Received: 18 March 2024 | Revised: 4 September 2024 | Accepted: 7 September 2024

DOI: 10.1111/cas.16354

ORIGINAL ARTICLE

Cancer Science WILEY

Tasurgratinib in patients with cholangiocarcinoma or gastric cancer: Expansion part of the first-in-human phase I study

Chigusa Morizane[1] | Makoto Ueno[2] | Tatsuya Ioka[3] | Masahiro Tajika[4] | Masafumi Ikeda[5] | Kensei Yamaguchi[6] | Hiroki Hara[7] | Hiroshi Yabusaki[8] | Atsushi Miyamoto[9] | Satoru Iwasa[1] | Manabu Muto[10] | Tsutomu Takashima[11] | Keiko Minashi[12] | Yoshito Komatsu[13] | Tomohiro Nishina[14] | Takako Eguchi Nakajima[15,16] | Atsuchi Takeno[17] | Toshikazu Moriwaki[18] | Masayuki Furukawa[19] | Takatoshi Sahara[20] | Hiroki Ikezawa[20] | Maiko Nomoto[20] | Shuya Takashima[20] | Taisuke Uehara[20] | Setsuo Funasaka[20] | Masakazu Yashiro[11] | Junji Furuse[2]

Correspondence
Chigusa Morizane, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Email: cmorizan@ncc.go.jp

Funding information
Eisai

Abstract

Fibroblast growth factor receptors (FGFRs) are a highly conserved family of transmembrane receptor tyrosine kinases with multiple roles in the regulation of key cellular processes. Specific *FGFR* mutations have been observed in several types of cancers, including gastric carcinoma and cholangiocarcinoma. Dose escalation data of 24 Japanese patients with solid tumors treated with Tasurgratinib (previously known as E7090), a potent, selective FGFR1–3 inhibitor, was reported in a phase I, first-in-human, single-center study. Based on the safety, pharmacokinetic, and pharmacodynamic profiles observed in this study, the recommended dose of 140 mg once daily was selected for the expansion part (Part 2), a multicenter expansion of the dose-finding study restricted to patients with tumors harboring *FGFR* gene alterations. Safety and preliminary efficacy were assessed in Part 2. Pharmacodynamic pharmacogenomic markers (serum phosphate, FGF23, and 1,25-$(OH)_2$-vitamin D, circulating tumor DNA) and pharmacokinetic profiles were also evaluated. A total of 16 patients were enrolled in Part 2, six with cholangiocarcinoma and 10 with gastric cancer. The most common treatment-emergent adverse events were hyperphosphatemia, palmar-plantar erythrodysesthesia syndrome, and paronychia. Five partial responses (83.3%) in cholangiocarcinoma patients and one partial response (11.1%) in gastric cancer patients were observed; median progression-free survival was 8.26 months (95% confidence interval [CI] 3.84, not evaluable [NE]) and 3.25 months (95% CI 0.95, 4.86), and overall survival was 22.49 months (95% CI 6.37, NE) and 4.27 months (95% CI 2.23, 7.95), respectively, in the two groups. In conclusion, Tasurgratinib 140 mg has a

Clinical trial registration: JapicCTI-142740; NCT02275910.

For affiliations refer to page 201.

tolerable safety profile with good clinical efficacy in patients with cholangiocarcinoma harboring *FGFR2* gene rearrangements.

KEYWORDS
cholangiocarcinoma, E7090, FGFR2, gastric cancer, Tasurgratinib

1 | INTRODUCTION

Fibroblast growth factor receptors (FGFRs), a family of four highly conserved transmembrane receptor tyrosine kinases (FGFR1–4) and one receptor that can bind fibroblast growth factor (FGF) ligands,[1] play important roles in a variety of biological functions, including cellular proliferation, differentiation, migration, and angiogenesis.[2] Genomic alterations in FGFRs, including gene amplifications and chromosomal translocations that trigger pathway activations,[3,4] have been identified in multiple types of solid tumors.[5,6] FGFR2 dysregulation has been reported in gastric carcinomas[7,8] and cholangiocarcinomas.[9,10]

Gastric cancer is the fifth most common cancer worldwide and the fourth most common cause of cancer mortality.[11] Cholangiocarcinoma represents approximately 3% of all gastrointestinal malignancies and has widely variable incidence rates; particularly high rates have been reported in Asian countries compared with the West, and currently there is evidence that incidence and mortality rates are rising globally.[12] *FGFR2* amplifications have been reported in 4.1% of gastric cancers,[13] whereas *FGFR2* gene fusions have been identified in approximately 14% of intrahepatic cholangiocarcinomas.[14] Significant positive correlation has been reported between *FGFR2* gene amplification and FGFR2 overexpression in gastric cancer.[15] Targeted anti-FGFR therapy therefore represents a promising avenue of drug development for these tumor types.

As first-generation FGFR-targeted agents, nonselective tyrosine kinase inhibitors (TKIs) have demonstrated efficacy in patients with advanced tumors harboring *FGFR* mutations.[16] However, trials of nonselective, multitarget TKIs have shown variable anti-FGFR activity and broad-spectrum off-target inhibition of other tyrosine kinases, notably vascular endothelial growth factor, leading to toxicities.[17] Second-generation selective FGFR inhibitors have subsequently been developed and evaluated in early-phase trials. Pemigatinib[18] and futibatinib[19] have recently received approval in Japan and the United States for the treatment of unresectable locally advanced or metastatic cholangiocarcinoma with an *FGFR2* gene fusion or other rearrangement; the response rates with these agents have been reported to be 35.5%, 23.1%, and 41.7%, respectively.

Tasurgratinib is an oral FGFR inhibitor developed at Eisai Tsukuba Research Laboratories that selectively targets the tyrosine kinase activities of FGFR1, −2, and −3. In preclinical studies using models harboring FGFR genetic alterations, Tasurgratinib demonstrated potent antitumor activity. Tasurgratinib kinetics are more similar to the type V inhibitors, which are characterized by rapid association and slow dissociation, such as lenvatinib.[20] The results from the dose-escalation portion (Part 1) of a first-in-human, phase I study of Tasurgratinib were reported for 24 patients with advanced solid tumors.[21] Whereas no dose-limiting toxicities were observed at daily oral doses of up to 140 mg of Tasurgratinib, one patient in the 180-mg cohort experienced a dose-limiting toxicity of grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increase. Dose-dependent increases in all evaluated pharmacodynamic markers (serum phosphate, FGF23, and 1,25-$(OH)_2$-vitamin D) were observed and reached a plateau at approximately 100–140 mg. The maximum tolerated dose was not determined, and the recommended dose for the expansion part (Part 2) was established as 140 mg once daily.[21]

Herein, we report the Part 2 analysis results of this phase I trial, comprising safety, tolerability, and preliminary antitumor activity from patients enrolled in the expansion part. In Part 2, Tasurgratinib 140 mg once daily was used, and patients with tumors harboring FGFR alterations, including gastric cancer with *FGFR2* gene amplification or FGFR2 protein high expression and cholangiocarcinoma with *FGFR2* gene rearrangement, were enrolled.

