF/FGFR abnormalities or unknown ($n = 30$)	All patients ($n = 21$)	FGFR2 CN <10 ($n = 10$)	FGFR2 CN ≥10 ($n = 11$)
Best response, *n* (%)								
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	1 (2.6)	5 (11.6)	6 (7.3)	6 (11.5)	0 (0.0)	4 (19.0)	0 (0.0)	4 (36.4)
SD	10 (25.6)	11 (25.6)	21 (25.6)	13 (25.0)	8 (26.7)	3 (14.3)	1 (10.0)	2 (18.2)
PD	23 (59.0)	23 (53.5)	46 (56.1)	27 (51.9)	19 (63.3)	12 (57.1)	7 (70.0)	5 (45.5)
NE	5 (12.8)	4 (9.3)	9 (11.0)	6 (11.5)	3 (10.0)	2 (9.5)	2 (20.0)	0 (0.0)
ORR, % (95% CI)	2.6 (0.1–13.5)	11.6 (3.9–25.1)	7.3 (2.7–15.2)	11.5 (4.4–23.4)	0 (0–11.6)	19.0 (5.4–41.9)	0 (0–30.8)	36.4 (10.9–69.2)
DCR, % (95% CI)	28.2 (15.0–44.9)	37.2 (23.0–53.3)	32.9 (22.9–44.2)	36.5 (23.6–51.0)	26.7 (12.3–45.9)	33.3 (14.6–57.0)	10.0 (0.3–44.5)	54.5 (23.4–83.3)

Abbreviations: CI, confidence interval; CN, copy number; CR, complete response; DCR, disease control rate (CR + PR + SD); FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GC, gastric cancer; NE, not evaluable; ORR, overall response rate (CR + PR); PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; TIW, three times a week.

resolved" serous retinal detachment, final outcomes were not determined because patient follow-up was discontinued.

Three ocular AEs (two events of corneal opacity and one of optic ischemic neuropathy) led to interruption of futibatinib and one (subretinal fluid) led to dose reduction, but none resulted in treatment discontinuation.

3.4 | Tumor response

Antitumor activity was observed for both TIW and QD regimens of futibatinib. The ORR across the DEP and EP was 7.3% (95% CI, 2.7–15.2) and the DCR was 32.9% (95% CI, 22.9–44.2) (Table 3). The best response included a confirmed PR in six patients and SD in 21 (Figure 1A). All six patients with confirmed PR had an *FGF/FGFR* abnormality (four with GC, one with breast cancer, and one with iCCA); these were: *FGFR2* amplification and overexpression in two GC patients treated with futibatinib 20 mg QD or 80 mg TIW (one of whom also had *FGF3/4/19* amplification), *FGFR2* amplification in one breast cancer patient and two patients with GC treated with 20 mg QD (one of whom also had *FGFR2* rearrangement), and *FGFR2* mutation (Y375C) in one patient with iCCA treated with 20 mg QD.

