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ORIGINAL REPORT

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

Lucia Nogova, Lecia V. Sequist, Jose Manuel Perez Garcia, Fabrice Andre, Jean-Pierre Delord, Manuel Hidalgo, Jan H.M. Schellens, Philippe A. Cassier, D. Ross Camidge, Martin Schuler, Ulka Vaishampayan, Howard Burris, G. Gary Tian, Mario Campone, Zev A. Wainberg, Wan-Teck Lim, Patricia LoRusso, Geoffrey I. Shapiro, Katie Parker, Xueying Chen, Somesh Choudhury, Francois Ringeisen, Diana Graus-Porta, Dale Porter, Randi Isaacs, Reinhard Buettner, and Jürgen Wolf

Author affiliations appear at the end of this article.

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Corresponding author: Jürgen Wolf, MD, Lung Cancer Group Cologne, Department of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, D-50937 Cologne, Germany; e-mail: juergen.wolf@uk-koeln.de.

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ABSTRACT

Purpose

This two-part, first-in-human study was initiated in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors (FGFRs) to determine the maximum tolerated dose (MTD), the recommended phase II dose (RP2D), and the schedule, safety, pharmacokinetics, pharmacodynamics, and antitumor activity of oral BGJ398, a selective FGFR1-3 tyrosine kinase inhibitor.

Patients and Methods

Adult patients were treated with escalating dosages of BGJ398 5 to 150 mg once daily or 50 mg twice daily continuously in 28-day cycles. During expansion at the MTD, patients with *FGFR1*-amplified squamous cell non–small-cell lung cancer (sqNSCLC; arm 1) or other solid tumors with *FGFR* genetic alterations (mutations/amplifications/fusions) received BGJ398 daily on a continuous schedule (arm 2), or on a 3-weeks-on/1-week-off schedule (arm 3).

Results

Data in 132 patients from the escalation and expansion arms are reported (May 15, 2015, cutoff). The MTD, 125 mg daily, was determined on the basis of dose-limiting toxicities in four patients (100 mg, grade 3 aminotransferase elevations [n = 1]; 125 mg, hyperphosphatemia [n = 1]; 150 mg, grade 1 corneal toxicity [n = 1] and grade 3 aminotransferase elevations [n = 1]). Common adverse events in patients treated at the MTD (n = 57) included hyperphosphatemia (82.5%), constipation (50.9%), decreased appetite (45.6%), and stomatitis (45.6%). A similar safety profile was observed using the 3-weeks-on/1-week-off schedule (RP2D). However, adverse event–related dose adjustments/interruptions were less frequent with the 3-weeks-on/1-week-off (50.0%) versus the continuous (73.7%) schedule. Antitumor activity (seven partial responses [six confirmed]) was demonstrated with BGJ398 doses ≥ 100 mg in patients with *FGFR1*-amplified sqNSCLC and *FGFR3*-mutant bladder/urothelial cancer.

Conclusion

BGJ398 at the MTD/RP2D had a tolerable and manageable safety profile and showed antitumor activity in several tumor types, including *FGFR1*-amplified sqNSCLC and *FGFR3*-mutant bladder/urothelial cancers.

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ASSOCIATED CONTENT

See accompanying Editorial on page 131

Appendix

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INTRODUCTION

The discovery of targetable genomic aberrations underlying cancer has led to impressive improvements in the treatment of a subset of patients with advanced cancers harboring such oncogenic drivers (eg, lung adenocarcinoma, melanoma).[1-3] However, novel personalized treatment strategies are missing in the vast majority of cancers.

Fibroblast growth factor receptor (FGFR) isoforms 1-4 and their 22 fibroblast growth factor

ligands interact in a tissue-specific manner to initiate downstream signaling pathways that regulate cell proliferation, migration, differentiation, and survival—processes required for a variety of cell functions including angiogenesis and calcium/phosphate homeostasis.[4-7] Genomic alterations in *FGFR1-3* (eg, gene amplifications, gain-of-function mutations, and chromosomal translocations) that trigger pathway activation[4,5,8] have been identified in bladder cancer,[9,10] squamous cell non–small-cell lung cancer (sqNSCLC),[11,12] squamous cell cancer of the head and neck,[13] endometrial cancer,[8,14] cholangiocarcinoma,[15] and breast cancer.[4,16-18]

