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Title:
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Date:
2020-10-01

Citation:
Bahleda, R., Meric-Bernstam, F., Goyal, L., Tran, B., He, Y., Yamamiya, I., Benhadji, K. A., Matos, I. & Arkenau, H. T. (2020). Phase I, first-in-human study of futibatinib, a highly selective, irreversible FGFR1–4 inhibitor in patients with advanced solid tumors. Annals of Oncology, 31 (10), pp.1405-1412. https://doi.org/10.1016/j.annonc.2020.06.018.

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ORIGINAL ARTICLE

Phase I, first-in-human study of futibatinib, a highly selective, irreversible FGFR1—4 inhibitor in patients with advanced solid tumors

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Available online 2 July 2020

Background: Futibatinib is an oral, irreversible, highly selective fibroblast growth factor receptor (FGFR)1—4 inhibitor with potent preclinical activity against tumors harboring *FGFR* aberrations. This first-in-human, phase I dose-escalation trial (NCT02052778) evaluates the safety and pharmacokinetics/pharmacodynamics of futibatinib in advanced solid tumors.

Patients and methods: Following a standard 3+3 dose-escalation design, eligible patients with advanced solid tumors refractory to standard therapies received 8—200 mg futibatinib three times a week (t.i.w.) or 4—24 mg once daily (q.d.).

Results: A total of 86 patients were enrolled in the nine t.i.w. ($n = 42$) and five q.d. cohorts ($n = 44$); 71 patients (83%) had tumors harboring *FGF/FGFR* aberrations. Three of nine patients in the 24-mg q.d. cohort experienced dose-limiting toxicities, including grade 3 increases in alanine transaminase, aspartate transaminase, and blood bilirubin ($n = 1$ each). The maximum tolerated dose (MTD) was determined to be 20 mg q.d.; no MTD was defined for the t.i.w. schedule. Across cohorts ($n = 86$), the most common treatment-emergent adverse events (TEAEs) were hyperphosphatemia (59%), diarrhea (37%), and constipation (34%); 48% experienced grade 3 TEAEs. TEAEs led to dose interruptions, dose reductions, and treatment discontinuations in 55%, 14%, and 3% of patients, respectively. Pharmacokinetics were dose proportional across all q.d. doses but not all t.i.w. doses evaluated, with saturation observed between 80 and 200 mg t.i.w. Serum phosphorus increased dose dependently with futibatinib on both schedules, but a stronger exposure—response relationship was observed with q.d. dosing, supporting 20 mg q.d. as the recommended phase II dose (RP2D). Overall, partial responses were observed in five patients [*FGFR2* fusion-positive intrahepatic cholangiocarcinoma ($n = 3$) and *FGFR1*-mutant primary brain tumor ($n = 2$)], and stable disease in 41 (48%).

Conclusions: Futibatinib treatment resulted in manageable safety, pharmacodynamic activity, and preliminary responses in patients with advanced solid tumors. The results of this phase I dose-escalation trial support 20 mg q.d. futibatinib as the RP2D.

Clinical trial registration: FOENIX-101 (ClinicalTrials.gov, NCT02052778).

Key words: FGFR inhibitor, futibatinib, pharmacokinetics, safety, TAS-120

INTRODUCTION

Aberrant fibroblast growth factor receptor (FGFR) signaling is associated with oncogenesis,[1] and genomic aberrations (amplifications, translocations, fusions, and activating point mutations) of *FGFR1—4* are found across several tumor types.[2]

FGFR has been shown to be a valid target in FGFR-deregulated cancers, with several FGFR inhibitors under clinical investigation.[3—7] Although promising activity and tolerability have been reported, most FGFR inhibitors in development are reversible ATP-competitive inhibitors,[3—7] and drug resistance is emerging as a major challenge with such inhibitors.[8—10] Newer, more potent FGFR inhibitors with less susceptibility to drug resistance are needed.

Futibatinib (TAS-120), a structurally novel, irreversible, highly selective FGFR1—4 inhibitor, inhibits all four FGFR subtypes at nearly equal subnanomolar concentrations *in vitro* and has exhibited potent antiproliferative activity in a number of FGFR-deregulated cell lines and xenograft models.[11] Futibatinib forms a rapid covalent adduct with a

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cysteine in the P-loop of the kinase domain and captures multiple FGFR P-loop conformations, unlike reversible ATP-competitive inhibitors.[12] In cell line experiments, futibatinib inhibited FGFR mutants resistant to ATP-competitive inhibitors with nearly the same potency as wild-type FGFR, and fewer drug-resistant clones emerged with prolonged futibatinib treatment than with ATP-competitive inhibitor treatment.[13]

Here we report results from the dose-escalation portion of a first-in-human phase I study of futibatinib in patients with advanced solid tumors. The objective was to investigate the safety, pharmacokinetics (PK), and preliminary activity of futibatinib to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D).

PATIENTS AND METHODS

Study design, patients, and treatment

This open-label, multicenter, phase I study (NCT02052778) enrolled patients with histologically/cytologically confirmed advanced metastatic solid tumors with any number of prior therapies. Enrollment was planned to be restricted to patients with *FGF/FGFR* aberrations (screened locally) from dose level 5 of both dosing schedules [56 mg three times a week (t.i.w.); 36 mg once daily (q.d.)]. An intermediate 20-mg q.d. dose cohort enrolling patients with tumors harboring *FGF/FGFR* aberrations was added per a protocol amendment dated 15 May 2017. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate alanine aminotransferase (ALT) and aspartate aminotransferase [AST; $\leq 3\times$ upper limit of normal (ULN); $\leq 5\times$ ULN if liver metastases were present], and adequate total bilirubin ($\leq 1.5\times$ ULN). Patients with evidence of endocrine alteration of calcium—phosphorus homeostasis, ectopic mineralization, or corneal disorder/keratopathy were excluded (see supplementary Methods, available at *Annals of Oncology* online, for additional screening/eligibility criteria).