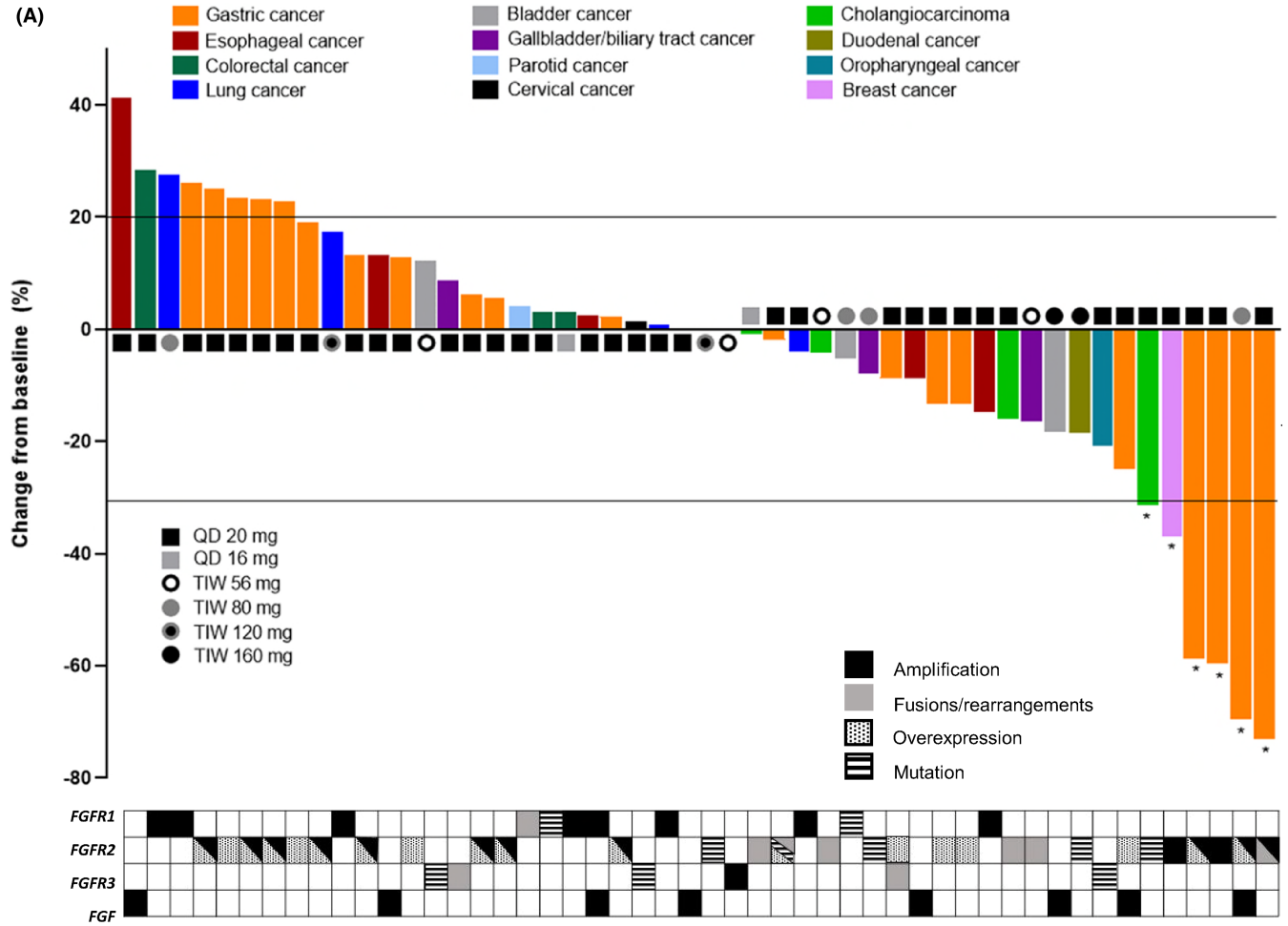
An *FGF/FGFR* abnormality was confirmed in 52/83 patients, resulting in an ORR in this subgroup of 11.5% (95% CI, 4.4–23.4) and DCR of 36.5% (95% CI, 23.6–51.0) (Table 3 and Figure 1A). There was no objective response in the 30 patients who did not harbor an *FGF/FGFR* abnormality or whose *FGF/FGFR* status was unknown, but 8/30 patients had SD, resulting in a DCR of 26.7% (95% CI, 12.3–45.9) (Table 3 and Figure 1B).

Twenty-one of the 22 patients with GC in the FAS (which included patients from both phases of the study) could be evaluated for response, and 4/21 achieved a confirmed PR, resulting in an ORR of 19.0% (Table 3 and Figure 2A). Among the GC patients, 0/10 of those with *FGFR2* CN <10 and 4/11 of those with *FGFR2* CN ≥10 had a best response of confirmed PR (Table 3 and Figure 2B). Therefore, the ORR was 0 in patients with *FGFR2* CN <10 versus 36.4% in those with *FGFR2* CN ≥10 (Table 3).

3.5 | Pharmacokinetics

Pharmacokinetic data were evaluable in 28 patients receiving futibatinib TIW and 10 receiving futibatinib QD (Table 4). The C_{max} and AUC values for the TIW regimens increased in a dose-proportional manner up to 160 mg following single and multiple administrations.

The mean accumulation ratios of C_{max} and AUC_{0-last} after multiple doses of 160 mg TIW were 0.85 (90% CI, 0.37–1.98) and 1.44 (90% CI, 0.91–2.30), respectively, and these ratios were consistent across all doses (36–160 mg), suggesting no obvious futibatinib accumulation following repeated administration in the TIW regimen. Renal excretion of unchanged futibatinib was negligible.