2 | MATERIALS AND METHODS

2.1 | Patients

The inclusion criteria for Part 1 have been reported previously.[21] Patients with histologically or cytologically confirmed advanced solid tumors refractory to standard therapy or for whom standard curative therapy does not exist, who were ≥20 years of age, had Eastern Cooperative Oncology Group performance status <2, and had corrected serum calcium and phosphate ≤upper limit of normal were eligible for inclusion. The new inclusion criterion for Part 2 was that eligible patients must have had gastric cancer with *FGFR2* gene amplification or FGFR2 protein high expression and cholangiocarcinoma with *FGFR2* gene rearrangement. The type of FGFR mutation and the methods used to diagnose the mutation (e.g., fluorescent in situ hybridization [FISH] or next-generation sequencing [NGS]) were collected from the patients' medical records, where available. The FGFR2 expression status of patients with gastric cancer for whom medical records of *FGFR2* gene amplification testing were not available was confirmed by a central laboratory using immunostaining; detailed information can be found in Appendix S1. There were no new exclusion criteria for

Part 2. Patients with unstable brain metastasis, current evidence or history of grade ≥2 corneal disorder, current evidence or history of active macula disorder, prior therapy targeting FGFR2, or a history of clinically significant cardiovascular impairment were excluded.

2.2 | Study design

This study was conducted in two parts. Part 1 was a dose escalation to determine the recommended dose for Part 2.[21] Part 2 was an expansion restricted to patients with tumors harboring FGFR alterations. Part 1 was conducted at a single center in Japan, whereas Part 2 was expanded to 18 study sites in Japan.

The Part 2 study design consisted of a pretreatment period, a treatment period, and a follow-up period. Patients participating in Part 2 received Tasurgratinib 140 mg once daily as oral tablets in a continuous schedule of 28-day cycles until any criterion for discontinuation was met, including refusal to continue participation or withdrawal of consent, major violations of inclusion criteria, meeting any exclusion criteria, intolerable adverse events (AEs), pregnancy, disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or at the investigator's discretion. Dose reductions and dose interruptions were allowed according to the protocol criterion. Tasurgratinib was administered at least 2 h after breakfast, and food intake was prohibited for 1 h after administration. On days 1 and 8 of cycle 1, Tasurgratinib was administered to subjects in the morning after an overnight fast of at least 10 h to evaluate the pharmacokinetics (PKs). Food consumption was prohibited for 2 h after the administration of Tasurgratinib, but drinking water was permitted.

The primary objective of Part 2 was to investigate the tolerability and safety of Tasurgratinib in patients with advanced gastric cancer and cholangiocarcinoma. Secondary objectives included the establishment of the recommended dose for phase II studies and the assessment of the preliminary antitumor activity of Tasurgratinib. Exploratory objectives included an assessment of the relationship between PK and pharmacodynamic (PD) markers and the assessment of pharmacogenomics (PGx). The study protocol was approved by the institutional review board or independent ethics committee of each participating institution, and the study was conducted in accordance with ICH-E6 (Good Clinical Practice) and all applicable local regulations. All patients provided written informed consent before participation. This study was registered in the Japan Pharmaceutical Information Center Clinical Trials Information registry (JapicCTI-142,740) and ClinicalTrials.gov (NCT02275910).

2.3 | Safety assessments

Routine clinical and laboratory assessments were conducted at baseline, on days 8, 15, and 22 of cycle 1, and weekly during subsequent cycles. Other safety assessments included ophthalmological examinations and electrocardiography. Data on treatment-emergent AEs (TEAEs) were collected, coded using the Medical Dictionary for Regulatory Activities v22.1, and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.03.

2.4 | Efficacy assessments

Efficacy outcomes included best overall response (BOR), objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and percentage changes from baseline in diameters of target tumor lesions. BOR was classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease, and not evaluable (NE), with a requirement for SD to have been achieved at ≥7 weeks after the first dose. ORR was defined as the proportion of patients having a BOR of CR or PR. DCR was defined as the proportion of patients having a BOR of CR, PR, or SD. PFS was defined as the time from the date of the first dose to the first documented date of event (disease progression or death from any cause, whichever occurred first). OS was defined as the time from the date of the first dose to the date of death from any cause. Responses were assessed using RECIST v1.1 by investigators, and tumor evaluations were performed using computed tomography and/or magnetic resonance imaging.

2.5 | PK assessments

In Part 2, blood samples for evaluating pharmacokinetic profiles of Tasurgratinib were collected at predose, 0.5, 1, 2, 3, 5, 10, and 24 h after the first dose on cycle 1, day 1, and repeated doses on cycle 1, day 8. Predose blood samples were also collected on day 15 of cycle 1 and day 1 of all subsequent cycles in the expansion part. Plasma concentrations of Tasurgratinib were subsequently measured by liquid chromatography–tandem mass spectrometry as described in the report of Part 1.[21]

2.6 | Pharmacodynamics, PGx, and biomarker assessments

Pharmacodynamics and PGx analyses were performed on blood and stored tumor samples. Stored tumor sampling was optional for participants. Samples were analyzed using a PGDx elio tissue complete NGS assay panel (PGDx; Personal Genome Diagnostics, Inc.). Markers of FGFR pathway inhibition included serum phosphate, FGF23, and 1,25-$(OH)_2$-vitamin D. Blood samples for PGx analysis were collected at pretreatment, on each day 1 of odd-numbered cycles while on-treatment, and at the discontinuation visit, and used to measure circulating tumor DNA analysis with the PGDx elio plasma resolve NGS panel (PGDx; Personal Genome Diagnostics, Inc.). PGx analysis was performed only in patients in the cholangiocarcinoma group.

2.7 | Statistical analyses

All patients who received at least one dose of Tasurgratinib were included in the safety analysis. Patients who received at least one dose of Tasurgratinib and had a baseline and at least one postbaseline tumor assessment result were included in the efficacy analysis. Any patients who discontinued due to disease progression or death prior to the first postbaseline tumor assessment were excluded from the efficacy analysis set. Patients with one or more target lesions, as defined by RECIST v1.1, were included in the analysis of BOR. Descriptive statistics were used to analyze the demographic and other baseline characteristics. ORR, DCR, and their corresponding two-sided 95% confidence intervals (CI) were calculated. PFS and OS were also summarized. Using noncompartmental analysis, plasma concentrations of Tasurgratinib were analyzed to determine the PK parameters, including maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), and area under the plasma concentration–time curve (AUC).

3 | RESULTS

3.1 | Patients

A total of 16 patients (cholangiocarcinoma, $n=6$; gastric cancer, $n=10$) were enrolled and received Tasurgratinib once daily 140 mg in Part 2. Treatment was discontinued because of disease progression ($n=14$), nontreatment-related AEs ($n=1$), and the physician's judgment (indication for resection, $n=1$). Treatment exposure between the two groups is shown in Table S1. Baseline patient characteristics are shown in Table 1. Among the 16 patients, there were 12 men (75%) and four women (25%), and Eastern Cooperative Oncology Group performance status was equally split between 0 (50%) and 1 (50%). Six patients (37.5%) had received prior surgery and two (12.5%) had received prior radiotherapy. All patients received prior chemotherapy; one patient (16.7%) and no patient had received one regimen, three (50%) and one (10.0%) had received two regimens, one (16.7%) and one (10.0%) had received three regimens, and one (16.7%) and eight (80.0%) had received four or more regimens, with cholangiocarcinoma and gastric cancer, respectively. All patients in the cholangiocarcinoma group had *FGFR2* rearrangements identified with break-apart FISH. Two patients (20%) in the gastric cancer group had *FGFR2* amplification and eight patients (80%) had high expression of FGFR2 protein, respectively.

TABLE 1 Patient demographic and baseline characteristics.

