

Multicenter Phase I Study of Erdafitinib (JNJ-42756493), Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients with Advanced or Refractory Solid Tumors



Rastislav Bahleda¹, Antoine Italiano², Cinta Hierro³, Alain Mita⁴, Andres Cervantes⁵, Nancy Chan⁶, Mark Awad⁷, Emiliano Calvo⁸, Victor Moreno⁹, Ramaswamy Govindan¹⁰, Alexander Spira¹¹, Martha Gonzalez¹², Bob Zhong¹², Ademi Santiago-Walker¹², Italo Poggesi¹², Trilok Parekh¹², Hong Xie¹², Jeffrey Infante¹², and Josep Tabernero³

Abstract

Purpose: Here, we report results of the first phase I study of erdafitinib, a potent, oral pan-FGFR inhibitor.

Patients and Methods: Patients age ≥ 18 years with advanced solid tumors for which standard antineoplastic therapy was no longer effective were enrolled (NCT01703481). Parts 2 to 4 employed molecular screening for activating *FGFR* genomic alterations. In patients with such alterations, two selected doses/schedules identified during part 1 dose-escalation [9 mg once daily and 10 mg intermittently (7 days on/7 days off), as previously published (Tabernero JCO 2015;33:3401-8)] were tested.

Results: The study included 187 patients. The most common treatment-related adverse events were hyperphosphatemia (64%), dry mouth (42%), and asthenia (28%), generally grade 1/2 severity. All cases of hyperphosphatemia were grade 1/2 except for 1 grade 3 event. Skin, nail, and eye changes were

observed in 43%, 33%, and 28% of patients, respectively (mostly grade 1/2 and reversible after temporary dosing interruption). Urothelial carcinoma and cholangiocarcinoma were most responsive to erdafitinib, with objective response rates (ORR) of 46.2% (12/26) and 27.3% (3/11), respectively, in response-evaluable patients with *FGFR* mutations or fusions. All patients with urothelial carcinoma and cholangiocarcinoma who responded to erdafitinib carried *FGFR* mutations or fusions. Median response duration was 5.6 months for urothelial carcinoma and 11.4 months for cholangiocarcinoma. ORRs in other tumor types were $<10\%$.

Conclusions: Erdafitinib shows tolerability and preliminary clinical activity in advanced solid tumors with genomic changes in the *FGFR* pathway, at two different dosing schedules and with particularly encouraging responses in urothelial carcinoma and cholangiocarcinoma.

¹Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France. ²Institut Bergonie, Bordeaux, France. ³Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Universitat Autònoma de Barcelona (UAB), Barcelona, Spain. ⁴Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California. ⁵Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain. ⁶Rutgers University, New Brunswick, New Jersey. ⁷Dana-Farber Cancer Institute, Boston, Massachusetts. ⁸START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain. ⁹START Madrid-FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain. ¹⁰Washington University School of Medicine, St. Louis, Missouri. ¹¹Virginia Cancer Specialists Research Institute, Fairfax, Virginia; and US Oncology Research, The Woodlands, Texas. ¹²Janssen Research & Development, Raritan, New Jersey.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

Corresponding Author: Josep Tabernero, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), P. Vall d'Hebron 119-129, 08035 Barcelona, Spain. Phone: 34-93-489-4301; Fax 34-93-274-6059; E-mail: jtabernero@vhio.net

Clin Cancer Res 2019;25:4888-97

doi: 10.1158/1078-0432.CCR-18-3334

©2019 American Association for Cancer Research.

Introduction

The FGF signaling pathway has been implicated in the development and progression of malignancy, with several *FGFR* alteration types shown to induce carcinogenesis in preclinical models, and in acquired treatment resistance (1-4). *FGFR* may drive malignancy via several mechanisms including enhanced kinase domain activation, ligand-independent receptor dimerization, or altered FGF ligand affinity, gene amplifications, or gene fusions involving *FGFR1-3* and a variety of different partners (e.g., *TACC1*, *TACC3*, *BAIAP2L1*, and *BICC1*; refs. 1, 3, 5-12). Although the underlying role of *FGFR* alterations in a given tumor type has not been fully elucidated, accumulating preclinical data supports that they have transforming activity and influence sensitivity to *FGFR* inhibition (3, 10). Reported prevalence rates of *FGFR* mutations and gene fusions for a given tumor type have typically been $<10\%$ but with some exceptions, most notably urothelial carcinoma, for which *FGFR3* mutations have been documented in up to 80% of nonmuscle-invasive cases and in up to 20% of muscle-invasive cases; *FGFR3* amplification and translocations have also been observed in urothelial carcinoma (1, 3). A recent analysis of 412 cases of muscle-invasive bladder cancer within The Cancer Genome Atlas identified 784 gene fusions in these samples, of which *FGFR3-TACC3* was the most common (11). In addition,

Translational Relevance

A first-in-human phase I study of erdafitinib was conducted to characterize erdafitinib pharmacokinetics/pharmacodynamics; determine recommended dosing for future development; and test the feasibility of molecular screening for *FGFR* genomic alterations. Two recommended phase 2 doses were established. Serum phosphate levels were identified as a robust pharmacodynamic marker for erdafitinib, and phosphate level increases were shown to correlate with clinical response to treatment. Data from this study established a clinical focus on patients with tumors positive for *FGFR* mutations and gene fusions, and identified urothelial carcinoma and cholangiocarcinoma as highly responsive tumor types to erdafitinib. The clinical observations across tumor types, the predictive value of specific *FGFR* alterations and types, and the utility of serum phosphate levels as a potential biomarker for erdafitinib treatment outcomes have the potential to influence future treatment of patients with *FGFR*-positive tumors, warranting further investigation.

fusions between *FGFR2* and *AHCYL1* or *BICC1* have been identified in 14% of cases of intrahepatic cholangiocarcinoma, which have been associated not only with oncogenic potential but also with sensitivity to *FGFR* inhibition (13).

Erdafitinib (JNJ-42756493) is a potent, oral pan-*FGFR* tyrosine kinase inhibitor with IC_{50} values in the low nanomolar range for all members of the *FGFR* family (*FGFR1* to *FGFR4*; ref. 14). It has demonstrated potent inhibition of cell proliferation in *FGFR* pathway-activated cancer cell lines from multiple origins and *in vivo* antitumor activity in mouse xenograft models of *FGFR*-driven tumors (14), as well as antiproliferative effects in *FGFR* fusion-overexpressing cell lines (10). Here, we report results of the first-in-human study of erdafitinib, a four-part study with a dose-escalation cohort (part 1) followed by several expansion cohorts (parts 2–4). Dose-escalation findings in part 1 have been published previously (15). This article captures the final safety and efficacy results in addition to key pharmacokinetic parameters in parts 1 and 2 and pharmacodynamic observations across all four parts of this phase I study.