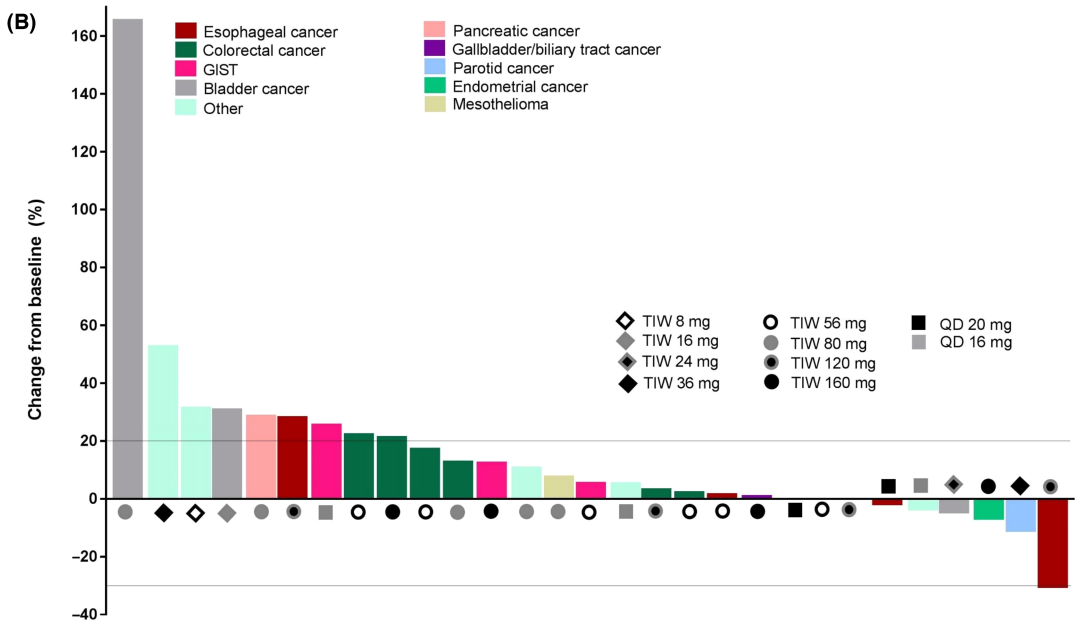


FIGURE 1 Waterfall plots showing the greatest overall change in tumor diameter in patients with advanced solid tumors treated with futibatinib. (A) Patients with all *FGF/FGFR* abnormalities ($n = 52$; 1 patient had no measurable lesion and 1 patient was not assessed for response). (B) Patients without *FGF/FGFR* abnormalities ($n = 30$; 1 patient had no measurable lesion). *Confirmed partial response. FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; QD, once daily; TIW, three times a week