	Cholangiocarcinoma ($N=6$)	Gastric cancer ($N=10$)
Age, years; mean (standard deviation)	53.7 (10.65)	67.5 (9.07)
Age, years; min, max	40, 65	55, 79
Sex, *n* (%)		
Male	5 (83.3)	7 (70.0)
Female	1 (16.7)	3 (30.0)
ECOG performance status, *n* (%)		
0	3 (50.0)	5 (50.0)
1	3 (50.0)	5 (50.0)
No. of prior regimens, *n* (%)		
1	1 (16.7)	0 (0.0)
2	3 (50.0)	1 (10.0)
3	1 (16.7)	1 (10.0)
≥4	1 (16.7)	8 (80.0)
Prior surgery, *n* (%)	3 (50.0)	3 (30.0)
Prior radiotherapy, *n* (%)	1 (16.7)	1 (10.0)
FGFR2 abnormality, *n* (%)		
Rearrangement	6 (100.00)	–
Amplification	–	2 (20.0)
Overexpression	–	8 (80.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor.

3.2 | Safety and tolerability

The most common any-grade TEAEs in ≥15% of the 16 evaluable patients were hyperphosphatemia (100%), palmar-plantar erythrodysesthesia (PPE) syndrome (62.5%), paronychia (56.3%), decreased appetite (43.8%), diarrhea (37.5%), dysgeusia (37.5%), stomatitis (37.5%), blood creatinine increased (31.3%), abdominal distension (25.0%), anemia (25.0%), AST increased (25.0%), ALT increased (18.8%), blood alkaline phosphatase increased (18.8%), constipation (18.8%), dry mouth (18.8%), dry skin (18.8%), hypoalbuminemia (18.8%), and pyrexia (18.8%). Eleven patients (68.8%) experienced a TEAE of grade ≥3. The most common any-grade treatment-related TEAE in ≥10% were hyperphosphatemia (100%), PPE syndrome (62.5%), paronychia (50.0%), stomatitis (37.5%), dysgeusia (31.3%), diarrhea (25.0%), blood creatinine increased (18.8%), AST increased (18.8%), dry mouth (18.8%), dry skin (18.8%), ALT increased (12.5%) decreased appetite (12.5%), malaise (12.5%), nail disorder (12.5%), and pruritus (12.5%). Two patients (12.5%) experienced grade ≥3 treatment-related TEAEs (AST increased, $n=1$; retinopathy, $n=1$; lipase increased, $n=1$; Table 2).

A total of 11 treatment-emergent serious AEs (SAEs) were reported in five patients (31.3%), but none were considered to be related to the study drug. The SAEs were one case each of ileus, pyrexia, cholangitis, acute cholecystitis, pneumonia, septic shock, decreased appetite, tumor obstruction, tumor pain, depressed level of consciousness, and thrombophlebitis migrans. There were no drug-related deaths. TEAEs leading to discontinuation of the study drug were reported in one patient (6.3%) with two TEAEs (cholecystitis acute and septic shock) that were not considered by the investigator to be related to Tasurgratinib treatment. Dose reductions due to treatment-related TEAEs were reported in six patients (37.5%) and were attributed to paronychia ($n=2$), PPE syndrome ($n=2$), decreased appetite ($n=1$), AST increased ($n=1$), and

TABLE 2 TEAEs occurring in ≥10% of the study population in Part 2.

	TEAEs ($N=16$)		TRAEs ($N=16$)	
AE, *n* (%) (MedDRA preferred term)	All grades	Grade ≥3	All grades	Grade ≥3
All AEs	16 (100.0)	11 (68.8)	16 (100.0)	2 (12.5)
Hyperphosphatemia	16 (100.0)	0 (0.0)	16 (100.0)	0 (0.0)
PPE syndrome	10 (62.5)	0 (0.0)	10 (62.5)	0 (0.0)
Paronychia	9 (56.3)	0 (0.0)	8 (50.0)	0 (0.0)
Decreased appetite	7 (43.8)	2 (12.5)	2 (12.5)	0 (0.0)
Diarrhea	6 (37.5)	1 (6.3)	4 (25.0)	0 (0.0)
Dysgeusia	6 (37.5)	0 (0.0)	5 (31.3)	0 (0.0)
Stomatitis	6 (37.5)	1 (6.3)	6 (37.5)	0 (0.0)
Blood creatinine increased	5 (31.3)	0 (0.0)	3 (18.8)	0 (0.0)
Abdominal distension	4 (25.0)	1 (6.3)	0 (0.0)	0 (0.0)
Anemia	4 (25.0)	2 (12.5)	1 (6.3)	0 (0.0)
AST increased	4 (25.0)	2 (12.5)	3 (18.8)	1 (6.3)
ALT increased	3 (18.8)	1 (6.3)	2 (12.5)	0 (0.0)
Blood alkaline phosphatase increased	3 (18.8)	2 (12.5)	1 (6.3)	0 (0.0)
Constipation	3 (18.8)	0 (0.0)	1 (6.3)	0 (0.0)
Dry mouth	3 (18.8)	0 (0.0)	3 (18.8)	0 (0.0)
Dry skin	3 (18.8)	0 (0.0)	3 (18.8)	0 (0.0)
Hypoalbuminemia	3 (18.8)	1 (6.3)	0 (0.0)	0 (0.0)
Pyrexia	3 (18.8)	0 (0.0)	1 (6.3)	0 (0.0)
Abdominal pain	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer pain	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Dry eye	2 (12.5)	0 (0.0)	1 (6.3)	0 (0.0)
Epistaxis	2 (12.5)	0 (0.0)	1 (6.3)	0 (0.0)
Headache	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)
Insomnia	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase increased	2 (12.5)	2 (12.5)	1 (6.3)	1 (6.3)
Malaise	2 (12.5)	0 (0.0)	2 (12.5)	0 (0.0)
Nail disorder	2 (12.5)	0 (0.0)	2 (12.5)	0 (0.0)
Nasopharyngitis	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	2 (12.5)	0 (0.0)	1 (6.3)	0 (0.0)
Pruritus	2 (12.5)	0 (0.0)	2 (12.5)	0 (0.0)
Tumor-associated fever	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor pain	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)
Vomiting	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)
Weight decreased	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities (v22.1); PPE, palmar-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event; TRAE, treatment-related TEAE.

stomatitis ($n=1$). Thirteen eye disorder events were reported in seven patients (43.8%), including dry eye ($n=2$, 12.5%) and events of macular edema, serous retinal detachment, subretinal fluid, retinal detachment, retinopathy, cataract, conjunctivitis allergic, corneal disorder, eyelid ptosis, keratitis, and periorbital edema ($n=1$ each, 6.3%). The majority of events were of grade 1 or 2 severity, except for one grade 3 event of retinopathy. No dose reductions or discontinuations were associated with any TEAEs coded as eye disorders; however, the case of grade 3 retinopathy led to dose interruption, with subsequent recovery of the event.

3.3 | Clinical efficacy

The antitumor activity of Tasurgratinib was evaluable in 15 patients (cholangiocarcinoma, $n=6$; gastric cancer, $n=9$) in Part 2; one patient

with gastric cancer who discontinued treatment at week 9 before the first tumor assessment was excluded from the denominator of ORR. The ORR was 83.3% (95% CI 35.9, 99.6) in cholangiocarcinoma patients and 11.1% (95% CI 0.3, 48.2) in evaluable gastric cancer patients. The efficacy data are summarized in Table 3.