The primary objective of the dose-escalation portion was to investigate the safety and tolerability of futibatinib administered on a t.i.w. (Monday, Wednesday, and Friday) dosing schedule or a continuous q.d. dosing schedule to determine MTD and RP2D. Secondary objectives included assessment of clinical PK, pharmacodynamics (PD), and preliminary antitumor activity of futibatinib. RP2D was based on the MTD and the safety, PK, PD, and preliminary efficacy data.

Dose escalation followed a 3+3 design in which three to six patients were enrolled into 8-, 16-, 24-, 36-, 56-, 80-, 120-, 160-, and 200-mg cohorts on a t.i.w. dosing schedule and 4-, 8-, 16-, 20-, and 24-mg cohorts on a q.d. dosing schedule. Escalation to the next level occurred if initially enrolled patients did not experience a dose-limiting toxicity (DLT; supplementary Methods, available at *Annals of Oncology* online). Dose escalation was initiated at t.i.w. dose level 1 (8 mg), and when t.i.w. dose escalation reached dose level 5 (56 mg), enrollment was initiated in the q.d. cohorts (supplementary Figure S1, available at *Annals of Oncology* online). Futibatinib was administered on an empty stomach (in 21-day treatment cycles) until disease progression [clinical or per Response Evaluation Criteria of Solid Tumors version 1.1 (RECIST v1.1)], unacceptable toxicity, or withdrawal of consent.

This trial was approved by the institutional review boards of participating centers and was conducted according to Good Clinical Practice principles and in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Assessments

Safety was monitored from first study drug dose until 30 days after the last dose (or initiation of another anticancer therapy). Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. A DLT was defined as one or more of the following drug-related toxicities occurring during cycle 1: grade ≥ 3 nonhematologic toxicity (excluding diarrhea/nausea/vomiting); grade ≥ 3 diarrhea or nausea/vomiting lasting >48 h; grade 4 neutropenia or thrombocytopenia, febrile neutropenia, hyperphosphatemia (defined as serum phosphorus of >7 mg/dl for >7 days, >9 mg/dl for 14 days despite phosphorus-lowering therapies, or >10 mg/dl), creatinine increase ($>1.5\times$ ULN for 7 days); grade 2 hypercalcemia for >7 days; ectopic *de novo* calcification in soft tissues; or any grade >2 treatment-related AE preventing completion of cycle 1 or initiation of cycle 2 (beyond a 21-day delay). Serum phosphorus was assessed at screening, on day 1 (predose), and on days 8 and 15 of cycles 1 and 2. Serum phosphorus continued to be monitored on day 8 of each subsequent cycle, if clinically indicated or if previous assessments showed serum phosphorus elevations. Hyperphosphatemia was managed with dose modifications, phosphate binders, and diet modifications. Dose-reduction and discontinuation criteria are detailed in supplementary Methods, available at *Annals of Oncology* online.

Tumor assessments were performed up to 28 days prior to cycle 1 initiation, at the end of cycles 2 and 4, and every 3 cycles thereafter. Tumor response was assessed according to RECIST v1.1.

Blood samples for PK and PD measurements were collected on day 1 and the last Wednesday of cycle 1 of the t.i.w. dosing schedule and on days 1 and 21 of the q.d. dosing schedule at the following time points: 0 h (predose) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h postdose on both schedules, as well as at 48 h on the t.i.w. schedule.

For PK assessments, futibatinib was measured in plasma and urine by validated liquid chromatography with tandem mass spectrometry (supplementary Methods, available at *Annals of Oncology* online). Serum phosphorus and FGF23 were assessed as PD markers.

Statistical considerations

The safety and efficacy analysis included all patients who received ≥ 1 dose of study drug. Patients who experienced a

DLT during cycle 1 or completed cycle 1 having received ≥80% of the planned study drug dose were considered DLT evaluable. Descriptive analyses were provided for efficacy end points.

Plasma PK parameters were calculated by standard non-compartmental methods using Phoenix WinNonlin Professional (version 6.3 or later; Certara, Princeton, NJ). Dose proportionality of futibatinib was assessed by power regression analyses.[14] PD analyses involved assessing the relationship between increases in serum phosphorus levels and futibatinib dose or systemic exposure (see supplementary Methods, available at *Annals of Oncology* online).

RESULTS

Patient demographics and disposition

Between 21 July 2014 and 29 August 2017, 86 patients were enrolled into nine t.i.w. ($n = 42$) and five q.d. dosing cohorts ($n = 44$; supplementary Figure S1, available at *Annals of Oncology* online). In the overall patient population ($n = 86$), the most common cancer types were cholangiocarcinoma [CCA; 24 patients (28%)], breast cancer [12 (14%)], colorectal cancer [12 (14%)], brain tumors [7 (8%)], and urothelial cancer [4 (5%); Table 1]; 50 patients (58%) had received ≥3 prior regimens. *FGF/FGFR* aberration status was available for 74 patients (86%), and 71 (83%) had tumors harboring ≥1 *FGF/FGFR* aberration (supplementary Table S1, available at *Annals of Oncology* online). The most common aberrations were *FGFR1* amplifications ($n = 15$) and *FGFR2* fusions ($n = 15$). At the time of data cut-off (12 July 2019), all patients in the dose-escalation cohorts had discontinued treatment, most [77 (90%)] because of disease progression.