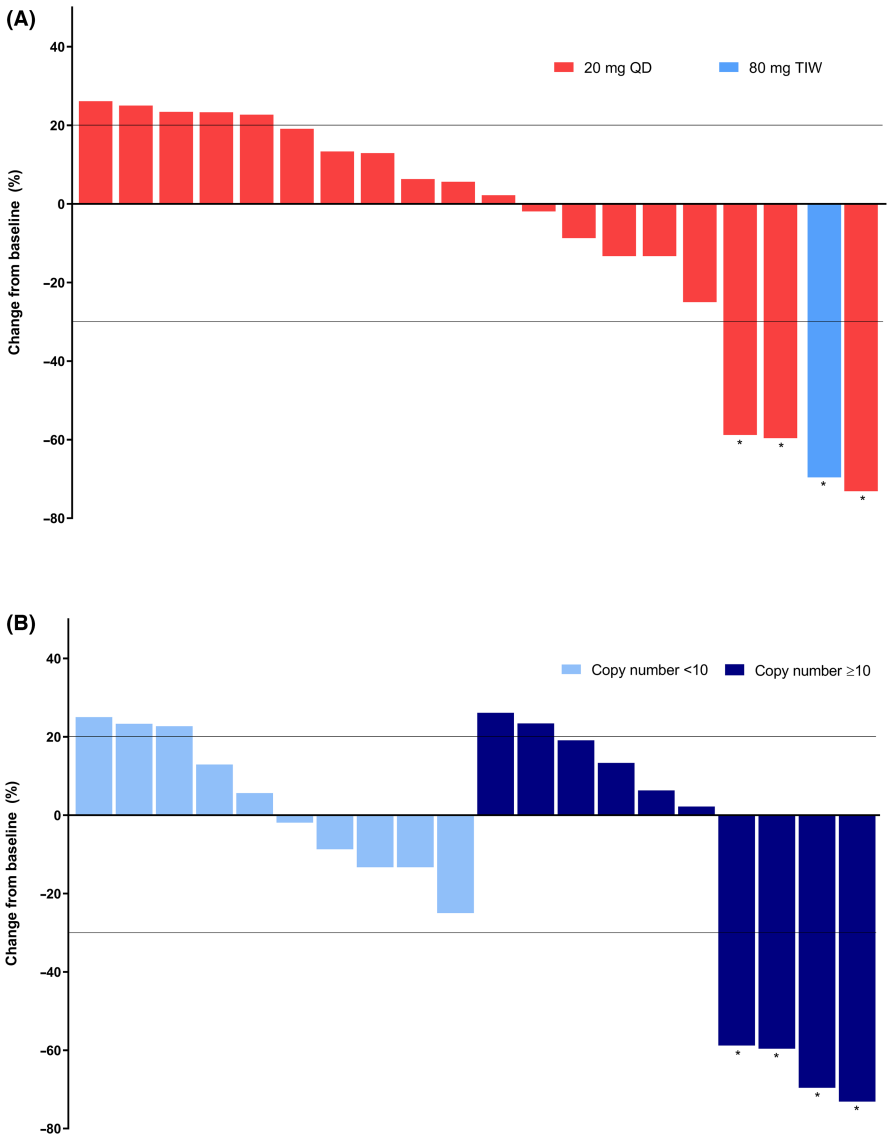


FIGURE 2 Waterfall plots showing the greatest overall change in tumor diameter in patients with gastric cancer treated with futibatinib. (A) Patients with *FGFR2* amplification ($n = 21$; 1 patient had no measurable lesion). (B) Patients with *FGFR2* amplification with copy number < 10 ($n = 10$) or ≥ 10 ($n = 11$; 1 patient had no measurable lesion). *Confirmed partial response. QD, once daily; TIW, three times a week

3.6 | Pharmacodynamics

Serum FGF23 levels started to decrease approximately 2–3 h after futibatinib treatment, reaching their minimum 8–24 h post dose; thereafter, they increased to baseline or higher levels by 24–48 h post dose. Serum FGF23 levels were markedly upregulated after repeated doses with both the TIW and QD regimens compared with baseline levels on day 1, and showed a trend towards dose dependency. Serum Pi levels started to increase at approximately 6–12 h after futibatinib treatment and were markedly upregulated after repeated doses with both the TIW and QD regimens compared with baseline levels on day 1. Increases in serum Pi levels also showed a dose-dependent trend.

3.7 | Post hoc analysis

All 43 patients who received futibatinib QD developed hyperphosphatemia, and 40/43 patients received a phosphate-binding agent, such as lanthanum carbonate, sevelamer, and ferric citrate hydrate (Table S6). Of the 40 patients treated with phosphate-binding therapy, 12 (30%) had a futibatinib dose interruption and five (12.5%) had a dose reduction, but none of the hyperphosphatemia events led to discontinuation of futibatinib.

Overall, the serum Pi decreased by −0.31 (1.36) mg/dl from just before initiation of phosphate-binding therapy to last futibatinib treatment (Table S7).

Among patients receiving futibatinib QD and phosphate-binding therapy for a minimum of two cycles, a serum Pi level < 5.5 mg/dl was achieved by 65.7% (95% CI, 47.8–80.9) at the last futibatinib administration (Table S8). There were no clinically important differences between the types of phosphate-binding therapy in achieving a serum Pi level of < 5.5 mg/dl. Of the 15 patients who required a futibatinib dose reduction after starting phosphate-binding therapy, 13 achieved the target serum Pi level (86.7%) compared with 10/20 (50.0%) who did not have a dose reduction after starting phosphate-binding therapy (Table S9).

No safety concerns were identified regardless of the presence or absence of phosphate-binding therapy (Table S10).