Patients and Methods

This study was initiated in 2012 and enrolled patients age ≥ 18 years with advanced solid tumors for which standard antineoplastic therapy was no longer effective (NCT01703481). Across all four parts, standard eligibility criteria applied, including radiographically measurable or clinically evaluable tumors; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate bone marrow, liver, and renal function. The study was conducted in accordance with the Declaration of Helsinki, the ICH GCP guidelines, and other applicable regulatory requirements. Human investigations were performed after approval by an ethical committee or Institutional Review Board at each study site, and a signed informed consent form was obtained from each patient.

Details regarding the methodology of parts 1 (dose escalation) and 2 (pharmacodynamics cohort) have been published previously (15). In brief, part 1 followed a 3+3 design, with patients receiving ascending doses of erdafitinib at 0.5, 2, 4, 6, 9, or 12 mg

once daily (21-day cycles). Later, two doses were also evaluated at 10 or 12 mg given as intermittent dosing, 7 days on/7 days off (28-day cycles). Two recommended phase 2 doses (RP2D) were established: parts 2 and 3 used the first RP2D of 9 mg daily dosing, and part 4 used the second RP2D of intermittent dosing schedule at 10 mg with the option to increase to 12 mg based on observed phosphate level. Parts 2 to 4 of the study employed molecular screening for activating *FGFR* genomic alterations, identified either via local screening or centrally at a Sponsor-appointed laboratory. In parts 2 and 3, tumors were required to be *KRAS* wild-type and have any of the following *FGFR* alterations: amplifications, activating mutations, or gene fusions; or other molecular alterations leading to activation of the *FGFR* pathway. Activating mutations were those outside of the valine gatekeeper position of the *FGFRs* (e.g., *FGFR1* V561; *FGFR2* V564; *FGFR3* V555; and *FGFR3* V550), which are predicted to confer resistance to reversible *FGFR* kinase inhibitors, and additional mutations not known to predict resistance to *FGFR* kinase inhibitors (per published literature). In part 4, tumors were required to have *FGFR*-activating mutations or *FGFR* fusions.

In anticipation of hyperphosphatemia, an expected effect of *FGFR* inhibition (a class effect due to *FGFR* inhibition in renal proximal tubules), a dose interruption guideline was developed: erdafitinib was to be withheld if phosphate levels reached 7.0 mg/dL, along with restriction of phosphate intake and treatment with sevelamer. If phosphate levels reached 9.0 mg/dL, treatment with acetazolamide was also to be instituted, and at 10.0 mg/dL, treatment was to be permanently discontinued.

Study evaluations

Safety was assessed by physical examination, eye exam, vital signs, ECOG performance status, hematology/biochemistry, and electrocardiography (ECG), which was performed at baseline; on days 0, 7 (intermittent) or 8 (daily), and 15 in cycle 1; on day 1 for subsequent cycles; and at study completion. Patients were monitored for treatment-emergent adverse events (TEAEs) until 30 days after the treatment period, and TEAEs were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Efficacy assessments using RECIST version 1.1 were performed every 8 weeks in parts 1 and 4 and every 6 weeks in parts 2 and 3, with the frequency extended to every 12 weeks after 1 year on study.

Pharmacokinetic and pharmacodynamic assessments

Details regarding the sampling performed for the pharmacokinetic and pharmacodynamic analyses in part 1 are published elsewhere (15). In part 2, serial blood samples were collected for drug concentration measurement on cycle 1 day 1 and cycle 2 day 1, up to 24 hours after dose. Pharmacokinetic parameters were estimated using noncompartmental analysis (Phoenix WinNonlin software; Pharsight Corporation, Certara, L.P.). Sparse pharmacokinetic blood samples were collected in parts 3 and 4 of the study. Phosphate changes from baseline were correlated with response to erdafitinib (as described in the Results).

Statistical analysis

Descriptive statistics were used for the analysis of all study data. Safety and antitumor efficacy outcomes were reported for all treated patients, with efficacy also reported for patients evaluable for response or patients with *FGFR* alterations. Time events were estimated using the Kaplan–Meier method.

Table 1. Patient demographic and baseline characteristics (N = 187)

Characteristic	Number of patients (%)
Age, y	
Median	60
Range	21–84
Sex	
Female	107 (57)
Male	80 (43)
Race	
White	170 (91)
Black	4 (2)
Asian	5 (3)
Unknown/not reported	8 (4)
ECOG performance status	
0	64 (34)
1	122 (65)
2	1 (<1)
Site of primary cancer	
Breast	36 (19)
Urothelial	30 (16)
Non–small cell lung	24 (13)
Glioblastoma	13 (7)
Cholangiocarcinoma	11 (6)
Ovarian	11 (6)
Head and neck	11 (6)
Gastric	2 (1)
Other	49 (26)
Prior cancer therapy	
Surgery	142 (76)
Radiotherapy	187 (100)
Systemic therapy	186 (99)
Biological	39 (21)
Chemotherapy	181 (97)
Immunotherapy	26 (14)

Results

A total of 187 patients were enrolled over the course of the study, for whom baseline demographic and clinical characteristics are shown in Table 1. As of the clinical cutoff of January 03, 2017, one patient in part 4 remained on treatment with most of the other 186 patients discontinuing treatment due to progression of disease ($n = 157$, 84%). Other reasons for discontinuation included an AE ($n = 13$, 7%), withdrawal of consent ($n = 7$, 4%), investigator decision to discontinue ($n = 5$, 3%), death ($n = 3$, 2%), and intolerability to sevelamer ($n = 1$, 0.5%). Note, at the time of clinical cutoff, one patient (0.5%) was still on treatment.

FGFR alterations by tumor type are presented in Table 2. Overall, 135 patients (72%) had an identifiable *FGFR* alteration, the most common being *FGFR* mutations and fusions in 58 patients

(31%). An additional 45 patients (24%) had *FGFR* amplifications, five patients (3%) had *FGFR* mutation/fusion coalterations (Supplementary Table S2), and 52 patients (28%) had an *FGFR* status that was undetermined or negative.

Across all dose levels, the median treatment duration was 1.7 months (range, 0.2–23.4 months). Patients received a median of 2.0 cycles (range, 1–31), and 45 patients (24%) had received ≥ 6 cycles, including 21 patients (11%) treated with ≥ 9 cycles.

As published previously (15), the MTD was not defined in part 1, as only one dose-limiting toxicity [aspartate transaminase (AST)] was observed among seven patients treated at the highest dose level of 12 mg daily.

Safety

Treatment-related TEAEs with an overall incidence $\geq 10\%$ are summarized in Table 3. The most common were hyperphosphatemia (64%), dry mouth (42%), and stomatitis (37%), generally of grade 1/2 severity. All cases of hyperphosphatemia were grade 1/2 in severity except for one patient with a grade 3 event. Skin changes were observed in 43% of patients [most commonly dry skin (29%) and hand–foot syndrome (11%)], nail changes in 33% of patients [most commonly onycholysis (11%) and nail dystrophy (9%)], and eye disorders in 28% of patients [most commonly dry eye (13%) and blurred vision (4%)]. Chorioretinopathy, retinal detachment, and retinal edema were reported by two patients each, and detachment of retinal pigment epithelium and retinopathy were reported by one patient each. The majority of skin, nail, and eye toxicities were grade 1/2 in severity and reversible once treatment was temporarily interrupted or, less frequently, permanently discontinued.