Table 1. Baseline demographics and disease characteristics

	Combined t.i.w. cohorts ($n = 42$)	Combined q.d. cohorts ($n = 44$)	Overall population ($N = 86$)
Age, y			
Mean (SD)	58.6 (12.6)	54.3 (14.1)	56.4 (13.5)
Sex, *n* (%)			
Male	19 (45)	15 (34)	34 (40)
Female	23 (55)	29 (66)	52 (60)
Race, *n* (%)			
White	31 (74)	28 (64)	59 (69)
Black	1 (2)	1 (2)	2 (2)
Asian	0 (0)	3 (7)	3 (3)
Other	1 (2)	1 (2)	2 (2)
Missing/unknown	9 (21)	11 (25)	20 (23)
ECOG PS, *n* (%)			
0	10 (24)	16 (36)	26 (30)
≥1	32 (76)	28 (64)	60 (70)
Cancer type, *n* (%)			
Cholangiocarcinoma	7 (17)	17 (39)	24 (28)
Intrahepatic	6 (14)	16 (36)	22 (26)
Extrahepatic	1 (2)	1 (2)	2 (2)
Breast	7 (17)	5 (11)	12 (14)
Colorectal	7 (17)	5 (11)	12 (14)
Brain	3 (7)	4 (9)	7 (8)
Urothelial	2 (5)	2 (5)	4 (5)
Other solid tumors[a]	16 (38)	11 (25)	27 (31)
Head and neck	3 (7)	0 (0)	3 (3)
Esophageal	2 (5)	1 (2)	3 (3)
Cervical	0 (0)	2 (5)	2 (2)
Gastric	1 (2)	1 (2)	2 (2)
NSCLC	2 (5)	0 (0)	2 (2)
Sarcoma	1 (2)	1 (2)	2 (2)
Skin	1 (2)	1 (2)	2 (2)
Number of prior regimens, *n* (%)[b]			
1	5 (12)	13 (30)	18 (21)
2	8 (19)	9 (20)	17 (20)
3	11 (26)	5 (11)	16 (19)
≥4	17 (40)	17 (39)	34 (40)

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non—small cell lung cancer; q.d., once daily; SD, standard deviation; t.i.w., 3 times a week.
[a] In the overall population, there was one patient each with appendix cancer, endometrial cancer, gallbladder cancer, mesothelioma, neuroendocrine tumor, neuroblastoma, ovarian cancer, prostate cancer, and renal cell carcinoma; there were two patients with adenocarcinoma of unknown primary site.
[b] One patient in the combined t.i.w. cohorts did not receive prior anticancer therapy.

Safety

The median duration of treatment was 49 (range, 8—359) and 68 days (range, 1—735) in the combined t.i.w. cohorts and q.d. cohorts, respectively, with a median of 2 (range, 0—15) and 2.5 treatment cycles (range, 0—35) completed.

One DLT [treatment-related grade 4 increased blood creatine phosphokinase (CPK)] was reported among six evaluable patients in the 8-mg t.i.w. cohort. However, no DLTs were reported in other t.i.w. cohorts including at the highest t.i.w. dose tested (200 mg); therefore, MTD was not defined for the t.i.w. schedule. Dose was not escalated beyond 200 mg on the t.i.w. schedule, because PK analyses showed saturation of futibatinib exposure beyond 80 mg. No DLTs were observed at 4, 8, 16, or 20 mg q.d. futibatinib, but of nine DLT-evaluable patients in the 24-mg q.d. cohort, three patients [with CCA ($n = 2$) and neuroendocrine tumor in liver ($n = 1$)] experienced DLTs [grade 3 elevations of ALT, AST, and blood bilirubin ($n = 1$, each)]. Therefore, dose escalation was halted in the q.d. cohorts, and 20 mg q.d. was defined as the MTD.

In the overall population, 41 patients (48%) experienced grade 3 treatment-emergent AEs (TEAEs), most frequently hyperphosphatemia (12%), hyponatremia (7%), and anemia (6%); 26 (30%) experienced treatment-related grade 3 AEs (Table 2). Five patients (6%) had grade 4 TEAEs [one patient each with increased lipase and increased CPK (t.i.w. cohorts); one patient each with increased gamma glutamyl transferase, increased CPK, and bile duct obstruction (q.d. cohorts)]; both cases of increased CPK were considered treatment related.

Hyperphosphatemia, an on-target effect of futibatinib via FGFR1 inhibition, was the most common TEAE, occurring in 21 of 42 patients [50%; grade 3: 3 (7%)] in the combined t.i.w. cohorts and 30 of 44 patients [68%; grade 3: 7 (16%)] in the combined q.d. cohorts. Hyperphosphatemia led to dosing interruptions in 15 patients (17%) and dose reductions in five (6%).