TABLE 4 Pharmacokinetic parameters among patients with advanced solid tumors treated with futibatinib ($n = 83$)

	T_{max}, h	$t_{1/2}$, h	C_{max}, ng/ml	AUC_{0-last}, ng·h/ml	AUC_{0-inf}, ng·h/ml	R_{Cmax}	$R_{AUC0-last}$
Day 1							
TIW							
8 mg, $n = 1$	1.87 (NA)[a] [NA]	1.58 (NC) [NC]	135 (NC) [NC]	387 (NC) [NC]	390 (NC) [NC]	NA	NA
16 mg, $n = 1$	1.95 (NA)[a] [NA]	5.72 (NC) [NC]	189 (NC) [NC]	1137 (NC) [NC]	1192 (NC) [NC]	NA	NA
24 mg, $n = 1$	1.95 (NA)[a] [NA]	1.55 (NC) [NC]	204 (NC) [NC]	621 (NC) [NC]	623 (NC) [NC]	NA	NA
36 mg, $n = 3$	1.92 (0.95, 2.92)[a]	3.94 (1.92) [48.7]	348 (48) [13.9]	1502 (351) [23.4]	1527 (326) [21.4]	NA	NA
56 mg, $n = 6$	1.97 (1.95, 2.00)[a]	6.93 (2.80) [40.4]	545 (180) [32.9]	3707 (2218) [59.8]	3749 (2247) [59.9]	NA	NA
80 mg, $n = 6$	1.95 (0.52, 2.87)[a]	5.48 (1.45) [26.4]	866 (366) [42.3]	5472 (2653) [48.5]	5490 (2656) [48.4]	NA	NA
120 mg, $n = 4$	2.49 (1.85, 3.98)[a]	6.64 (1.08) [16.3][b]	1310 (452) [34.5]	10,792 (3782) [35.0]	9957 (4131) [41.5][b]	NA	NA
160 mg, $n = 6$	2.46 (1.92, 4.07)[a]	7.11 (2.47) [34.8]	1578 (515) [32.7]	10,589 (2559) [24.2]	10,677 (2519) [23.6]	NA	NA
QD							
16 mg, $n = 3$	0.95 (0.95, 0.95)[a]	2.68 (0.48) [18.0]	235 (87) [37.2]	1010 (330) [32.6]	1018 (324) [31.8]	NA	NA
20 mg, $n = 7$	2.00 (1.00, 3.95)[a]	2.18 (0.83) [38.0]	253 (161) [63.4]	977 (714) [73.0]	983 (717) [72.9]	NA	NA
Week 3 (day 21)[c]							
TIW							
8 mg, $n = 1$	2.00 (NA)[a] [NA]	1.74 (NC) [NC]	167 (NC) [NC]	653 (NC) [NC]	663 (NC) [NC]	1.24 (NC) [NC]	1.69 (NC) [NC]
16 mg, $n = 1$	2.90 (NA)[a] [NA]	5.27 (NC) [NC]	182 (NC) [NC]	1576 (NC) [NC]	1580 (NC) [NC]	0.96 (NC) [NC]	1.39 (NC) [NC]
24 mg, $n = 1$	3.98 (NA)[a] [NA]	1.47 (NC) [NC]	146 (NC) [NC]	499 (NC) [NC]	502 (NC) [NC]	0.72 (NC) [NC]	0.80 (NC) [NC]
36 mg, $n = 3$	1.93 (1.88, 12.18)[a] [111.3]	3.64 (NC) [NC][d]	317 (183) [57.8]	2169 (310) [14.3]	2160 (NC) [NC]	0.88 (0.44) [49.7]	1.51 (0.47) [30.9]
56 mg, $n = 6$	1.95 (0.95, 6.05)[a] [NA]	5.12 (1.77) [34.6]	643 (136) [21.2]	4893 (2844) [58.1]	4919 (2858) [58.1]	1.25 (0.36) [28.8]	1.36 (0.44) [32.5]
80 mg, $n = 5$	2.87 (1.93, 6.03)[a] [NA]	6.44 (1.09) [16.9]	899 (277) [30.8]	7394 (3731) [50.5]	7434 (3758) [50.6]	0.96 (0.09) [9.1]	1.25 (0.25) [20.0]
120 mg, $n = 3$	2.98 (2.90, 6.00)[a] [NA]	8.19 (4.95) [60.4]	1093 (297) [27.2]	11,966 (4157) [34.7]	12,368 (4822) [38.9]	1.02 (0.34) [33.2]	1.27 (0.29) [23.1]
160 mg, $n = 4$	2.93 (2.88, 11.92)[a] [NA]	5.83 (1.29) [22.2][b]	1444 (509) [35.2]	15,254 (4787) [31.4]	13,964 (4876) [34.9]	1.05 (0.82) [78.2]	1.54 (0.64) [41.6]
QD							
20 mg, $n = 2$	1.44 (0.98, 1.90)[a] [NA]	3.05 (NC) [NC]	173 (NC) [NC]	727 (NC) [NC]	729 (NC) [NC]	0.91 (NC) [NC]	1.29 (NC) [NC]

Note: Values are mean (standard deviation) [coefficient of variation %], unless otherwise specified.