Anemia was the most frequently reported grade 3 TEAE ($n = 17$, 9%), followed by stomatitis ($n = 12$, 6%). Other grade 3 TEAEs with an incidence $\geq 5\%$ were general physical health deterioration (6%), asthenia (5%), AST increased (5%), and hyponatremia (6%).

Eighty-eight patients (47%) experienced serious TEAEs. General physical health deterioration was the most common serious TEAE ($n = 13$, 7%), an indication of the advanced cancer status of the study population and this study's database setup of capturing clinical progression as TEAEs. Abdominal pain, intestinal obstruction, and dyspnea each occurred in seven patients (4%). Treatment-related serious TEAEs were recorded for 13 patients (7%); of these, only anemia ($n = 2$) was reported in >1 patient.

A total of 32 patients (17%) died during the conduct of the study, with 26 deaths (14%) within 30 days of last dose. Progression of disease was identified as the primary cause of death for 23 patients (12%). The primary cause of death was AEs for nine

Table 2. *FGFR* alterations by tumor type

Indication (n)	<i>FGFR</i> alteration					Any alteration
	Unknown ^a	Amplification	Mutation	Fusion	Coalteration ^b	
Cholangiocarcinoma ($n = 11$)	0	1 (9%)	3 (27%)	8 (73%)	0	11 (100%)
Glioblastoma ($n = 13$)	0	4 (31%)	3 (23%)	13 (100%)	3 (23%)	13 (100%)
Urothelial ($n = 30$)	3 (10%)	4 (13%)	17 (57%)	11 (37%)	1 (3%)	27 (90%)
Non–small cell lung ($n = 24$)	4 (17%)	5 (21%)	10 (42%)	8 (33%)	0	20 (83%)
Breast ($n = 36$)	7 (19%)	21 (58%)	7 (19%)	6 (17%)	0	29 (81%)
Ovarian ($n = 11$)	3 (27%)	2 (18%)	3 (27%)	6 (55%)	1 (9%)	8 (73%)
Head and neck ($n = 11$)	5 (45%)	1 (9%)	5 (45%)	1 (9%)	0	6 (55%)
Gastric ($n = 2$)	1 (50%)	1 (50%)	0	0	0	1 (50%)
Other ($n = 49$)	29 (59%)	6 (12%)	9 (18%)	5 (10%)	0	20 (41%)

^aUnknown includes subjects for whom *FGFR* alteration (amplification, mutation, or fusion) status was undetermined or negative and includes one subject with activated *FGFR* pathway (*FRS2* gene amplification) but no known *FGFR* alteration.

^bCoalteration includes subjects with two categories of *FGFR* alterations (fusion, mutation).

Table 3. Treatment-emergent drug-related AEs

	≤4 mg (QD) n = 14	6 mg (QD) n = 10	9 mg (QD) n = 65	10 mg (7d on/7d off) n = 78	12 mg (QD) n = 7	12 mg (7d on/7d off) n = 13	Total N = 187
Any TEAE	10 (71%)	9 (90%)	63 (97%)	71 (91%)	7 (100%)	13 (100%)	173 (93%)
Hyperphosphatemia	5 (36%)	7 (70%)	56 (86%)	33 (42%)	5 (71%)	13 (100%)	119 (64%)
Dry mouth	1 (7%)	6 (60%)	28 (43%)	29 (37%)	6 (86%)	8 (62%)	78 (42%)
Stomatitis	1 (7%)	3 (30%)	34 (52%)	24 (31%)	5 (71%)	2 (15%)	69 (37%)
Asthenia	2 (14%)	4 (40%)	19 (29%)	17 (22%)	6 (86%)	4 (31%)	52 (28%)
Dry skin	0	1 (10%)	18 (28%)	19 (24%)	6 (86%)	5 (38%)	49 (26%)
Dysgeusia	1 (7%)	1 (10%)	19 (29%)	18 (23%)	4 (57%)	5 (38%)	48 (26%)
Decreased appetite	0	0	18 (28%)	16 (21%)	3 (43%)	5 (38%)	42 (22%)
Diarrhea	1 (7%)	1 (10%)	16 (25%)	18 (23%)	0	2 (15%)	38 (20%)
Alopecia	0	1 (10%)	15 (23%)	10 (13%)	5 (71%)	2 (15%)	33 (18%)
Nausea	0	2 (20%)	17 (26%)	10 (13%)	0	1 (8%)	30 (16%)
Constipation	1 (7%)	0	14 (22%)	8 (10%)	1 (14%)	2 (15%)	26 (14%)
Dry eye	0	1 (10%)	11 (17%)	8 (10%)	2 (29%)	3 (23%)	25 (13%)
Fatigue	0	0	11 (17%)	12 (15%)	0	1 (8%)	24 (13%)
Onycholysis	0	0	5 (8%)	9 (12%)	3 (43%)	3 (23%)	20 (11%)
Hand-foot syndrome	0	0	9 (14%)	6 (8%)	3 (43%)	2 (15%)	20 (11%)
Vomiting	1 (7%)	1 (10%)	11 (17%)	4 (5%)	0	2 (15%)	19 (10%)

Abbreviation: QD, once daily.

patients (5%), two of which were considered related to study drug (intracranial hemorrhage, in a patient with glioblastoma who received two doses of erdafitinib 10-mg intermittent and tumor bleeding in a patient with squamous cell carcinoma of the head and neck who received 14 doses of erdafitinib 10-mg intermittent).

Twenty-two patients (12%) discontinued treatment due to TEAEs; the most common TEAEs included general health deterioration ($n = 5$), asthenia ($n = 2$), and AST increase ($n = 2$), of whom eight (4%) were considered to be treatment related (individual cases of onycholysis, hand-foot syndrome, keratitis, dry mouth, tumor hemorrhage, intracranial hemorrhage, prolonged ECG QT, and increased AST). Dose modifications included 99 patients (53%) with dose interruptions and 33 patients (18%) with dose reductions. Hyperphosphatemia was the most common reason for both dose interruption ($n = 47$, 25%) and dose reduction ($n = 10$, 5%); however, there were no treatment discontinuations for hyperphosphatemia. Sevelamer was taken by 39% of patients, acetazolamide by 10%, and sevelamer carbonate by 2%.

ECGs were collected extensively throughout the study from all patients. The overall ECG interpretation of nearly 250,000 tracings found no abnormal, clinically significant findings on treatment. No subjects had an average change from baseline in QTcF or QTcB that exceeded 60 msec. Furthermore, average of triplicate ECG records showed that average QTc values did not exceed 500 msec postbaseline except for two patients. One patient who had >500 msec QTcB postbaseline had average QTcB above 500 msec at baseline. The other patient who had >500 msec postbaseline value in average QTcF was 3 weeks from the last dose with concomitant condition of worsening chronic kidney disease (grades 2–3). The investigator reported this abnormal ECG as grade 3 prolonged ECG QTc and withdrew the patient.