Figure 1A shows the maximum percentage change from the baseline of sum of diameters of target lesions for the 15 assessed patients. Five of the six patients with cholangiocarcinoma achieved a reduction in tumor burden from baseline; all five tumor reductions met the criteria of partial response by RECIST 1.1. Among the four patients with gastric cancer who achieved a reduction in tumor burden from baseline, one had a reduction >30%. BOR by treatment duration and dose, as well as by the time of treatment discontinuation, is shown for each patient in Figure 1B. Two patients with cholangiocarcinoma maintained a PR even after dose reduction to 70 mg once daily. The median duration of treatment in cholangiocarcinoma and gastric cancer patients was 8.28 months (95% CI 3.88, 34.04) and 1.87 months (95% CI 0.92, 3.61), respectively. Among cholangiocarcinoma patients, the median duration of prior first-line chemotherapy was 3.25 months (95% CI 0.95, 7.43) (Figure S1). Median PFS was 8.26 months (95% CI 3.84, NE) in cholangiocarcinoma patients and 3.25 months (95% CI 0.95, 4.86) in gastric cancer patients. Median OS was 22.49 months (95% CI 6.37, NE) in cholangiocarcinoma patients and 4.27 months (95% CI:2.23, 7.95) in gastric cancer patients.

TABLE 3 Efficacy of Tasurgratinib presented as investigator-assessed tumor response.

	Cholangiocarcinoma (*N* = 6)	Gastric cancer (*N* = 9)
BOR, *n* (%)		
CR	0 (0.0)	0 (0.0)
PR	5 (83.3)	1 (11.1)
SD	1 (16.7)	4 (44.4)
PD, *n* (%)	0 (0.0)	4 (44.4)
ORR (CR + PR), *n* (%)	5 (83.3)	1 (11.1)
DCR (CR + PR + SD), *n* (%)	6 (100.0)	5 (55.6)
PFS (months), median (95% CI)	8.26 (3.84, NE)	3.25 (0.95, 4.86)
PFS rate, % (95% CI)		
At 6 months	66.7 (19.5, 90.4)	0.0 (NE, NE)
At 12 months	33.3 (4.6, 67.6)	0.0 (NE, NE)
OS (months), median (95% CI)	22.49 (6.37, NE)	4.27 (2.23, 7.95)
OS rate, % (95% CI)		
At 6 months	100.0 (100.0, 100.0)	22.2 (3.4, 51.3)
At 12 months	83.3 (27.3, 97.5)	11.1 (0.6, 38.8)

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

3.4 | PK outcomes

Table 4 shows the PK parameters of Tasurgratinib for each tumor type and all subjects of Part 2. C_{max} was achieved with median values of ~3 to 4 h after the first dose and at a steady state in patients with each tumor type. After the first dose, the mean C_{max} and AUC_{0-24h} of Tasurgratinib in patients with cholangiocarcinoma were approximately 0.3- to 0.5-fold lower than those in patients with gastric cancer (78.8 ng/mL and 770 ng·h/mL in patients with cholangiocarcinoma vs. 211 ng/mL and 1940 ng·h/mL in patients with gastric cancer). These differences in C_{max} and AUC between tumor types were similar at steady state. The mean plasma concentration profiles of Tasurgratinib over time at a steady state are shown in Figure S2.

3.5 | Pharmacodynamics, PGx, and biomarker outcomes

Figure 2 shows the relationship between AUC_{0-tau} at steady state and PD markers (1,25-$(OH)_2$-vitamin D, FGF23, and serum phosphate) with samples from Part 1 and Part 2. Spearman correlation coefficients (*R*) were 0.62, 0.62, and 0.61, respectively, each for the relationship of serum phosphate, FGF23, and 1,25-$(OH)_2$-vitamin D with AUC_{0-tau} at a steady state. All *P* values were <0.001. These results support positive correlations between AUC_{0-tau} at steady state and the evaluated PD markers.

Table 5 shows BOR and a summary of the *FGFR2* gene status of patients with cholangiocarcinoma before Tasurgratinib treatment. Fusion gene partners in *FGFR2* rearrangements were detected in baseline blood samples from three of the six patients and identified as *BICC1* (*n* = 2) and *SLMAP* (*n* = 1). Among six archival tumor tissue samples, one was of insufficient quality for inclusion in the NGS assay. Fusion gene partners in *FGFR2* rearrangements were identified in four of the five tumor tissues as *BICC1*, *CCDC6*, *POC1B*, and *SLMAP* (*n* = 1 each). A summary of gene alterations from archival tumor tissue samples is shown in Figure S3.

Figure 3A–C shows changes over time in the number of distinct mutant reads for *FGFR2* fusion gene in blood samples. In all three patients, mutant reads were decreased after the initiation of Tasurgratinib treatment and were increased slightly at the time of discontinuation. Figure 3D,E shows changes over time in the variant allele fraction (%) of *FGFR2* mutations detected in blood samples. FGFR2 mutations (L617F, M537I) were detected in blood from two patients at the discontinuation visit. Mutations other than FGFR2 are shown in Figure S4.

4 | DISCUSSION

This report from Part 2 of the first-in-human, phase I study demonstrated that Tasurgratinib 140 mg once daily is well tolerated with an acceptable safety profile. No treatment-related SAEs were observed, and treatment-related AEs ≥ grade 3 were reported in two