Abbreviations: AUC_{0-inf}, area under the curve from baseline to infinity; AUC_{0-last}, area under the curve from baseline to the last measurement; C_{max}, maximal plasma concentration; NA, not applicable; NC, not calculable; QD, once daily; R, ratio; TIW, three times a week; $t_{1/2}$, elimination half-life; T_{max}, time to C_{max}.

[a]Median (minimum, maximum).

[b]$n = 3$.

[c]Day 21 for patients receiving futibatinib QD and Wednesday of the third week for patients receiving futibatinib TIW.

[d]$n = 2$.

4 | DISCUSSION

In the present phase 1 study, futibatinib had a generally predictable and manageable safety profile in Japanese patients with advanced solid tumors. No DLTs were observed at doses up to 160 mg TIW, so based on the results of the global phase I study,[18] the dose escalation was discontinued at 160 mg TIW. For QD treatment, no DLTs were reported in patients who received 16 mg or 20 mg. Based on the pharmacokinetics/pharmacodynamics and safety results of this study, and the results of the global phase I study that was undertaken in parallel with this study,[18] the RD for phase II (and further) futibatinib studies was determined to be 20 mg QD.

Antitumor activity was seen in patients with *FGF/FGFR* abnormalities (11.5%), particularly those with GC and *FGFR2* CN ≥10 (36.4%). The futibatinib safety profile seen in this study was similar to that of other FGFR inhibitors in patients with advanced solid tumors.[20,21,23,26] Hyperphosphatemia is an on-target effect of FGFR inhibitors due to decreased FGF23–FGFR1 signaling and decreased urinary phosphate excretion.[27] Hyperphosphatemia was more frequent in the current study than in the phase II trials of pemigatinib, infigratinib, or erdafitinib,[20,22,28] occurring in 82.5% of patients receiving futibatinib TIW and 100% of those receiving QD, compared with 77% of patients receiving infigratinib QD and 60% of patients receiving pemigatinib in patients with advanced or metastatic cholangiocarcinoma,[20,28] and 77% of patients receiving erdafitinib in patients with urothelial carcinoma.[22] This may in part reflect differences between these trials in dosing schedules, utilization of phosphate-binding agents, and the timing of safety assessments. Hyperphosphatemia in the current study was mostly asymptomatic and could be managed without futibatinib discontinuation by administering phosphate-binding therapy or reducing the dose, although these data should be confirmed in a larger cohort of patients. All the phosphate binders used in the current study were effective during futibatinib therapy.

Serous retinal detachment/subretinal fluid accumulation was the most frequently reported ocular AE in our study, and the incidence of retinal AEs was broadly similar with either dosing regimen. Most of these events were resolved without medication. The mechanism of retinal AEs with FGF/FGFR inhibitors is probably similar to the mechanism for MEK-associated retinal disorders, as the FGF/FGFR pathway is upstream of the MEK signaling pathway.[29,30] However, while approximately 74% of patients on MEK inhibitors develop subretinal fluid accumulation,[31] the incidence in our study was much lower (9.3%). As in our study, the retinal AEs reported with other FGFR inhibitors were mostly grade 1 or 2 events and few required dose interruption or treatment discontinuation (two discontinuations of infigratinib and one dose interruption with pemigatinib).[20,28] In the phase II study with erdafitinib, 13% of patients discontinued treatment because of retinal detachment.[22]

The RD of 20 mg QD and the safety profile are consistent with data obtained from the global phase I study.[18] There was a similar rate of dose delays and reductions as in the global phase I study.[18]

The pharmacokinetic profile of futibatinib in our study of Japanese patients was consistent with data from the other phase I study, which included 64% Caucasian patients.[18] In that study, C_{max} and AUC were statistically dose-proportional between 4 mg and 24 mg QD.[18] Similarly, our study found dose-proportional changes in C_{max} and AUC_{0-last} and no obvious accumulation with repeated doses of futibatinib in either regimen. The dynamic changes of FGF23 levels in the current study were consistent with preclinical results (data on file), and indicated target modulation by futibatinib during either TIW or QD dosing.