Other frequent any-grade TEAEs in the overall population included diarrhea (37%), constipation (34%), dry mouth (29%), nausea (29%), and anemia (26%). Six patients (7%) experienced palmar plantar erythrodysesthesia syndrome (all grade 1/2 events). Most nail toxicities [nail changes

Table 2. Treatment-emergent adverse events

	Combined t.i.w. cohorts (n = 42)[a] n (%)					Combined q.d. cohorts (n = 44)[b] n (%)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Any TEAE	42 (100)	3 (7)	14 (33)	20 (48)	2 (5)	44 (100)	5 (11)	11 (25)	21 (48)	3 (7)
Any treatment-related AE	37 (88)	12 (29)	14 (33)	10 (24)	1 (2)	41 (93)	13 (30)	11 (25)	16 (36)	1 (2)
Action taken because of TEAE										
Dosing delay/interruption	21 (50)	0 (0)	6 (14)	14 (33)	1 (2)	26 (59)	1 (2)	9 (20)	16 (36)	0 (0)
Dose reduction	4 (10)	0 (0)	3 (7)	1 (2)	0 (0)	8 (18)	0 (0)	1 (2)	6 (14)	1 (2)
Treatment discontinuation	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	2 (5)	0 (0)	1 (2)	1 (2)	0 (0)
TEAEs in ≥10% of patients[c]										
Hyperphosphatemia	21 (50)	7 (17)	11 (26)	3 (7)	0 (0)	30 (68)	13 (30)	10 (23)	7 (16)	0 (0)
Constipation	11 (26)	10 (24)	1 (2)	0 (0)	0 (0)	18 (41)	13 (30)	4 (9)	1 (2)	0 (0)
Diarrhea	17 (40)	12 (29)	5 (12)	0 (0)	0 (0)	15 (34)	9 (20)	5 (11)	1 (2)	0 (0)
Nausea	12 (29)	11 (26)	0 (0)	1 (2)	0 (0)	13 (30)	8 (18)	3 (7)	2 (5)	0 (0)
ALT increased	5 (12)	3 (7)	1 (2)	1 (2)	0 (0)	11 (25)	4 (9)	4 (9)	3 (7)	0 (0)
AST increased	4 (10)	1 (2)	3 (7)	0 (0)	0 (0)	11 (25)	4 (9)	5 (11)	2 (5)	0 (0)
Dry mouth	14 (33)	13 (31)	1 (2)	0 (0)	0 (0)	11 (25)	10 (23)	1 (2)	0 (0)	0 (0)
Vomiting	9 (21)	5 (12)	3 (7)	1 (2)	0 (0)	11 (25)	6 (14)	3 (7)	2 (5)	0 (0)
Anemia	13 (31)	2 (5)	8 (19)	3 (7)	0 (0)	9 (20)	1 (2)	6 (14)	2 (5)	0 (0)
Asthenia	9 (21)	5 (12)	4 (10)	0 (0)	0 (0)	9 (20)	3 (7)	6 (14)	0 (0)	0 (0)
Stomatitis	5 (12)	2 (5)	1 (2)	2 (5)	0 (0)	9 (20)	6 (14)	2 (5)	1 (2)	0 (0)
Decreased appetite	9 (21)	5 (12)	3 (7)	1 (2)	0 (0)	7 (16)	5 (11)	2 (5)	0 (0)	0 (0)
Fatigue	7 (17)	2 (5)	5 (12)	0 (0)	0 (0)	7 (16)	3 (7)	3 (7)	1 (2)	0 (0)
Abdominal pain	8 (19)	4 (10)	2 (5)	2 (5)	0 (0)	6 (14)	1 (2)	4 (9)	1 (2)	0 (0)
Alopecia	4 (10)	4 (10)	0 (0)	0 (0)	0 (0)	6 (14)	6 (14)	0 (0)	0 (0)	0 (0)
Dry skin	7 (17)	6 (14)	1 (2)	0 (0)	0 (0)	6 (14)	6 (14)	0 (0)	0 (0)	0 (0)
Back pain	3 (7)	2 (5)	1 (2)	0 (0)	0 (0)	5 (11)	3 (7)	2 (5)	0 (0)	0 (0)
Cough	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)	5 (11)	5 (11)	0 (0)	0 (0)	0 (0)
Dry eye	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)	5 (11)	4 (9)	1 (2)	0 (0)	0 (0)
Pyrexia	5 (12)	4 (10)	0 (0)	1 (2)	0 (0)	5 (11)	3 (7)	1 (2)	1 (2)	0 (0)
Hypomagnesemia	5 (12)	4 (10)	1 (2)	0 (0)	0 (0)	3 (7)	3 (7)	0 (0)	0 (0)	0 (0)
Headache	7 (17)	6 (14)	1 (2)	0 (0)	0 (0)	2 (5)	0 (0)	1 (2)	1 (2)	0 (0)
Hyponatremia	5 (12)	1 (2)	0 (0)	4 (10)	0 (0)	2 (5)	0 (0)	0 (0)	2 (5)	0 (0)
Onycholysis	5 (12)	4 (10)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Rash	5 (12)	5 (12)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Hypercalcemia	5 (12)	1 (2)	1 (2)	3 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract infection	5 (12)	0 (0)	4 (10)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; q.d., once daily; TEAE, treatment-emergent adverse event; t.i.w., 3 times a week.
[a] Three patients had grade 5 events [hematemesis (n = 1), disease progression (n = 1), and respiratory distress (n = 1)], none of which were reported to be treatment related.
[b] Four patients had grade 5 events [disease progression (n = 3) and respiratory failure (n = 1)], none of which were reported to be treatment related.
[c] By decreasing order in the combined q.d. cohorts.

(17%) and nail infection (7%)] or ocular toxicity [vision disorders (10%), dry eye (9%), and corneal/retinal disorders (3%)] were grade 1/2 in severity. Overall, TEAEs were managed with dosing interruptions [in 47 patients (55%)] and dose reductions [12 (14%)]. One patient in the 24-mg cohort discontinued treatment owing to treatment-related nausea and vomiting. Unrelated AEs leading to treatment discontinuation were grade 3 spinal cord compression (n = 1; 24-mg q.d. cohort) and grade 3 hemiparesis (n = 1; 120-mg t.i.w. cohort).