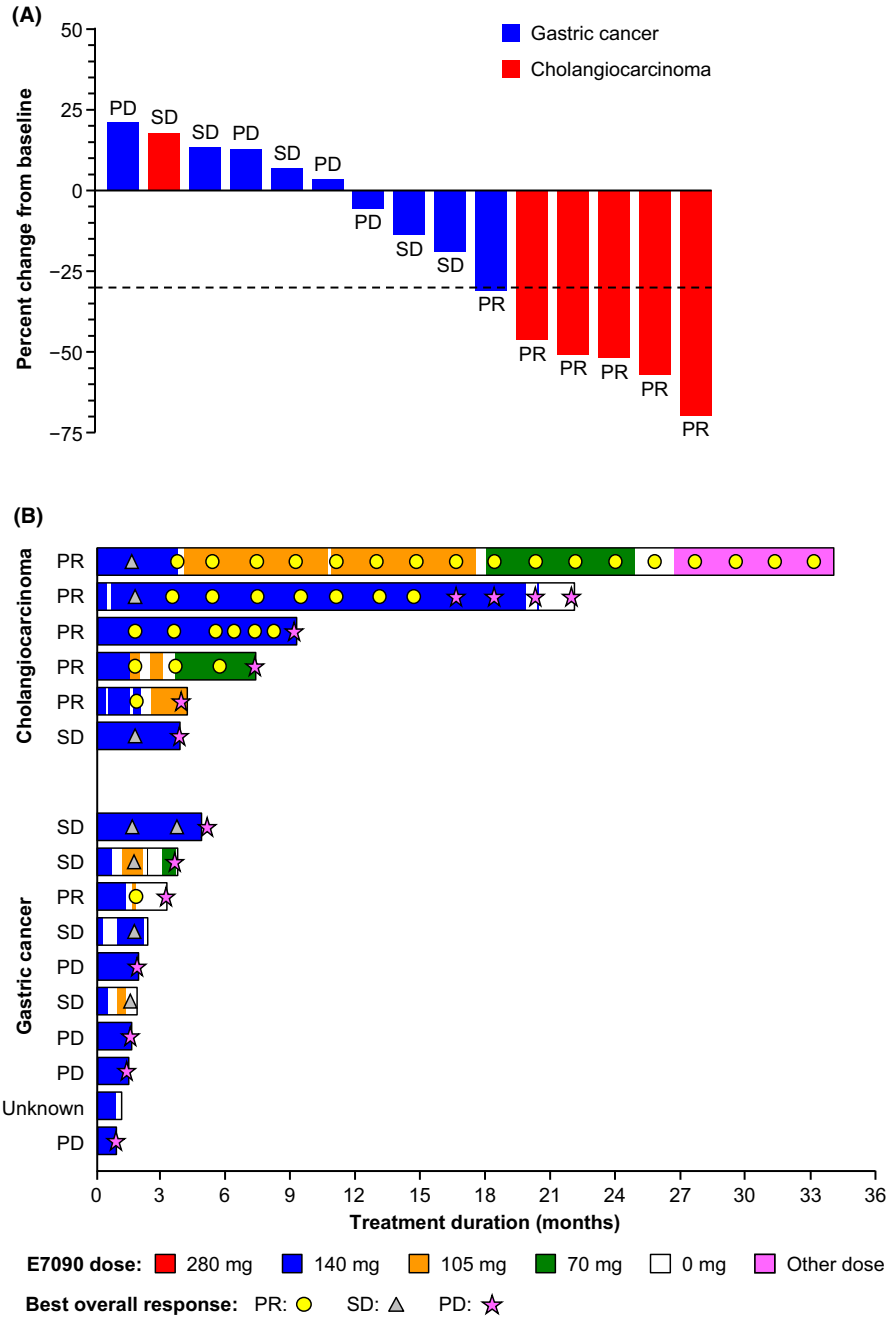

FIGURE 1 Efficacy of Tasurgratinib presented as (A) percentae change from baseline in the sum of diameter of the target lesion (dashed line represents a 30% reduction in tumor burden) and (B) a swimmer plot showing the duration of treatment, dosing history, and BOR. BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease.

of 16 patients (12.5%) receiving Tasurgratinib 140 mg once daily in Part 2. This dose was selected as the recommended dose for the expansion part based on the PK/PD data and because no AEs ≥grade 3 or dose-limiting toxicities were observed in Part 1 among patients receiving Tasurgratinib 140 mg once daily.[21] The AE profile observed in Part 2 was similar to that observed in Part 1 and is consistent with the known downstream effects of FGFR inhibition. The most common TEAEs of hyperphosphatemia, PPE syndrome and nail changes such as paronychia, have previously been reported among patients receiving FGFR inhibitor treatment.[22–25] Hyperphosphatemia, an established toxicity and a biomarker of FGFR inhibition, appears to be mediated by FGF23 signaling through FGFR1,[26] which is a target of Tasurgratinib. All hyperphosphatemia events were considered low severity (grade 1 or 2) and managed using a low phosphate diet or phosphate binders; as such, none of the events led to dose reductions or interruptions. As reported with other FGFR inhibitors,[18–20] ocular toxicities were observed in seven out of 16 patients in the present study; these may be attributable to interference in the maintenance of the outer retinal barrier and/or phagocytic/pump functions of the retinal pigment epithelium through FGFR inhibition and consequent downstream inhibition of the mitogen-activated protein kinase pathway.[27]

C_{max} and AUC_{0-24h} in patients with cholangiocarcinoma were 0.3- to 0.5-fold lower than in those with gastric cancer after the first dose and at a steady state. The differences in C_{max} and AUC between the tumor types may be due to the low solubility of Tasurgratinib in the gut of patients with cholangiocarcinoma because of bile stasis associated with cholangiocarcinoma. Bile acids have a role in enhancing

TABLE 4 PK parameters of Tasurgratinib in the expansion part.

Parameter	Gastric cancer $N=10$	Cholangiocarcinoma $N=6$	Total $N=16$
First dose (cycle 1, day 1)			
t_{max} (h)	2.96 (1.90–5.07)	3.97 (2.95–4.98)	3.01 (1.90–5.07)
C_{max} (ng/mL)	211 ± 111	78.8 ± 57.7	162 ± 113
AUC_{0-24h} (ng × h/mL)	1940 ± 1430	770 ± 512	1500 ± 1280
Steady state (cycle 1, day 8)			
t_{max} (h)	3.98 (2.95–9.62)	3.95 (2.92–9.52)	3.97 (2.92–9.62)
C_{max} (ng/mL)	294 ± 186	95.1 ± 66.2	219 ± 179
AUC_{0-tau} (ng × h/mL)	4270 ± 3730	1110 ± 660	3080 ± 3320

Note: Data are shown as mean ± standard deviation, except for t_{max}, where the median (range) is shown.

Abbreviations: AUC_{0-24h}, area under the plasma concentration–time curve from 0 to 24 h; AUC_{0-tau}, area under the plasma concentration–time curve over the dosing interval (once daily); C_{max}, maximum observed concentration; PK, pharmacokinetic; t_{max}, time at which the highest drug concentration occurs.

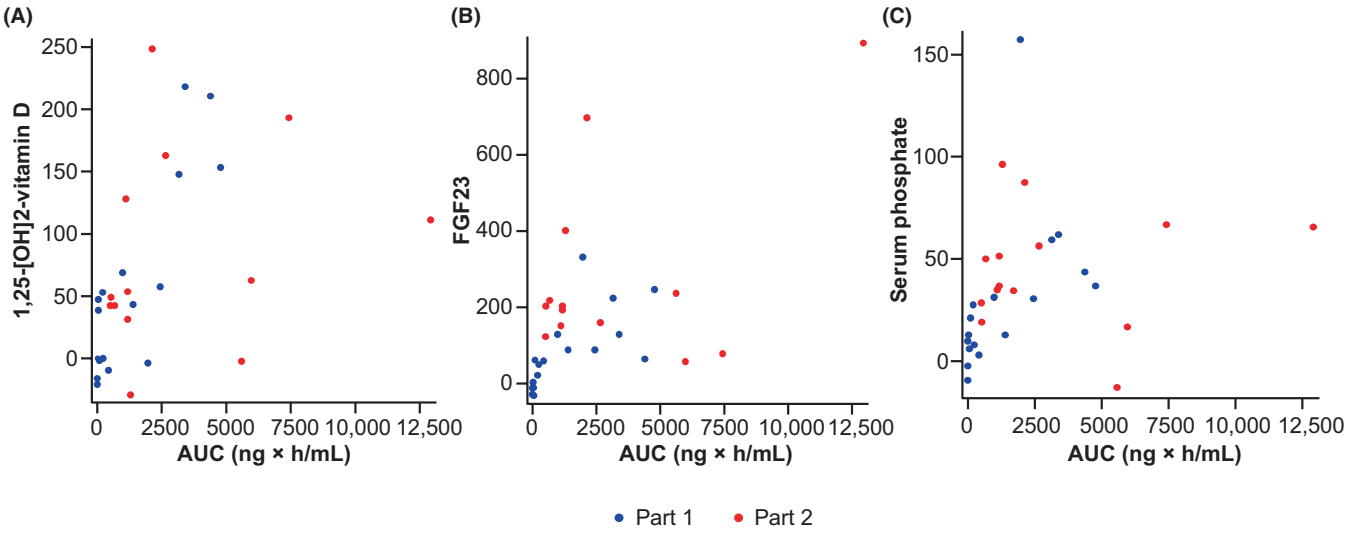

FIGURE 2 AUC correlation with (A) 1,25-$(OH)_2$-vitamin D, (B) FGF23, and (C) serum phosphate. For 1,25-$(OH)_2$-vitamin D ($n=30$), Spearman correlation coefficients (R) = 0.61609, $p=0.0003$. For FGF23 ($n=30$), $R=0.62499$, $p=0.0002$. For serum phosphate ($n=32$), $R=0.60931$, $p=0.0002$. AUC, area under the plasma concentration–time curve; FGF23, fibroblast growth factor 23.

drug absorption by acting as drug solubilizing and permeation-modifying agents[28]; therefore, bile stasis in cholangiocarcinoma may lead to a decrease in the absorption of drugs. However, although exposure of Tasurgratinib was lower in patients with cholangiocarcinoma than patients with gastric cancer, Tasurgratinib appeared to have greater antitumor activity in patients with cholangiocarcinoma; moreover, there were no prominent safety issues in patients with cholangiocarcinoma.