Antitumor efficacy

Analysis of objective response rate (ORR) by tumor type identified urothelial carcinoma and cholangiocarcinoma as cancer types that responded to erdafitinib. Analysis of response-evaluable patients harboring *FGFR* genomic alterations (mutations or fusions) resulted in an ORR of 46% (12/26) in urothelial carcinoma and 27% (3/11) in cholangiocarcinoma. All patients with urothelial carcinoma and cholangiocarcinoma who

responded to treatment with erdafitinib carried *FGFR* mutations or gene fusions.

Of 30 urothelial carcinoma patients enrolled, 27 exhibited an *FGFR* mutation and/or gene fusion (17 with an *FGFR3* mutation, 11 with *FGFR* fusion, and two harboring both an *FGFR3* mutation and *FGFR2* fusion). One patient, enrolled in part 1 of the study, was negative for *FGFR* alterations, and another patient in part 3 of the study harbored an amplification in the *FRS2* gene, a downstream mediator of *FGFR* signaling. The ORR in the all treated urothelial carcinoma population was 12 of 30 (40%), and 12 of 26 (46%) in the *FGFR* mutation and fusion-positive population. For urothelial carcinoma patients, 10 were treated with continuous dosing (9 mg daily), and 16 were treated with intermittent schedule (15 at 10 mg and 1 at 12 mg) and the response rate was numerically higher at 70% with 9 mg daily than 32% with intermittent dosing (Table 4; Fig. 1A). The median duration of response for all 12 responders with urothelial carcinoma was 5.6 months, with median progression-free survival (PFS) of 5.1 months (Fig. 2A).

All 11 cholangiocarcinoma patients enrolled harbored an *FGFR* mutation or gene fusion (three with *FGFR* mutations and eight with *FGFR* fusions). The ORR in the all-treated and *FGFR* alteration-positive population was three of 11 (27%) for cholangiocarcinoma. For cholangiocarcinoma patients, 10 of 11 were treated with intermittent schedule, and the sole patient treated at 9 mg daily did not respond (Table 4; Fig. 1B). The median duration of response for all three cholangiocarcinoma responders was 11.4 months.

Among 92 response-evaluable patients with *FGFR* mutations or fusions, there were 19 partial responses (21%) and 19 patients (21%) with SD (Table 4; Fig. 1C).

Across indications, 23 response-evaluable patients were enrolled on study whose tumors harbored *FGFR* gene amplification in the absence of a reported *FGFR* mutation or fusion. Nineteen patients harbored an *FGFR1* amplification [13 breast, one colorectal cancer, two endometrial, one melanoma, one neuroendocrine carcinoma, and one non-small cell lung cancer (NSCLC)]; three patients harbored *FGFR2* amplification (two breast and one NSCLC); and one gallbladder patient harbored an *FGFR3* amplification. Aside from two responders with breast cancer (both harboring *FGFR2* amplification), little activity was observed in patients harboring *FGFR* gene amplifications.

Table 4. Best overall response

	≤4 mg (QD)	6 mg (QD)	9 mg (QD)	10 mg (7d on/7d off)	12 mg (QD)	12 mg (7d on/7d off)	Total
All treated patients	n = 14	n = 10	n = 65	n = 78	n = 7	n = 13	N = 187
ORR (95% CI)	0 NE	0 NE	9 (14%) (7%–25%)	11 (14%) (7%–24%)	0 NE	1 (8%) (0.2%–36%)	21 (11%) (7%–17%)
Partial response	0	0	9 (14%)	11 (14%)	0	1 (8%)	21 (11%)
Stable disease	1 (7%)	2 (20%)	11 (17%)	11 (14%)	2 (29%)	2 (15%)	29 (16%)
Progressive disease	12 (86%)	7 (70%)	36 (55%)	35 (45%)	5 (71%)	9 (69%)	104 (56%)
NE/unknown	1 (7%)	1 (10%)	9 (14%)	21 (27%)	0	1 (8%)	33 (18%)
All tumor types, evaluable with FGFR mutations or gene fusions		n = 2	n = 30	n = 56		n = 4	n = 92
ORR (95% CI)		0 NE	7 (23%) (10%–42%)	11 (20%) (10%–32%)		1 (25%) (0.6%–81%)	19 (21%) (13%–30%)
Partial response		0	7 (23%)	11 (20%)		1 (25%)	19 (21%)
Stable disease		1 (50%)	7 (23%)	10 (18%)		1 (25%)	19 (21%)
Progressive disease		0	14 (47%)	30 (54%)		2 (50%)	46 (50%)
NE/unknown		1 (50%)	2 (7%)	5 (9%)		0	8 (9%)
Urothelial carcinoma, evaluable with FGFR mutations or gene fusions			n = 10	n = 15		n = 1	n = 26
ORR (95% CI)			7 (70%) (35%–93%)	5 (33%) (12%–62%)		0 NE	12 (46%) (27%–67%)
Partial response			7 (70%)	5 (33%)		0	12 (46%)
Stable disease			1 (10%)	2 (13%)		1 (100%)	4 (15%)
Progressive disease			2 (20%)	7 (47%)		0	9 (35%)
NE/unknown			0	1 (7%)		0	1 (4%)
Cholangiocarcinoma, evaluable with FGFR mutations or gene fusions			n = 1	n = 10			n = 11
ORR (95% CI)			0 NE	3 (30%) (7%–65%)			3 (27%) (6%–61%)
Partial response			0	3 (30%)			3 (27%)
Stable disease			0	3 (30%)			3 (27%)
Progressive disease			1 (100%)	4 (40%)			5 (45%)
NE/unknown			0	0			0

Abbreviations: NE, not evaluable; QD, once daily.

Partial response was achieved for 21 of 187 patients (11%) based on the all-treated population (Table 4) and for 21 of 164 patients (12.8%) based on the response-evaluable population. ORRs in other tumor types were all less than 10%: ovarian, breast, NSCLC, and other cancers were 9% (1/11), 9% (3/34), 5% (1/21), and 2% (1/58), respectively. Among responders, time to initial response was rapid, with a median of 1.8 months (range, 1.1–17.0 months). Median duration of response for responding patients was 9.0 months. Median PFS for all patients was 2.3 months with a follow-up period of 6 months.

Pharmacokinetics/pharmacodynamics

Pharmacokinetics of erdafitinib. Selected pharmacokinetic parameters and concentration–time profiles derived at day 1 of cycle 1 and cycle 2 are presented in Supplementary Table S1 and Supplementary Fig. S1, respectively. After a single dose, median time to maximum concentration (T_{max}) was dose-independent and ranged from 1 to 3 hours after dose across the 0.5–12 mg dose range (Supplementary Table S1). At steady state, median T_{max} values ranged from 2 to 4 hours, similar to those observed after a single dose. After continuous daily or intermittent dosing, systemic erdafitinib exposure (C_{max} , AUC) increased in direct proportion with the dose following both single and repeated dosing. Erdafitinib was characterized by a low total apparent plasma clearance (on average 0.2–0.5 L/h), restricted by the avid protein binding (free fraction on average 0.25%–0.5%). The unbound fraction was inversely related to AGP concentrations. The accumulation ratio for AUC ranged

from three- to fivefold after 21 days of continuous daily dosing; the effective half-life, calculated based on the accumulation ratio, was 42–74 hours, with predicted attainment of steady-state conditions after approximately 2 weeks of dosing.