No treatment-related deaths were reported. Seven deaths that occurred (within 30 days of drug administration) were related to disease progression [disease progression (n = 4), hematemesis (n = 1), respiratory distress (n = 1), and respiratory failure (n=1)].

Pharmacokinetics

In the t.i.w. dosing cohorts, the area under the concentration—time curve (AUC) and the maximum plasma concentration of futibatinib (C_{max}) increased with dose from 8 to 80 mg; however, mean PK parameters in the 120-, 160-, and 200-mg cohorts were similar to those in the 80-mg cohort (Table 3). An analysis with a power regression model suggested that C_{max} increased in less than a dose-proportional manner in the 8—200-mg dose range (supplementary Table S2 and Figure S2A—C, available at *Annals of Oncology* online). However, in the q.d. dosing cohorts, C_{max} and AUC increased with dose across all doses tested (Table 3), and both parameters were observed to be statistically dose proportional between 4 and 24 mg q.d. (supplementary Table S2 and Figure S2D—F, available at *Annals of Oncology* online). On both schedules, no significant accumulation was observed with repeated doses (Table 3), and mean plasma concentrations were comparable at predose and postdose on the last dosing day of cycle 1, indicating a steady state by cycle 1 end (supplementary Figure S3, available at *Annals of Oncology* online). On days 1 and 21, C_{max} values for the MTD (20 mg q.d.) were 256.70 and 170.58 ng/ml, respectively (reached 1.9 and 3.5 h after dose administration); on both days, plasma concentrations decreased with a mean half-life of ≈3 h (Table 3). Urinary excretion of futibatinib was lower than 0.01% of the dose.

Table 3. Descriptive PK parameters of futibatinib in the t.i.w. and q.d. dosing cohorts during cycle 1

Dose level	Day 1						Last Wednesday (t.i.w.) or Day 21 (q.d.)					
	Statistic[a]	T_{max} (h)	$T_{1/2}$ (h)	C_{max} (ng/ml)	AUC_{0-last} (ng·h/ml)	AUC_{0-inf} (ng·h/ml)	T_{max} (h)	$T_{1/2}$ (h)	C_{max} (ng/ml)	AUC_{0-last} (ng·h/ml)	R_{Cmax}	R_{AUC}
8 mg t.i.w.	*n*	6	6	6	6	6	4	4	4	4	4	4
	Mean	1.04	2.08	85.54	304.22	314.71	1.48	2.01	105.50	471.68	1.43	1.53
	SD	(1.00—4.05)	0.90	46.34	217.59	217.45	(0.60—2.08)	1.26	35.94	329.37	0.82	0.911
16 mg t.i.w.	*n*	3	3	3	3	3	3	3	3	3	3	3
	Mean	1.00	2.11	206.60	736.13	743.71	1.00	2.75	213.46	1047.97	1.00	1.35
	SD	(1.00—2.00)	1.12	41.32	504.26	508.41	(1.00—1.92)	1.89	99.79	958.08	0.26	0.45
24 mg t.i.w.	*n*	3	2	3	3	2	3	2	3	3	3	3
	Mean	3.00	3.52	257.94	1791.54	2204.22	1.05	5.99	360.82	2206.22	1.26	1.09
	SD	(1.00—3.98)	NC	87.86	686.01	NC	(1.00—2.33)	NC	246.06	1544.77	0.64	0.56
36 mg t.i.w.	*n*	3	3	3	3	3	2	2	2	2	2	2
	Mean	2.00	4.84	556.11	2673.12	2678.16	2.56	6.57	735.91	4490.81	1.81	2.72
	SD	(1.00—2.00)	2.25	419.09	2074.83	2076.27	(2.05—3.08)	NC	NC	NC	NC	NC
56 mg t.i.w.	*n*	3	3	3	3	3	3	3	3	3	3	3
	Mean	3.08	5.97	695.30	3291.27	3297.87	2.00	6.24	929.75	4579.39	1.34	1.66
	SD	(2.27—4.08)	2.20	440.01	1827.04	1826.57	(2.00—3.08)	2.80	597.45	1595.43	0.72	1.07
80 mg t.i.w.	*n*	4	3	4	4	3	5	5	5	5	4	4
	Mean	2.50	4.77	964.22	7472.25	9557.05	3.00	5.28	756.96	6772.54	1.15	1.27
	SD	(1.50—5.82)	1.69	575.42	5566.05	4978.57	(2.00—4.00)	1.15	246.27	3128.50	1.05	1.09
120 mg t.i.w.	*n*	4	3	4	4	3	3	3	3	3	3	3
	Mean	3.04	6.18	712.99	6635.74	5313.53	3.17	10.62	909.67	10 641.51	1.12	1.22
	SD	(2.05—3.95)	1.02	168.70	2993.76	938.91	(3.00—6.08)	8.69	645.05	10 684.25	0.68	0.79
160 mg t.i.w.	*n*	8	6	8	8	6	3	3	3	2	3	2
	Mean	2.52	8.75	819.22	7983.30	10 012.85	5.57	3.99	862.83	9135.52	0.95	0.70
	SD	(2.00—4.50)	3.28	363.18	6866.19	6940.93	(2.00—8.00)	1.88	296.09	NC	0.22	NC
200 mg t.i.w.	*n*	7	6	7	7	6	1	0	1	1	1	1
	Mean	2.00	9.55	1291.87	10 083.94	11 725.92	—	—	845.09	5780.39	0.83	0.68
	SD	(2.00—4.50)	5.72	918.52	9019.26	9022.04	—	—	NC	NC	NC	NC
4 mg q.d.	*n*	4	4	4	4	4	3	3	3	3	3	3
	Mean	0.96	1.75	33.10	114.08	116.96	1.08	1.63	52.47	134.17	2.07	2.06
	SD	(0.50—2.02)	0.51	20.38	85.89	87.00	(1.00—3.00)	0.75	38.13	100.47	0.33	0.72
8 mg q.d.	*n*	5	4	5	5	4	5	5	5	5	5	5
	Mean	2.00	2.26	168.89	666.07	523.74	2.00	2.75	98.16	550.41	1.32	1.37
	SD	(1.00—25.50)	0.78	149.75	504.84	421.23	(1.00—3.08)	0.59	56.52	442.30	1.53	1.12
16 mg q.d.	*n*	14	14	14	14	14	9	9	9	9	9	9
	Mean	2.00	2.73	148.35	536.16	549.25	2.07	2.53	171.67	736.73	1.24	1.65
	SD	(1.00—3.00)	1.76	67.04	283.78	290.38	(0.93—3.07)	1.13	72.65	373.30	0.61	0.67
20 mg q.d.	*n*	7	6	7	7	6	2	2	2	2	2	2
	Mean	1.92	2.94	256.70	1189.00	1301.45	3.52	3.44	170.58	1179.48	0.73	1.17
	SD	(1.00—3.00)	0.78	70.07	647.98	654.98	(3.05—3.98)	NC	NC	NC	NC	NC
24 mg q.d.	*n*	14	13	14	14	13	3	2	3	3	3	3
	Mean	1.98	3.13	245.76	1217.25	1270.29	2.00	3.12	193.56	1415.66	0.92	1.51
	SD	(0.98—3.08)	0.94	112.73	656.03	668.46	(1.98—6.07)	NC	112.37	903.24	0.31	0.86