Although the sample size is limited, five PRs in six subjects (83.3%, 95% CI 35.9, 99.6), median PFS (8.26 months, 95% CI 3.84, NE), and median OS (22.49 months, 95% CI 6.37, NE) reported for Tasurgratinib as a second-line or later chemotherapy in patients with cholangiocarcinoma appear to be particularly promising. In addition, conversion surgery was conducted in a subject with PR. Currently, patients with intrahepatic cholangiocarcinoma have a poor prognosis[29]; surgery is potentially curative, but recurrence is common, and patients have few other treatment options.[30] Although direct comparisons are not possible due to differences in patient selection and study design, Tasurgratinib as a second-line or later therapy compared favorably to the use of first-line standard chemotherapy combination treatment with gemcitabine and cisplatin in patients with cholangiocarcinoma (ORR, 26%; median PFS, 8.0 months; median OS, 11.7 months).[31] Additionally, the median duration of treatment of 8.28 months with Tasurgratinib as a second-line or later therapy in this study was favorable compared to the duration of treatment (3.25 months) of first-line therapy observed in cholangiocarcinoma patients enrolled in this study. Other FGFR inhibitors (pemigatinib and futibatinib, respectively)[18,19] have demonstrated favorable clinical efficacy (ORR 35.5% and 42%, median PFS 6.9 and 9.0 months, median OS 21.1 and 21.7 months) in cholangiocarcinoma patients. In the current study, an ORR of 83% (95% CI 35.9, 99.6) with Tasurgratinib treatment was numerically higher than these FGFR inhibitors; however, the CI was wide due to the small number of evaluable patients. Overall, based on the notable clinical efficacy

TABLE 5 Summary of genetic analysis.

Patient no.	FISH (% of rearrangement-positive cells)	*FGFR2* gene fusion status in archival tissue	*FGFR2* gene fusion status in baseline blood samples	BOR (change in peak tumor diameter)
1	90	ND	*FGFR2-BICC1*	PR (−57%)
2	89	*FGFR2-POC1B*	ND	PR (−52%)
3	15	QC failed	ND	PR (−62%)
4	87	*FGFR2-CCDC6*	ND	PR (−46%)
5	69	*FGFR2-BICC1*	*FGFR2-BICC1*	PR (−51%)
6	87	*FGFR2-SLMAP*	*FGFR2-SLMAP*	SD (+18%)

Abbreviations: BOR, best overall response; FGFR, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; ND, not determined; PR, partial response; QC, quality control; SD, stable disease.

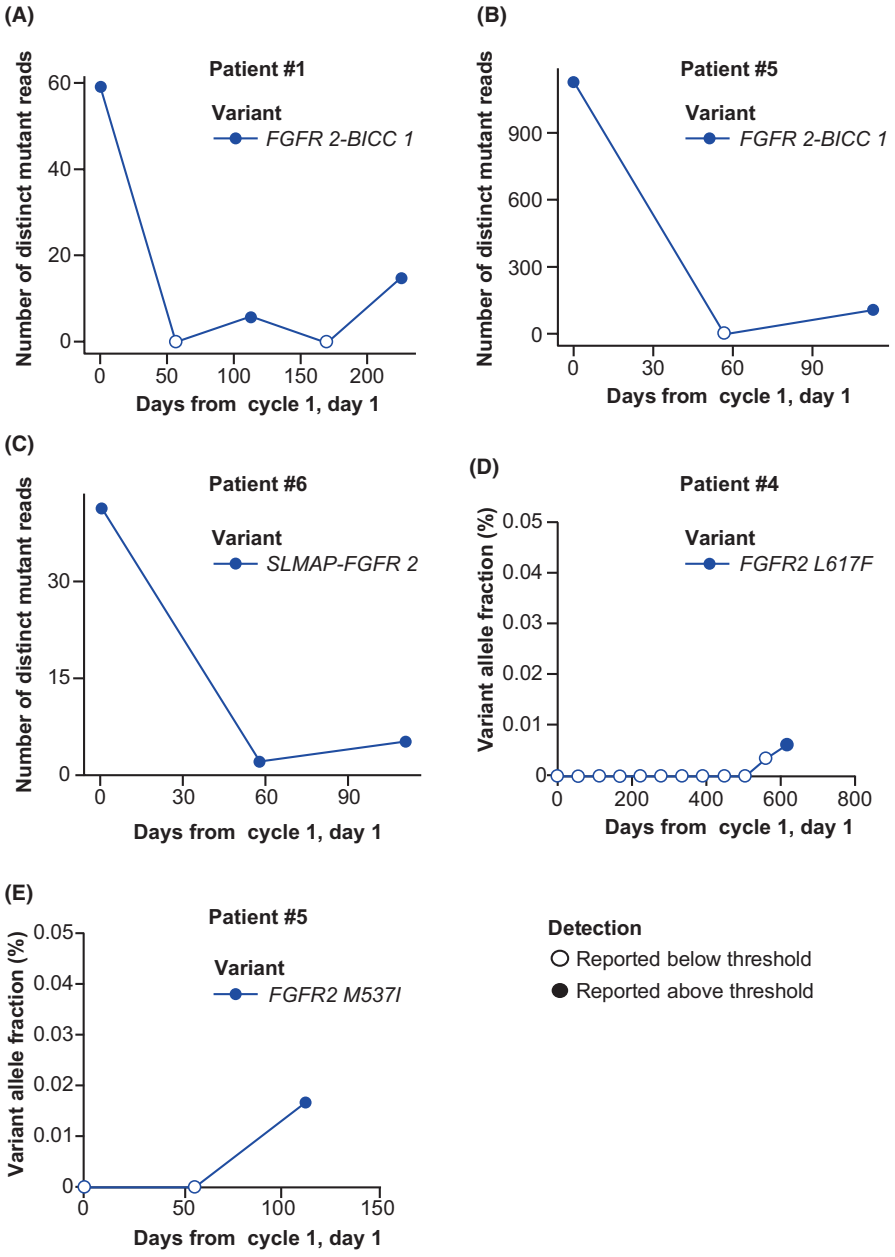

FIGURE 3 Circulating tumor DNA genetic analysis for fusions in patient #1 (A), patient #5 (B), and patient #6 (C), and for *FGFR2* mutations in patient #4 (D) and patient #5 (E). Baseline samples were collected within 4 days before cycle 1, day 1.

observed with FGFR inhibitors, *FGFR2* gene fusions or other rearrangements in cholangiocarcinoma patients are considered to be driver genes.

In this study of patients with gastric cancer who received Tasurgratinib as third-line or later chemotherapy, antitumor activity was similar to that observed with other therapies[32]; specifically, in this

study, ORR was 11.1%, median PFS was 3.25 months, and median OS was 4.27 months. Considering that no significant differences in dose intensity (mg/day) were observed between patients with gastric cancer or cholangiocarcinoma, and that C_{max} and AUC_{0-24h} were higher in patients with gastric cancer than in those with cholangiocarcinoma, FGFR inhibition in patients with gastric cancer might be comparable in patients with cholangiocarcinoma. However, gastric cancer is characterized by a high incidence of intratumoral heterogeneity.[33] The frequency of heavily treated patients (80.0%), who had received four or more regimens, in this study was high compared with the frequency in the clinical trial for other therapies (22.8%).[32] As such, further investigation is required to enhance the efficacy of FGFR inhibition in gastric cancer patients.