Pharmacokinetic parameters for erdafitinib were similar for both solution and capsule formulations, when the compound was given with or without sevelamer, and in patients with urothelial carcinoma and with cholangiocarcinoma compared with other tumor types at the same dose and schedule (data not shown).

Analysis of change from baseline in QTcF (Fridericia) versus total or unbound plasma concentration of erdafitinib showed no effect of erdafitinib plasma concentration on change in QTcF.

Correlation of phosphate with erdafitinib concentrations. The relationships between serum phosphate and erdafitinib plasma concentration (total and unbound) were explored assuming phosphate increases in serum were directly related to the observed plasma concentrations. The exploration was performed only when phosphate levels were measured in serum samples obtained in a ±15-minute window from the collection of the corresponding pharmacokinetic plasma sample. The modeling indicated a significant relationship between phosphate serum concentrations and total erdafitinib plasma concentrations. The relationship was best described using an E_{max} model (Supplementary Fig. S2).

Correlation of phosphate with response to erdafitinib. At 9-mg daily dosing, an average change of serum phosphate from baseline of

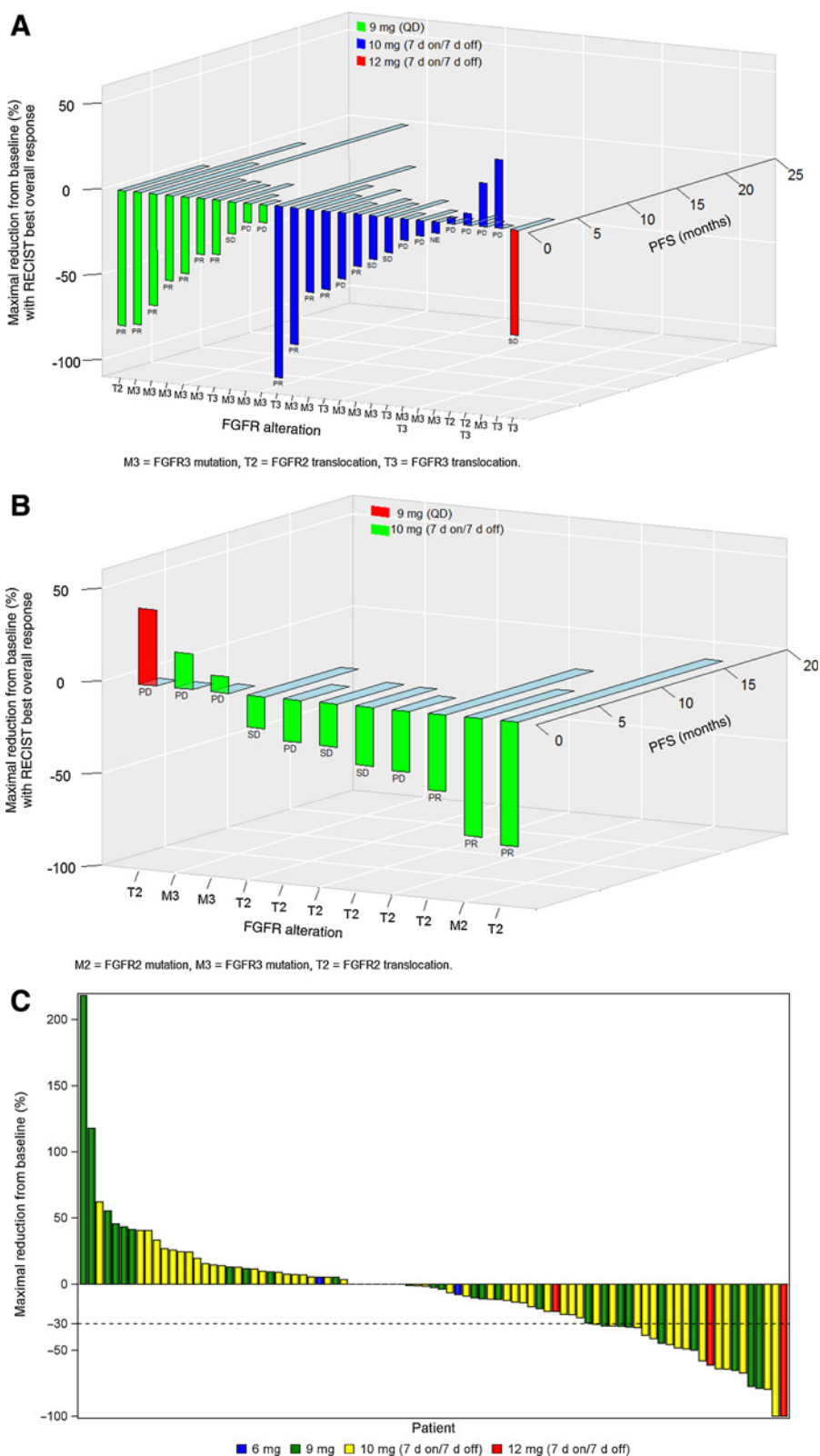
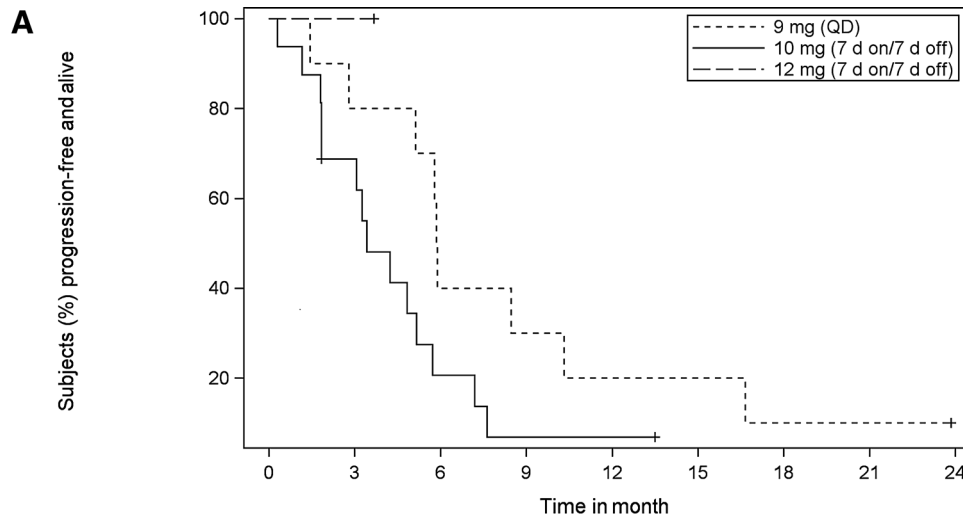


Figure 1. Maximal percentage reduction of the sum of the diameters of targeted lesions from baseline in response-evaluable patients with *FGFR* mutations or gene fusions with urothelial cancer (A), cholangiocarcinoma (B), and all tumor types (C).