AUC_{0-last}, area under the concentration—time curve from time 0 to the last observable concentration; AUC_{0-inf}, area under the concentration—time curve from time 0 to infinite time; C_{max}, maximum plasma concentration; NC, not calculable; PK, pharmacokinetics; q.d., once daily; SD, standard deviation; R_{AUC}, accumulation ratio calculated based on AUC_{0-last}; R_{Cmax}, accumulation ratio calculated based on C_{max}; SD, standard deviation; $T_{1/2}$, terminal half-life time; T_{max}, time to maximum plasma concentration; t.i.w.., 3 times a week.

[a] Mean and SD are displayed for all parameters except T_{max}, for which the median (minimum—maximum) is presented.

Pharmacodynamics

Because FGFRs play an important role in phosphorus homeostasis through renal FGF23-mediated signaling,[15] serum phosphorus was selected as a PD biomarker for FGFR inhibition and for assessing dose—response correlations with futibatinib. Serum phosphorus increased with repeated futibatinib doses on both schedules. Across t.i.w. and q.d. cohorts, the average phosphorus concentration (C_{avg}) correlated positively with futibatinib dose (supplementary Figure S4A, available at *Annals of Oncology* online) and exposure (AUC_{0-inf}) (supplementary Figure S4B, available at *Annals of Oncology* online). However, the correlation between serum phosphorus levels and dose/exposure was stronger in the q.d. than in the t.i.w. cohorts, as indicated by the steeper slopes of the q.d. regression lines. Serum FGF23 levels initially decreased with futibatinib dosing, reached minimum levels 8—24 h postdose, and then increased to baseline or higher levels at 24—48 h postdose. Repeated doses resulted in increased FGF23 levels, which showed a trend of dose dependency with t.i.w. and q.d. dosing.

Antitumor activity

Across cohorts, five patients experienced a best overall response of confirmed partial response (PR), and 41 (21 with t.i.w. and 20 with q.d. dosing) experienced stable disease (SD; Figure 1). Most patients with PRs or SD had tumors harboring *FGF/FGFR* aberrations; in several patients,