Although inhibitors targeting multiple receptor tyrosine kinases, including FGFR, are clinically active in several cancers,[5] no FGFR-selective tyrosine kinase inhibitor (TKI) has been approved, and no TKI has been approved in a disease with a defined *FGFR* genetic alteration. BGJ398, an orally bioavailable, selective FGFR1 to 3 inhibitor (half maximal inhibitory concentration values range from 0.9 to 1.4 nM for FGFR1-3 to 60 nM for FGFR4),[19] inhibits proliferation and tumor growth in preclinical cancer models bearing *FGFR1-3* genetic alterations.[19,20]

On the basis of these preclinical data, we conducted a global, personalized phase I single-agent study to determine the maximum tolerated dose (MTD), recommended phase II dose (RP2D), schedule, safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of BGJ398 in patients with solid tumors bearing *FGFR* alterations (ClinicalTrials.gov identifier NCT01004224).

PATIENTS AND METHODS

Patients

Adults with solid tumors harboring *FGFR* alterations (eg, amplification, mutation, fusion) for whom no effective standard therapy exists were enrolled.

Patient selection criteria relative to *FGFR* genetic alterations are defined in the Appendix (online only). *FGFR* genetic alterations not specified in the protocol were compared with those in public databases (eg, COSMIC and dbSNP) and were adjudicated to determine suitability for enrollment, allowing for continual review and enrollment of patients with newly reported *FGFR* alterations suggestive of potential sensitivity to FGFR inhibition (Appendix Table A1, online only).

Patients with measurable/evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.0[21] and a WHO performance status ≤ 2[22] were eligible (Appendix). Patients with prior FGFR inhibitor (except TKI258) or MEK inhibitor treatment, a history or evidence of endocrine alteration of calcium/phosphate homeostasis or ectopic calcification/mineralization, or evidence of corneal disorder/keratopathy were excluded. Concomitant therapies increasing calcium/phosphate serum levels were not permitted.

Patient screening was conducted in seven countries at 18 study sites, with protocol and amendment approvals granted by each institution's review board/independent ethics committee. All applicable local regulations and principles of the Declaration of Helsinki were followed.[23] Patients provided written, informed consent before enrollment.

Study Design

The primary objective of this two-part phase I study was to determine the MTD, RP2D, and schedule of oral BGJ398. Secondary objectives included BGJ398 safety, tolerability, PK, PD, and antitumor activity. During dose escalation, sequential patient cohorts received BGJ398 5 (starting dose), 10, 20, 40, 60, 100, 125, and 150 mg once daily in continuous 28-day cycles (Fig 1). A twice daily 50-mg dose was also explored (after MTD/RP2D was established). At least three evaluable patients were treated in each cohort, and at least six patients were treated at the MTD/RP2D. During dose expansion, patients enrolled in one of three arms were treated at the MTD/RP2D: daily treatment of patients with *FGFR1*-amplified sqNSCLC (arm 1) or other *FGFR*-altered, advanced solid tumors (arm 2); and daily treatment on a 3-weeks-on/1-week-off schedule of patients with advanced solid tumors (excluding sqNSCLC; arm 3).

Dose-escalation decisions were guided by two adaptive Bayesian logistic regression models using the escalation-with-overdose-control principle, which estimated the rate of dose-limiting toxicities (DLTs), whether specific DLTs (Appendix) or adverse events (AEs)/laboratory abnormalities possibly related to BGJ398, resulting in failure to meet retreatment criteria. These models were reviewed, together with PK, PD, and safety assessments, and site investigator/personnel input to determine subsequent dose cohorts; intrapatient dose escalation was not allowed. The MTD was defined as the highest BGJ398 dose administered for ≥ 21 days resulting in DLTs in $\leq 33\%$ of patients during cycle 1. The probability of the dose with excessive toxicity ($> 33\%$) was $< 25\%$. DLT characterization and MTD determination were based on data from the dose-determining set, including patients who received the planned dose for ≥ 21 days in cycle 1 and were evaluated for safety for ≥ 28 days after the first dose or who experienced a DLT during cycle 1.