Across our entire study, the best ORR was 11.5%. Six patients harboring FGFR2 abnormalities had confirmed PR: four with GC, one with breast cancer, and one with iCCA. *FGFR2* amplification and FGFR2 overexpression have been associated with poor prognosis in patients with GC.[13–15] Compared with tumors without FGFR2 overexpression, GC with FGFR2 overexpression shows deeper invasion and a higher rate of lymph node metastasis.[32]

We detected a possible association between *FGFR2* CN and the response to futibatinib. In the subset of patients with GC harboring *FGFR2* amplification, the ORR and DCR were higher among those with CN ≥10 compared with <10, warranting further research of these outcomes. A similar association was reported with the selective FGFR inhibitor AZD4547.[33]

As with our study, previous studies have used IHC or FISH to identify patients with FGFR2 overexpression or amplification. The FIGHT study with bemarituzumab (an investigational inhibitor of FGFR2b) defined FGFR2 overexpression as an IHC score of 2+ or 3+ in patients with human epidermal growth factor receptor 2-negative gastric or gastroesophageal junction cancer,[34] whereas a study with AZD4547 in patients with locally advanced or metastatic GC defined *FGFR2* amplification and polysomy as *FGFR2*/centromere of chromosome 10 (CEN10) ratio ≥2 or *FGFR2* gene clusters in ≥10% of tumor cells using FISH.[35] Further research is needed to determine the best measure of FGFR2 expression to use with futibatinib. Irrespective of the method used to measure FGFR2 expression, cumulative data indicate that this parameter is a relevant biomarker for GC patients who are likely to respond to FGFR inhibitors. Among gastric cancer patients in this study, ORR was 0% in patients with *FGFR2* gene CN <10 and 36.4% in patients with *FGFR2* gene CN ≥10, and preliminary antitumor activity of futibatinib was observed in gastric cancer patients with *FGFR2* gene amplification with CN ≥10. In contrast, no clinically significant differences in efficacy were observed when the IHC scores were categorized. Therefore, it is considered necessary to measure the CN of the *FGFR2* gene in GC patients before treatment with FGFR inhibitors and to administer futibatinib in patients with a CN of *FGFR2* gene of ≥10.

The limitations of our study are typical of those for a phase I study, including its open-label design, limited number of patients at each dose level, the intratumoral heterogeneity, and the influence of pretreatment across patients, as well as the short duration of follow-up. The weak positive signal could be because GC is heterogeneous and prone to resistance.[36] Notwithstanding these limitations, our study shows that futibatinib has promising preliminary antitumor activity in patients with advanced GC and *FGFR2* amplification CN ≥10, and is therefore being investigated in such patients in a global phase II study (TAS-120-202 study, NCT04189445). In addition, phase II studies are underway with futibatinib in a range of other cancer types (lung cancer, breast cancer, hematologic malignancies, urothelial carcinoma, and iCCA) and phase III studies are underway in iCCA.

In conclusion, this phase I study showed that futibatinib was safe and tolerable for patients with advanced cancer at dosages of up to 160 mg TIW and 20 mg QD, with a generally predictable, monitorable, and clinically manageable safety profile. The most common AE was hyperphosphatemia, which was mostly asymptomatic and could be safely managed with futibatinib dose reductions and phosphate-binding therapy. This study showed preliminary antitumor activity of futibatinib by FGFR inhibition in patients with advanced solid tumors with *FGF/FGFR* gene abnormalities, particularly in patients with advanced GC and *FGFR2* amplification CN ≥10. A futibatinib RD of 20 mg QD was selected for global phase II and further studies, consistent with data from previous reports in Caucasian patients.

AUTHOR CONTRIBUTIONS

Toshihiko Doi and Hiroshi Hirai designed the study. Toshihiko Doi, Kohei Shitara, Takashi Kojima, Yasutoshi Kuboki, Nobuaki Matsubara, Hideaki Bando, Kiyotaka Yoh, Yoichi Naito, Yukinori Kurokawa, Terufumi Kato, and Chigusa Morizane were involved in data acquisition. All authors contributed to study conduct, data analysis, and data interpretation, critically reviewed each draft of the manuscript, and approved the final version for submission.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data will not be shared according to the Sponsor policy on data sharing.

ETHICAL APPROVAL

The study is registered on the Japan Pharmaceutical Information Center clinical trials registry (JapicCTI-142552). The study was designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki, and was conducted only after institutional review board protocol approval at all participating study sites. Written informed consent was obtained from all patients prior to any study procedures being undertaken.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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