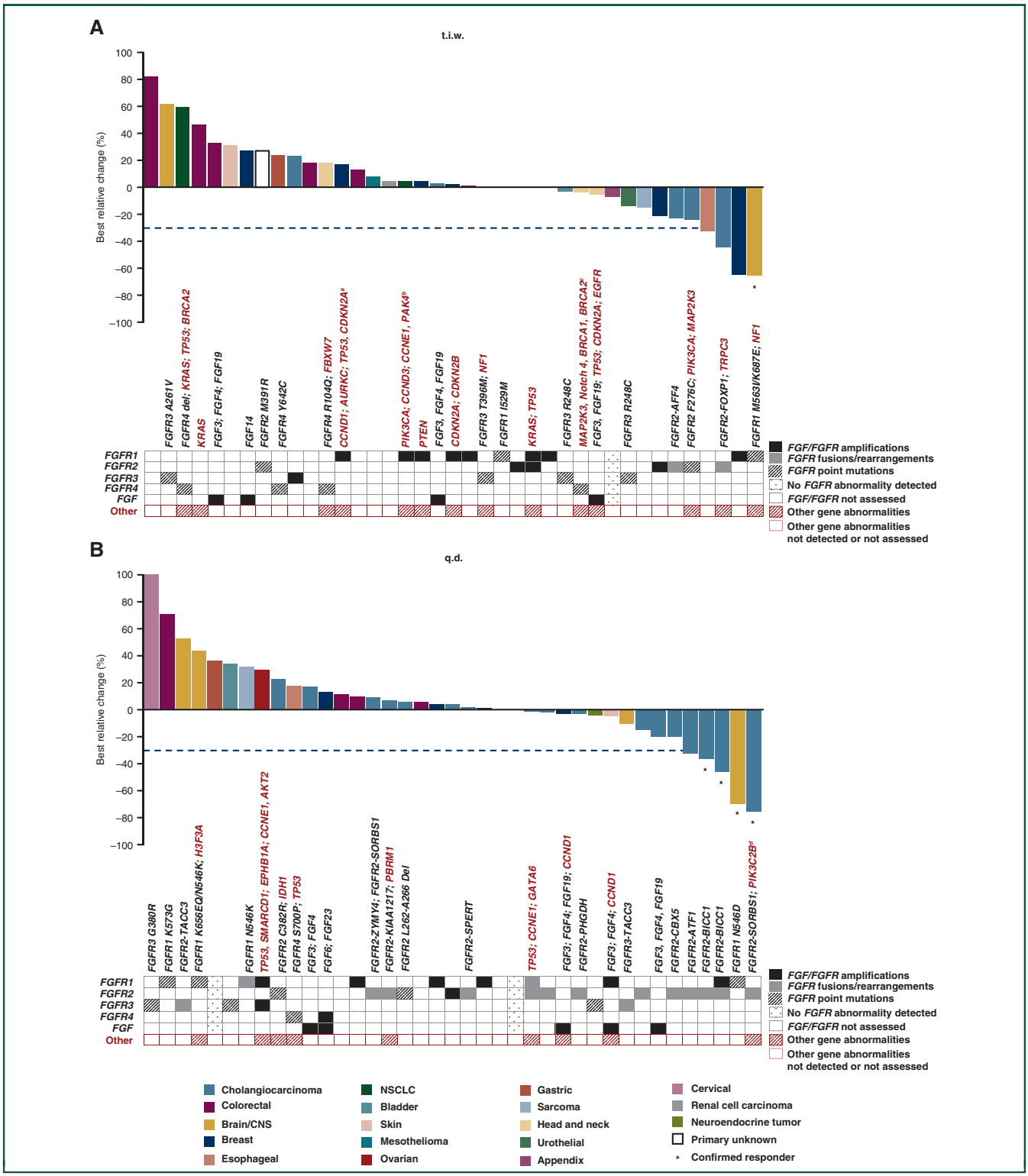

Figure 1. Best percentage change in target lesions from baseline by patient in the (A) t.i.w. cohorts and (B) the q.d. cohorts.
Types of *FGF* or *FGFR* abnormalities detected in pretreatment biopsies are indicated in the grids underneath the plots. Any available genetic characterization of *FGFR* abnormalities (black type) or unrelated gene abnormalities (burgundy type) is provided above the grid. Asterisks indicate confirmed partial responses. [a]Patient had abnormalities in ∼30 genes in addition to those indicated. Patients had, in addition to those indicated, abnormalities in the following genes: [b]*AKT2*, *TGFB1*, and *HDAC8*; [c]*MAP3K1* and *MLL3*; and [d]*MDM4*, *IKBE*, and *BAP1*. CNS, central nervous system; FGFR, fibroblast growth factor receptor; NSCLC, non—small cell lung cancer.

other genetic abnormalities were also detected. Confirmed PRs were observed in three patients with intrahepatic CCA (iCCA) harboring *FGFR2—SORBS1* or *FGFR2—BICC1* fusions ($n = 2$, 16-mg q.d. cohort; $n = 1$, 24-mg q.d. cohort), one patient with glioblastoma (*FGFR1* N546D mutation; 16-mg q.d. cohort), and one patient with anaplastic oligodendroglioma (*FGFR1* M563I/K687E mutation; 160-mg t.i.w. cohort; supplementary Table S3, available at *Annals of*

Oncology online). Four of five responses occurred within 3 months of initiating futibatinib, and responses lasted >6 months in three patients, and >12 months in two patients. One responder with iCCA had experienced disease progression on prior infigratinib (BGJ398), and was subsequently treated with futibatinib for 15.6 months. As much as 18 of 24 patients (75%) with CCA experienced PR or SD.

DISCUSSION

Futibatinib, an irreversible, highly selective FGFR1—4 inhibitor, has demonstrated potent antitumor activity against FGFR-deregulated tumors in preclinical studies; both once-daily and intermittent dosing schedules resulted in antitumor activity in animal models.[11,16] This first-in-human dose-escalation study evaluated futibatinib administered on t.i.w. and q.d. dosing schedules in patients with advanced solid tumors. Three DLTs, all related to liver enzyme elevations, were observed at the highest dose tested (24 mg) on the q.d. schedule; therefore, 20 mg q.d. was defined as the MTD. RP2D dose selection was also based on PK/PD data. Although MTD was not defined for the t.i.w. schedule, saturation of PK parameters was observed at higher doses, because of which dose escalation was halted. PD analyses showed a steeper dose—response correlation with q.d. dosing.

Futibatinib demonstrated a tolerable safety profile: although >50% of patients experienced grade ≥3 TEAEs, toxicities were managed with dosing adjustments, and treatment discontinuations were rare. Hyperphosphatemia, an expected on-target effect of FGFR1 inhibition, was more frequent with q.d. (68%) than with t.i.w. dosing (50%), which correlated with the stronger exposure—response relationship observed with the q.d. dosing schedule. Overall, futibatinib safety was consistent across dosing schedules; frequencies of diarrhea, constipation, dry mouth, nausea, and anemia were lower with q.d. dosing or were similar between the two schedules. The toxicity profile of futibatinib, an irreversible inhibitor, was consistent with that of reversible FGFR inhibitors such as infigratinib and erdafitinib,[3—7] although the incidence of grade 3 hyperphosphatemia was slightly higher than that observed with erdafitinib in urothelial carcinoma.[4] However, less than one-third of all hyperphosphatemia events with futibatinib were grade 3 in severity and were managed by sevelamer, decreasing dietary phosphorus intake, and dosing adjustments; no treatment discontinuations occurred due to hyperphosphatemia. This result indicated that the clinical impact of this AE was limited.