58% (5.4 mg/mL) was observed on cycle 1 day 8 with 62 of 65 subjects assessed. In the 10-mg 7 days on/7 days off cohort, average changes from baseline phosphate were 64% (5.2 mg/dL)

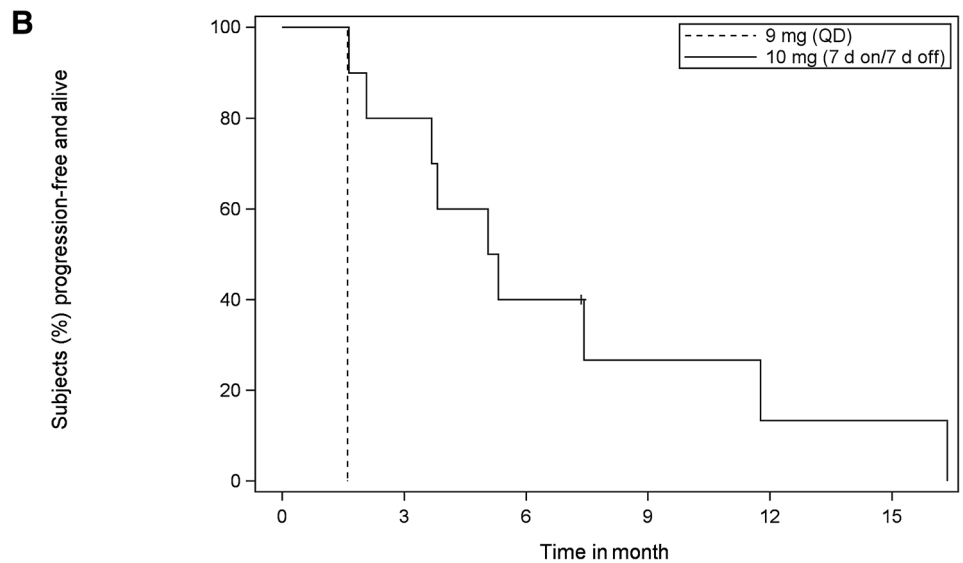
at cycle 1 day 7 with 76 of 78 patients assessed. Maximum phosphate elevations were transient with serum phosphate concentrations stabilizing over time. For the pharmacodynamic



Number of subjects at risk

	0	3	6	9	12	15	18	21	24
9 mg (QD)	10	8	4	3	2	2	1	1	
10 mg (7 d on/7 d off)	16	10	3	1	1				
12 mg (7 d on/7 d off)	1	1							

Censored patients are marked by "+".



Number of subjects at risk

Time in month	0	3	6	9	12	15
9 mg (QD)	1	0	0	0	0	0
10 mg (7 d on/7 d off)	10	8	4	2	1	1

Censored patients are marked by "+".

Figure 2. PFS for patients with *FGFR* mutations or gene fusions with urothelial cancer (**A**) and cholangiocarcinoma (**B**).

analysis, patients were grouped within a dose cohort based on maximum postbaseline phosphate values into the following groups: <5.5 mg/dL; 5.5 to <7 mg/dL; 7 to < 9 mg/dL; and ≥9 mg/dL. A target pharmacodynamic increase in phosphate of ≥5.5 mg/dL [which was initially chosen based on empirical knowledge from chronic hemodialysis patients (16), and represented 35% over the phosphate upper limit of normal as well as ~60% increase from baseline average in this study] by the end of the first cycle with continuous dosing was selected for use in determining if optimal pharmacodynamic range had been achieved.

Of 21 clinical responders, 16 patients (76%) had maximum postbaseline phosphate values ≥5.5 mg/dL. Seven of 21 (33%)

responders exhibited maximum phosphate values in the 5.5 to <7 mg/dL range, whereas nine of 21 responders (43%) had maximum phosphate values in the 7 to <9 mg/dL range. Five responses (24%) were observed in patients with maximum postbaseline phosphate levels <5.5 mg/dL; these were all in the 10-mg intermittent dosing cohort.

Discussion

This phase I single-agent study of the oral pan-FGFR inhibitor erdafitinib, conducted in patients with advanced stage solid tumors with no standard treatment options, demonstrated the

tolerability of the two RP2Ds of 9-mg daily and 10-mg intermittent dosing. The safety profile described here is both tolerable and manageable, consistent with those previously reported for part 1 of this study (15) and the expected TEAEs of a potent and selective FGFR inhibitor. Preliminary evidence of antitumor activity was seen in *FGFR* mutation- and fusion-positive, previously treated advanced urothelial carcinoma and cholangiocarcinoma, two tumor types where FGFR pathophysiology is known to play a role.

Since our study was initiated, additional insights have been gained into the role of *FGFR* alterations in urothelial carcinoma, cholangiocarcinoma, and other human malignancies and their potential as therapeutic targets (1, 3, 10, 11, 13). This first-in-human trial of the erdafitinib represents the largest clinical evaluation of FGFR inhibition in advanced urothelial carcinoma to date, a patient population with substantial unmet needs, given the high rate of comorbidities that complicate treatment decisions and the lack of an accepted standard of care after first-line chemotherapy (17–19). Interestingly, whereas efficacy results for erdafitinib were similar between the two RP2Ds in the overall sample, a difference was noted with respect to ORR in the response-evaluable urothelial carcinoma subgroup with *FGFR* alterations treated at 9-mg daily (70%) and 10-mg intermittent (33%) dosing. Cholangiocarcinoma also represents a patient population with significant unmet needs, and this study highlighted the potential for clinical benefit. For cholangiocarcinoma, in which all patients were treated at 10-mg intermittent except for one patient who received 9 mg daily, the sample size was smaller and the ORR was lower relative to urothelial carcinoma; however, the duration of response was notable at 11.4 months. Although other clinical trial data regarding the antitumor activity of FGFR inhibition in urothelial carcinoma and cholangiocarcinoma remain limited, emerging data are showing responses across several investigational anti-FGFR compounds in early clinical development, including BGJ398 (20) and AZD4547 (21) in urothelial carcinoma, ARQ 087 (22) in cholangiocarcinoma, and Debio 1347 (23) in both urothelial carcinoma and in cholangiocarcinoma. Across clinical trials of FGFR inhibitors irrespective of histology, it appears that the most common type of alteration (*FGFR1* amplification) is not the most sensitive to treatment and that identifying patients with relatively uncommon *FGFR* mutations and *FGFR* gene fusions may provide the highest likelihood for clinical response, posing some challenges with respect to clinical trial designs while reinforcing the importance for comprehensive screening (24, 25). Recent preclinical investigations have demonstrated the oncogenic effects of both *FGFR2* and *FGFR3* fusion genes and their sensitivity to various investigational FGFR inhibitors, of which erdafitinib exhibited the highest potency (10). Although the current study hypothesized that targeting the FGFR signaling pathway could result in antitumor effect irrespective of tumor histology, different histologies harboring *FGFR* amplifications, mutations, or fusions did not respond uniformly to erdafitinib treatment. The response was higher in urothelial carcinoma or cholangiocarcinoma relative to other tumor types included in the study, and responses were observed for both *FGFR* mutation-positive and fusion-positive patients. *FGFR* alterations do not behave uniformly across cancer types; thus, a deeper understanding of biomarker strategies is warranted.