As observed with other FGFR inhibitors,[19,34] fusion partners of *FGFR2* were detected in five of six cholangiocarcinoma patients by NGS assay of tumor tissue samples ($n=4$) or blood samples ($n=3$). Of these detected by blood samples, two patients whose mutant reads of *FGFR2* gene fusion were decreased markedly below the threshold after initiation of Tasurgratinib treatment experienced PRs, and another patient whose mutant reads were not reduced below the threshold had a BOR of SD. The one remaining cholangiocarcinoma patient, in whom fusion partners were not detected, experienced a PR with the highest tumor shrinkage rate (−62%). It was previously reported that *FGFR2* rearrangement, including 3′-UTR-truncated *FGFR2*, induced higher RNA expression in patients found to be FISH positive but without *FGFR2* gene fusions. Thus, during patient screening in future studies, we need to consider that not only *FGFR2* gene fusions but also *FGFR2* rearrangements may be oncogenic drivers and appropriate targets for FGFR inhibitors in patients with cholangiocarcinoma. During Tasurgratinib administration, in blood samples obtained from two patients at the discontinuation visit, FGFR2 mutations (L617F, M537I) similar to the acquired resistance mutations reported with other FGFR inhibitors were detected.[35,36] The relationship between efficacy and genetic analysis results should be investigated in a larger patient cohort in a phase II clinical trial. Because harboring *FGFR2* gene mutations, including *FGFR2* fusions and the *FGFR2* rearrangements, were detected by FISH in all six cholangiocarcinoma patients, FISH testing will be useful for patient screening in future studies.

In summary, the overall data from this first-in-human phase I study support a manageable safety profile and favorable preliminary antitumor activity of Tasurgratinib, particularly in patients with cholangiocarcinoma harboring *FGFR2* gene rearrangements. Tasurgratinib 140 mg once daily was confirmed as the recommended dose for subsequent phase II evaluation. The present study had some limitations, including the small sample size and inclusion of a Japanese-only population. A global phase II study (NCT04238715) is ongoing in this specific patient population to confirm the efficacy and the safety of Tasurgratinib.

AUTHOR CONTRIBUTIONS

Chigusa Morizane: Investigation; writing – original draft; writing – review and editing. **Makoto Ueno:** Investigation; writing – review and editing. **Tatsuya Ioka:** Investigation; writing – review and editing. **Masahiro Tajika:** Investigation; writing – review and editing. **Masafumi Ikeda:** Investigation; writing – review and editing. **Kensei Yamaguchi:** Investigation; writing – review and editing. **Hiroki Hara:** Investigation; writing – review and editing. **Hiroshi Yabusaki:** Investigation; writing – review and editing. **Atsushi Miyamoto:** Investigation; writing – review and editing. **Satoru Iwasa:** Investigation; writing – review and editing. **Manabu Muto:** Investigation; writing – review and editing. **Tsutomu Takashima:** Investigation; writing – review and editing. **Keiko Minashi:** Investigation; writing – review and editing. **Yoshito Komatsu:** Investigation; writing – review and editing. **Tomohiro Nishina:** Investigation; writing – review and editing. **Takako Eguchi Nakajima:** Investigation; writing – review and editing. **Atsuchi Takeno:** Investigation; writing – review and editing. **Toshikazu Moriwaki:** Investigation; writing – review and editing. **Masayuki Furukawa:** Investigation; writing – review and editing. **Takatoshi Sahara:** Conceptualization; writing – original draft; writing – review and editing. **Hiroki Ikezawa:** Formal analysis; writing – review and editing. **Maiko Nomoto:** Methodology; writing – review and editing. **Shuya Takashima:** Formal analysis; writing – review and editing. **Taisuke Uehara:** Methodology; writing – review and editing. **Setsuo Funasaka:** Conceptualization; writing – review and editing. **Masakazu Yashiro:** Investigation; writing – review and editing. **Junji Furuse:** Investigation; supervision; writing – review and editing.

AFFILIATIONS

[1]National Cancer Center Hospital, Tokyo, Japan
[2]Kanagawa Cancer Center, Yokohama, Japan
[3]Oncology Center, Yamaguchi University Hospital, Ube, Japan
[4]Aichi Cancer Center Hospital, Nagoya, Japan
[5]National Cancer Center Hospital East, Kashiwa, Japan
[6]The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan
[7]Saitama Cancer Center, Saitama, Japan
[8]Niigata Cancer Center Hospital, Niigata, Japan
[9]National Hospital Organization Osaka National Hospital, Osaka, Japan
[10]Kyoto University Hospital, Kyoto, Japan
[11]Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan
[12]Chiba Cancer Center, Chiba, Japan
[13]Hokkaido University Hospital, Sapporo, Japan
[14]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan
[15]St. Marianna University School of Medicine, Kawasaki, Japan
[16]Department of Early Clinical Development, Kyoto University Graduate School of Medicine, Kyoto, Japan
[17]Kansai Rosai Hospital, Amagasaki, Japan
[18]University of Tsukuba Hospital, Tsukuba, Japan
[19]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan
[20]Eisai Co., Ltd., Tokyo, Japan

ACKNOWLEDGMENTS

The authors thank the investigators and site staff who participated in the expansion part (Part 2).

FUNDING INFORMATION

This study was funded by Eisai Co., Ltd., Tokyo, Japan.

CONFLICT OF INTEREST STATEMENT

C. Morizane received personal fees from Astra Zeneca, Taiho Pharmaceutical, and Nihon Servier and research funds from

Eisai, Yakult, Ono Pharmaceutical, Taiho Pharmaceutical, J-Pharma, AstraZeneca, Merck Biopharma, Daiichi Sankyo, and Boehringer Ingelheim. M. Ueno received personal fees from Taiho Pharmaceutical, AstraZeneca, K.K, Yakult Honsha, Nihon Servier, Incyte Biosciences Japan GK, and Chugai Pharmaceutical, and research funds from Taiho Pharmaceutical, AstraZeneca, MSD K.K, Nihon Servier, Ono Pharmaceutical, Incyte Biosciences Japan Company, Chugai Pharmaceutical, Boehringer Ingelheim GmbH, J-Pharma, Eisai, Novartis Pharma K.K, Astellas Pharma Inc., DFP (Delta Fly Pharma), Novocure GmbH, and Chiome Bioscience. T. Ioka received personal fees from Taiho and Astra Zeneca. M. Ikeda received fees from AstraZeneca, Chugai Pharma, Eisai, Incyte, Lilly Japan, MSD, Novartis, Ono Pharmaceutical, Takeda, Teijin Pharma, Nihon Servier, Taiho Pharmaceutical; research funds from Astra Zeneca, Bayer, Bristol-Myers Squibb, Chiome Bioscience, Chugai, Eisai, Eli Lilly Japan, Delta-Fly Pharma, Invitae, J-Pharma, Merck Biopharma, Merus N.V., MSD, Novartis, Nihon Servier, Ono Pharmaceutical, Syneos Health, and Rakuten Medical, and is an editorial board member of *Cancer Science*. T. Takashima received personal fees from Eisai. K. Minashi received research funds from Astellas, Taiho Pharma., Amgen, Daiichi-Sankyo Pharma., MSD, and PPD-SNBL K.K. Y. Komatsu received fees from Taiho Pharmaceutical, Daiichi Sankyo, MSD, Chugai Pharmaceutical, Ono Pharmaceutical, and Takeda Pharmaceutical, grants from Taiho Pharmaceutical, Chugai Pharmaceutical, and Nippon Kayaku, and research funds from National Cancer Center Japan and Aichi Cancer Center. T. Nishina received fees from Ono Pharmaceutical. T. Nakajima received research funds from KBBM and Takeda Pharmaceutical. M. Furukawa received researched funds from Merck Biopharma, MSD, Ono Pharma, J-Pharma, Taiho Pharmaceutical, Incyte Japan, and Astellas Pharma. T. Sahara, H. Ikezawa, M. Nomoto, S. Takashima, T. Uehara, and S. Funasaka are all employees of Eisai. J. Furuse received fees from Ono Pharma, Chugai Pharma, Incyte Biosciences Japan, Fuji Film, Eisai, Eli Lilly, Astra Zeneca, and Yakult, grants from Eisai and Taiho Pharmaceutical, and research funds from MSD, J-Pharma, and Delta-Fly Pharma. M. Tajika, K. Yamaguchi, H. Hara, H. Yabusaki, A. Miyamoto, S. Iwasa, M. Muto, A. Takeno, T. Moriwaki, and M. Yashiro have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data for this study will not be shared in a publicly available repository.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Review Board: The study protocol was approved by the institutional review board or independent ethics committee of each participating institution, and the study was conducted in accordance with ICH-E6 (Good Clinical Practice) and all applicable local regulations.