Greater dose proportionality and a stronger exposure—response relationship supported the choice of the q.d. dosing regimen for further investigation. Linear PK was observed with q.d. but not t.i.w. dosing. Serum phosphorus increases correlated with increasing doses and exposure on both the q.d. and t.i.w. schedules, but this effect was greater in the q.d. than in the t.i.w. cohorts. As phosphorus elevation is a PD marker of FGFR inhibition,[15] these results suggested a greater potential treatment effect with q.d. dosing.

Encouraging preliminary activity was observed with futibatinib in this heavily pretreated patient population: nearly half of all patients experienced SD, and confirmed PRs were observed in three patients with iCCA with *FGFR2* fusions, including one patient who had received prior FGFR inhibitors and two patients with *FGFR1*-mutant primary brain tumors; many patients with tumor shrinkage had comutations in addition to *FGF/FGFR* aberrations. Responses were rapid (mostly occurring within 3 months) and lasted for >12 months in two of five responders, indicating durable clinical benefit. Four of five PRs occurred in the 16- and 24-mg q.d. cohorts. The antitumor activity of futibatinib was particularly pronounced in patients with iCCA, a difficult-to-treat tumor type with poor prognosis and no standard treatment options for inoperable, refractory advanced disease.[17]

In summary, this phase I dose-escalation trial demonstrated tolerability, PD activity, and preliminary antitumor activity of futibatinib in heavily pretreated patients with advanced solid tumors. Safety and PK data supported 20 mg futibatinib q.d. as the RP2D. On the basis of these results, futibatinib has been evaluated in the phase I dose-expansion portion of this study in multiple tumor types (recently completed) and in a phase II registrational trial (NCT02052778) in iCCA with *FGFR2* fusions/rearrangements. The phase II trial has completed recruitment, and results of interim analyses are expected in 2020. In addition, recruitment is ongoing in other phase II [NCT04024436 (breast cancer)] and phase III [NCT04093362 (iCCA)] trials.

ACKNOWLEDGEMENTS

Medical writing and editorial assistance were provided by Vasupradha Vethantham, PhD, and Jennifer Robertson, PhD, of Ashfield Healthcare Communications (Lyndhurst, NJ, USA) and funded by Taiho Oncology, Inc.

FUNDING

This study was sponsored by Taiho Oncology, Inc., and Taiho Pharmaceutical Co., Ltd. (no grant number).

DISCLOSURE

RB does not have conflicts of interests to disclose. FM-B reports research support from Aileron Therapeutics, Inc., AstraZeneca, Bayer Healthcare Pharmaceutical, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc., Daiichi Sankyo Co. Ltd., Debiopharm International, eFFECTOR Therapeutics, Genentech Inc., Guardant Health Inc., K Group, Millennium Pharmaceuticals Inc., Novartis, Pfizer Inc., PPD Investigator Services LLC, Puma Biotechnology Inc., Seattle Genetics, Taiho Pharmaceutical Co., and Zymeworks Inc.; has served on the advisory committees of ClearLight Diagnostics, Darwin Health, Grail, Immunomedics, Inflection Biosciences, Mersana Therapeutics, Puma Biotechnology Inc., Seattle Genetics, and Silverback Therapeutics, Spectrum Pharmaceuticals; has a consulting role for eFFECTOR Therapeutics, PACT Pharma, Zymeworks, Jackson Laboratory, Genentech Inc., F. Hoffman-La Roche Ltd., Parexel International, Pfizer Inc., IBM Watson, Samsung Bioepis, Aduro

Biotech Inc., Kolon Life Science, OrigiMed, Sumitomo Dainippon Pharma Co., Seattle Genetics Inc., DebioPharm, Dialectica, Piers Pharmaceuticals, Xencor, and Tyra Biosciences; and has received fees/honoraria from Chugai Biopharmaceuticals, Dialectica, Mayo Clinic, and Sumitomo Dainippon Pharma. LG has a consulting/advisory role for Debiopharm, H3 Biomedicine, Incyte, QED, Alentis, Pieres, Agios, and Sirtex; serves on the IDMC for AstraZeneca; has received research funding from Taiho; and has received reimbursement for travel, accommodation, and other expenses from Taiho. BT has served in an advisory role at Amgen, Astellas, Bayer, Sanofi, BMS, Janssen-Cilag, MSD, Novartis, Tolmar, Ipsen; has received research funding from Amgen, Astellas, AstraZeneca, Bayer, BMS, Ipsen, Janssen-Cilag, Pfizer, and Servier; has served on the Speaker Bureau for Amgen, Astellas, BMS, and Janssen-Cilag; and has received travel expenses from Amgen, Astellas, Bayer, and Sanofi. BT's institution receives funding from Amgen, Aslan, Akeso, AstraZeneca, Aptevo, GSK, MSD, Novartis, Servier, and Taiho. YH, KAB, and IY are full-time employees at Taiho Oncology. KAB was an employee at Eli Lilly and owns stock in Eli Lilly. HTA is an investigator in studies sponsored by Taiho and reports an advisory role in Guardant, Roche, and Servier. IM has no conflicts of interest to disclose.

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