Hyperphosphatemia was the most frequently reported TEAE, reported by 65% of patients, but was limited to grade 1/2 severity and was not responsible for any treatment discontinuations.

Hyperphosphatemia is an expected effect of FGFR inhibitors, in light of prior findings that FGFR inhibition counteracts renal FGF-23/Klotho signaling, resulting in CYP27B1 and CYP24A1 deregulation and hypervitaminosis D and hyperphosphatemia induction (26). Phosphate levels were related to erdafitinib dose and concentration, and mean phosphate levels peaked across doses and schedules between day 7/day 8 and day 35/36. When hyperphosphatemia was first noted by investigators in the current trial, it resulted in frequent dose interruptions, particularly in the first and second cycles. Over time, it became apparent that hyperphosphatemia was an isolated effect which was not accompanied by other metabolic abnormalities and was not associated with skeletal events or renal dysfunction reported as TEAEs. Subsequent clinical studies with erdafitinib initiated treatment at less than a 9-mg daily dose to avoid the frequent interruptions caused by hyperphosphatemia in the first cycle. Pharmacodynamic data from this study revealed serum phosphate levels as a robust pharmacodynamic biomarker for erdafitinib, with preliminary data from this study indicating that achieving target increases in serum phosphate ≥ 5.5 mg/dL under continuous daily dosing may be associated with clinical response. A target pharmacodynamic increase in phosphate of ≥ 5.5 mg/dL by the end of the first cycle was selected for use in determining if optimal PD range had been achieved, and to aid in dose up-titration in subsequent studies where appropriate based on modeling data and accumulated clinical data including those from this study (data not shown). The proportion of responders increased in the patient population for which the target phosphate threshold was achieved; with continuous dosing, no responders were observed at maximum postbaseline phosphate levels < 5.5 mg/dL. Achieving target increases in serum phosphate ≥ 5.5 mg/dL under continuous daily dosing may facilitate individualized erdafitinib dosing to maximize opportunities with clinical response. Individualizing erdafitinib dosing to achieve the target phosphate level would be warranted.

Erdafitinib is characterized by linear pharmacokinetics following oral dosing; plasma concentrations increased in direct proportion with the dose in the 0.5–12 mg range; and pharmacokinetics were time-independent after both continuous daily and intermittent dosing. We found that pharmacokinetic parameters did not appear to be influenced by the formulation (solution, capsules), concomitant use of phosphate-lowering agents, or tumor type (urothelial carcinoma vs. the all-comers population). The erdafitinib plasma concentration–time profile after repeated daily oral dosing was relatively flat. Due to the sampling strategy, terminal half-life could not be calculated using standard noncompartmental pharmacokinetic analysis. However, the mean accumulation ratios based on AUC after repeated daily dosing allowed estimation of mean effective half-life ranging from 42 to 74 hours, in agreement with the values observed in healthy subjects (data on file). Based on these observations, full steady-state conditions should be achieved within 14 days of dosing in most patients.

We acknowledge several limitations to our study findings, including limitations inherent to phase 1 clinical trials in oncology, which are designed primarily to assess dosing and safety/tolerability. In addition, the molecular selection methods were varied in this relatively small study, with a wide spectrum of specific *FGFR* alterations/variants represented in small numbers and across multiple tumor types (confounding the ability to characterize true response rates per specific *FGFR* alteration). No

analyses were performed to assess efficacy among *FGFR* variants (specific mutations or fusions) or between variant types (mutation vs. fusion) for urothelial carcinoma or cholangiocarcinoma patients due to small sample sizes. The *FGFR* variants correlating with response to erdafitinib will be better defined by the results of ongoing and future investigations. This study also provides no insight into coalterations involving genes outside of *FGFR* variants or circulating free DNA as potential correlative markers. Based on our findings, outstanding questions also remain regarding the optimal dosing of erdafitinib, given the association of the continuous dose with not only a higher ORR but also frequent dose interruptions due to hyperphosphatemia.

In conclusion, erdafitinib shows tolerability and preliminary evidence of clinical activity in advanced solid tumors, at two different dosing schedules and with particularly encouraging responses in urothelial carcinoma and cholangiocarcinoma. Pharmacokinetics were dose linear and time independent with steady-state concentrations reached at approximately 2 weeks of dosing. The observations in urothelial carcinoma and cholangiocarcinoma, the predictive value of specific *FGFR* alterations and types, and the potential use of serum phosphate levels as a pharmacodynamic biomarker for dose modification during erdafitinib therapy warrant further investigation.

Disclosure of Potential Conflicts of Interest

C. Hierro reports receiving commercial research grants from Bayer, and other remuneration from Ignyta, Lilly, and Roche. A. Mita reports receiving speakers bureau honoraria from Genentech. M. Awad is a consultant/advisory board member for Nektar, Maverick, and Blueprint. E. Calvo is an employee of HM Hospitales Group, reports receiving commercial research grants from AstraZeneca, Novartis, BeiGene, and START, other commercial research support from Roche/Genentech, speakers bureau honoraria from Novartis, holds ownership interest (including patents) in START and Oncoart Associated, and is a consultant/advisory board member for Novartis, Nanobiotix, Janssen-Cilag, PsiOxus, Seattle Genetics, EUSA Pharma, Abbvie, Celgene, AstraZeneca, Guidepoint, Roche/Genentech, GLG, Pfizer, Servier, and amcure. V. Moreno is a consultant/advisory board member for Bristol-Myers Squibb. R. Govindan reports receiving speakers bureau honoraria from AstraZeneca, Pfizer, Merck, Abbvie, Celgene, Roche, and Nektar. A. Spira reports receiving commercial research grants from Janssen, and is a consultant/advisory board member for AbbVie, Merck, CytomX, Array, and AstraZeneca/Medimmune. M. Gonzalez, T. Parekh, H. Xie hold ownership interest (including patents) in Johnson & Johnson. A. Santiago-Walker holds ownership interest (including patents) in Janssen. J. Infante is a consultant/advisory board member for Armo Biosciences and BioMed Valley. J. Tabernero is a consultant/advisory board member for

Amgen, ImClone Systems, Lilly, Merck KGaA, Millennium/Takeda, Novartis, Roche/Genentech, Sanofi, Celgene, Chugai Pharma, and Taiho Pharmaceutical. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: R. Bahleda, C. Hierro, R. Govindan, B. Zhong, A. Santiago-Walker, T. Parekh, J. Infante, J. Tabernero

Development of methodology: R. Bahleda, M. Gonzalez, B. Zhong, A. Santiago-Walker, I. Poggesi, T. Parekh, H. Xie, J. Infante, J. Tabernero

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Bahleda, A. Italiano, A. Mita, A. Cervantes, M. Awad, E. Calvo, V. Moreno, R. Govindan, A. Spira, B. Zhong, H. Xie, J. Infante, J. Tabernero