Informed Consent: All patients provided written informed consent before participation.

Registry and the Registration No. of the study/trial: This study was registered in the Japan Pharmaceutical Information Center Clinical Trials Information registry (JapicCTI-142,740) and ClinicalTrials.gov (NCT02275910).

Animal Studies: N/A.

ORCID

Masafumi Ikeda https://orcid.org/0000-0002-4050-2086
Satoru Iwasa https://orcid.org/0000-0003-3863-9582
Manabu Muto https://orcid.org/0000-0002-3127-8203
Yoshito Komatsu https://orcid.org/0000-0002-1570-6802
Masakazu Yashiro https://orcid.org/0000-0001-5743-7228

REFERENCES

1. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer*. 2017;17:318-332.
2. Wesche J, Haglund K, Haugsten EM. Fibroblast growth factors and their receptors in cancer. *Biochem J*. 2011;437:199-213.
3. Helsten T, Schwaederle M, Kurzrock R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications. *Cancer Metastasis Rev*. 2015;34:479-496.
4. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer*. 2010;10:116-129.
5. Courjal F, Cuny M, Simony-Lafontaine J, et al. Mapping of DNA amplifications at 15 chromosomal localizations in 1875 breast tumors: definition of phenotypic groups. *Cancer Res*. 1997;57:4360-4367.
6. Weiss J, Sos ML, Seidel D, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. *Sci Transl Med*. 2010;2:62ra93.
7. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513:202-209.
8. Zhang J, Tang PMK, Zhou Y, et al. Targeting the oncogenic FGF-FGFR axis in gastric carcinogenesis. *Cells*. 2019;8:8.
9. Borad MJ, Gores GJ, Roberts LR. Fibroblast growth factor receptor 2 fusions as a target for treating cholangiocarcinoma. *Curr Opin Gastroenterol*. 2015;31:264-268.
10. Ross JS, Wang K, Gay L, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. *Oncologist*. 2014;19:235-242.
11. International Agency for Research on Cancer, World Health Organization. Globocan factsheets 2018: World cancer statistics. https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf 2020.
12. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: epidemiology and risk factors. *Liver Int*. 2019;39(Suppl 1):19-31.
13. Matsumoto K, Arao T, Hamaguchi T, et al. FGFR2 gene amplification and clinicopathological features in gastric cancer. *Br J Cancer*. 2012;106:727-732.
14. Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology*. 2014;59:1427-1434.
15. Ahn S, Lee J, Hong M, et al. FGFR2 in gastric cancer: protein overexpression predicts gene amplification and high H-index predicts poor survival. *Mod Pathol*. 2016;29:1095-1103.
16. Chae YK, Ranganath K, Hammerman PS, et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. *Oncotarget*. 2017;8:16052-16074.
17. Brooks AN, Kilgour E, Smith PD. Molecular pathways: fibroblast growth factor signaling: a new therapeutic opportunity in cancer. *Clin Cancer Res*. 2012;18:1855-1862.
18. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic

cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21:671-684.
19. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. *N Engl J Med*. 2023;388(3):228-239.
20. Watanabe Miyano S, Yamamoto Y, Kodama K, et al. E7090, a novel selective inhibitor of fibroblast growth factor receptors, displays potent antitumor activity and prolongs survival in preclinical models. *Mol Cancer Ther*. 2016;15:2630-2639.
21. Koyama T, Shimizu T, Iwasa S, et al. First-in-human phase I study of E7090, a novel selective fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. *Cancer Sci*. 2020;111:571-579.
22. Javle M, Lowery M, Shroff RT, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol*. 2018;36:276-282.
23. Nogova L, Sequist LV, Perez Garcia JM, et al. Evaluation of BGJ398, a fibroblast growth factor receptor 1-3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. *J Clin Oncol*. 2017;35:157-165.
24. Saka H, Kitagawa C, Kogure Y, et al. Safety, tolerability and pharmacokinetics of the fibroblast growth factor receptor inhibitor AZD4547 in Japanese patients with advanced solid tumours: a phase I study. *Investig New Drugs*. 2017;35:451-462.
25. Voss MH, Hierro C, Heist RS, et al. A phase I, open-label, multicenter, dose-escalation study of the oral selective FGFR inhibitor Debio 1347 in patients with advanced solid tumors harboring FGFR gene alterations. *Clin Cancer Res*. 2019;25:2699-2707.
26. Cheng CY, Kuro-o M, Razzaque MS. Molecular regulation of phosphate metabolism by fibroblast growth factor-23-klotho system. *Adv Chronic Kidney Dis*. 2011;18:91-97.
27. Nti AA, Serrano LW, Sandhu HS, et al. Frequent subclinical macular changes in combined BRAF/MEK inhibition with high-dose hydroxychloroquine as treatment for advanced metastatic BRAF mutant melanoma: preliminary results from a phase I/II clinical treatment trial. *Retina*. 2019;39:502-513.
28. Pavlović N, Goločorbin-Kon S, Danić M, et al. Bile acids and their derivatives as potential modifiers of drug release and pharmacokinetic profiles. *Front Pharmacol*. 2018;9:1283.
29. Blechacz B. Cholangiocarcinoma: current knowledge and new developments. *Gut Liver*. 2017;11:13-26.
30. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Hepatobiliary cancers. v5.2020. 2020 https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
31. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362:1273-1281.
32. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19:1437-1448.
33. Hierro C, Alsina M, Sanchez M, Serra V, Rodon J, Tabernero J. Targeting the fibroblast growth factor receptor 2 in gastric cancer: promise or pitfall? *Ann Oncol*. 2017;28:1207-1216.
34. Hollebecque A, Silverman I, Owens S, et al. Comprehensive genomic profiling and clinical outcomes in patients (pts) with fibroblast growth factor receptor rearrangement-positive (FGFR2+) cholangiocarcinoma (CCA) treated with pemigatinib in the FIGHT-202 trial (poster 720). *Ann Oncol*. 2019;30(suppl_5):v276.
35. Goyal L, Saha SK, Liu LY, et al. Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma. *Cancer Discov*. 2017;7:252-263.
36. Goyal L, Shi L, Liu LY, et al. TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. *Cancer Discov*. 2019;9:1064-1079.

SUPPORTING INFORMATION

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

How to cite this article: Morizane C, Ueno M, Ioka T, et al. Tasurgratinib in patients with cholangiocarcinoma or gastric cancer: Expansion part of the first-in-human phase I study. *Cancer Sci*. 2025;116:192-203. doi:10.1111/cas.16354