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Bahleda, A. Italiano, A. Mita, M. Awad, V. Moreno, R. Govindan, A. Spira, M. Gonzalez, B. Zhong, A. Santiago-Walker, I. Poggesi, T. Parekh, H. Xie, J. Infante, J. Tabernero

Writing, review, and/or revision of the manuscript: R. Bahleda, A. Italiano, C. Hierro, A. Mita, A. Cervantes, N. Chan, M. Awad, E. Calvo, V. Moreno, R. Govindan, A. Spira, M. Gonzalez, B. Zhong, A. Santiago-Walker, I. Poggesi, T. Parekh, H. Xie, J. Infante, J. Tabernero

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Gonzalez, I. Poggesi, J. Tabernero

Study supervision: R. Bahleda, N. Chan, E. Calvo, A. Spira, H. Xie, J. Infante, J. Tabernero

Acknowledgments

Investigational compound erdafitinib (JNJ-42756493) was discovered in collaboration with Astex Pharmaceuticals. The authors thank the patients and their families; the participating centers and investigators; and Vijay Peddaredigari (formerly of Janssen Research & Development) for study conception and design; Jean-Charles Soria, a former primary investigator who contributed to study design and oversaw clinical efforts at Institut Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France; Jayaprakash Karkera, Dana Gaffney, Katherine Bell, Gabriela Martinez Cardona, and Joseph Portale of Janssen Research & Development for development of the RT-PCR method used for central *FGFR* screening; and Suso Platero (formerly of Janssen Research & Development) for translational research support. Editorial support for this publication was provided by Laurie Orloski, funded by Janssen Research & Development.

This study was supported by Janssen Research & Development.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received October 11, 2018; revised February 26, 2019; accepted May 10, 2019; published first May 14, 2019.

References

- Babina IS, Turner NC. Advances and challenges in targeting *FGFR* signalling in cancer. *Nat Rev Cancer* 2017;17:318–32.
- Chae YK, Ranganath K, Hammerman PS, Vaklavas C, Mohindra N, Kalyan A, et al. Inhibition of the fibroblast growth factor receptor (*FGFR*) pathway: the current landscape and barriers to clinical application. *Oncotarget* 2017; 8:16052–74.
- Touat M, Ileana E, Postel-Vinay S, André F, Soria JC. Targeting *FGFR* signaling in cancer. *Clin Cancer Res* 2015;21:2684–94.
- Wesche J, Haglund K, Haugsten EM. Fibroblast growth factors and their receptors in cancer. *Biochem J* 2011;437:199–213.
- Andre F, Job B, Dessen P, Tordai A, Michiels S, Liedtke C, et al. Molecular characterization of breast cancer with high-resolution oligonucleotide comparative genomic hybridization array. *Clin Cancer Res* 2009;15: 441–51.
- Billery C, Chopin D, Aubriot-Lorton MH, Ricol D, Gil Diez de Medina S, Van Rhijn B, et al. Frequent *FGFR3* mutations in papillary non-invasive bladder (pTa) tumors. *Am J Pathol* 2001;158:1955–9.
- Cappellen D, De Oliveira C, Ricol D, de Medina S, Bourdin J, Sastre-Garau X, et al. Frequent activating mutations of *FGFR3* in human bladder and cervix carcinomas. *Nat Genet* 1999;23:18–20.
- Dutt A, Ramos AH, Hammerman PS, Mermel C, Cho J, Sharifnia T, et al. Inhibitor-sensitive *FGFR1* amplification in human non-small cell lung cancer. *PLoS One* 2011;6:e20351.
- Katoh M. Genetic alterations of *FGF* receptors: an emerging field in clinical cancer diagnostics and therapeutics. *Expert Rev Anticancer Ther* 2010;10:1375–9.
- Karkera JD, Cardona GM, Bell K, Gaffney D, Portale JC, Santiago-Walker A, et al. Oncogenic characterization and pharmacologic sensitivity of activating fibroblast growth factor receptor (*FGFR*) genetic alterations to the selective *FGFR* inhibitor erdafitinib. *Mol Cancer Ther* 2017;16:1717–26.
- Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, et al. TCGA Research Network, Weinstein JN, Kwiatkowski DJ, Lerner SP. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell* 2017;171:540–56.

12. Weiss J, Sos ML, Seidel D, Peifer M, Zander T, Heuckmann JM, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. *Sci Transl Med* 2010;2:62ra93.
13. Arai Y, Totoki Y, Hosoda F, Shirota T, Hama N, Nakamura H, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology* 2014;59:1427–34.
14. Perera TPS, Jovcheva E, Mevellec L, Vialard J, De Lange D, Verhulst T, et al. Discovery and pharmacological characterization of JNJ-42756493 (erdafitinib), a functionally selective small-molecule FGFR family inhibitor. *Mol Cancer Ther* 2017;16:1010–20.
15. Taberero J, Bahleda R, Dienstmann R, Infante JR, Mita A, Italiano A, et al. Phase I dose-escalation study of JNJ-42756493, an oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. *J Clin Oncol* 2015;33:3401–8.
16. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998;31:607–17.
17. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A; ESMO Guidelines Working Group. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(suppl 3):iii40-8.
18. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bladder cancer, Version 5.2018. National Comprehensive Cancer Network Plymouth Meeting, PA; 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
19. Witjes AJ, Lebret T, Comp erat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol* 2017;71:462–75.
20. Nogova L, Sequist LV, Perez Garcia JM, Andre F, Delord JP, Hidalgo M, 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;35:157–65.
21. Andre F, Ranson M, Dean E, Varga A, van der Noll R, Stockman PK, et al. Abstract LB-145: results of a phase I study of AZD4547, an inhibitor of fibroblast growth factor receptor (FGFR), in patients with advanced solid tumors. *Cancer Res* 2013;73(8 Supplement).
22. Mazzaferro V, Droz M, Busset D, El-Rayes B, Harris WP, Damjanov N, et al. ARQ 087, an oral pan-fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with advanced intrahepatic cholangiocarcinoma (iCCA) with FGFR2 genetic aberrations. *J Clin Oncol* 2017;35:4017.
23. Henner Voss M, Hierro C, Suk Heist R, Cleary JM, Meric-Bernstam F, Gandhi L, et al. Debio 1347, an oral FGFR inhibitor: results from a first-in-human, phase I dose-escalation study in patients with FGFR genomically activated advanced solid tumors. *J Clin Oncol* 2017;35:2500.
24. Bunney TD, Wan S, Thiyagarajan N, Sutto L, Williams SV, Ashford P, et al. The effect of mutations on drug sensitivity and kinase activity of fibroblast growth factor receptors: a combined experimental and theoretical study. *EBioMedicine* 2015;2:194–204.
25. Leroy L, Cousin S, Italiano A. Genetic determinants of response to fibroblast growth factor receptor inhibitors in solid tumours. *Eur J Cancer* 2017;81:102–5.
26. W ohrle S, Bonny O, Beluch N, Gaulis S, Stamm C, Scheibler M, et al. FGF receptors control vitamin D and phosphate homeostasis by mediating renal FGF-23 signaling and regulating FGF-23 expression in bone. *J Bone Miner Res* 2011;26:2486–97.