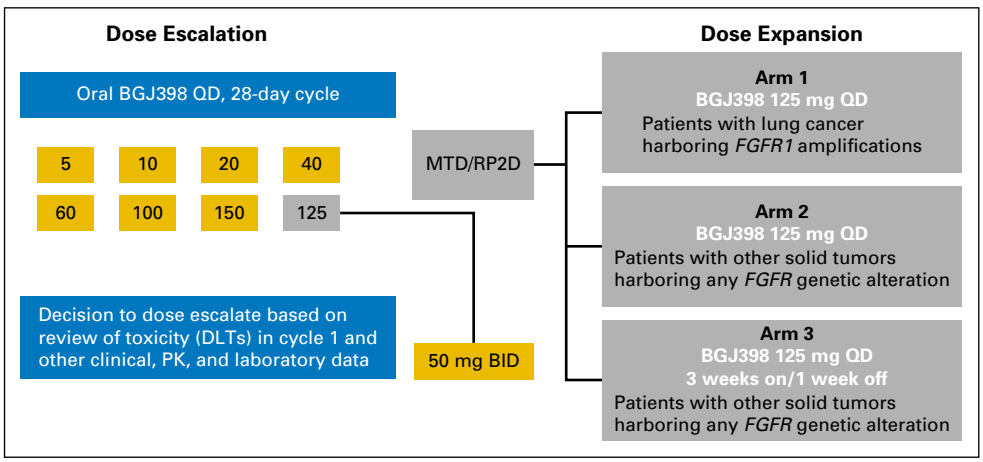

Fig 1. Study scheme. DLT, dose-limiting toxicity; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended phase II dose. BID, twice daily; QD, once daily.

Study Evaluations

Investigators assessed tumors at baseline and at every second treatment cycle until discontinuation (Appendix). Tumor evaluations were performed according to RECIST (version 1.0).[21] A best overall response (BOR) (either a complete response or a partial response [PR]) required a response lasting ≥ 4 weeks. A BOR of stable disease (SD) required a tumor assessment demonstrating SD for ≥ 6 weeks after treatment initiation.

Safety was assessed using Common Terminology Criteria for Adverse Events (version 3),[24] with monitoring of AEs until 28 days after the final dose, and periodic physical examinations, laboratory evaluations, and electrocardiograms. FGFRs contribute to phosphate/vitamin D metabolism[6,7]; thus, ophthalmologic examinations and assessments of calcium/phosphate homeostasis and renal function were performed (Appendix). PK and PD analyses are described in the Appendix.

Statistical Analyses

Descriptive statistics and/or contingency tables were used to summarize patient characteristics, efficacy and safety measurements, and PK. In a prespecified analysis, data from patients treated during dose escalation were used to determine the MTD/RP2D; subsequently, data were pooled with data from patients in the expansion phase who had the same dose and treatment schedule.

RESULTS

Patient Disposition and Baseline Characteristics

Data are reported from 132 heavily pretreated patients who started treatment between December 21, 2009, and April 7, 2015 (Table 1). At data cutoff (May 15, 2015), most patients (96.2%) had discontinued treatment, primarily because of disease progression (PD; 67.4%), AEs (12.9%), patient decision (10.6%), or death (3.8%; Appendix Table A2, online only).

Table 1. Patient Demographics and Disease History

Baseline Characteristic	All Patients (N = 132)
Age	
Median (range), years	60 (25-86)
≥ 65 years	37 (28.0)
Sex, male	62 (47.0)
WHO performance status	
0	64 (48.5)
1	65 (49.2)
2	3 (2.3)
Prior antineoplastic regimens	
1	26 (19.7)
2	33 (25.0)
3	21 (15.9)
4	13 (9.8)
> 4	39 (29.5)
Primary site of cancer	
Lung	48 (36.4)
Breast	43 (32.6)
Bladder/urothelial	12 (9.1)
Colon	5 (3.8)
Liver	3 (2.3)
Head and neck	3 (2.3)
Other*	18 (13.6)
Dose level, mg once daily	
5	3 (2.3)
10	3 (2.3)
20	4 (3.0)
40	6 (4.5)
60	3 (2.3)
100	6 (4.5)
125	57 (43.2)
125, 3 weeks on/1 week off	40 (30.3)
150	6 (4.5)
50†	4 (3)

NOTE. Data are presented as No. (%) unless indicated otherwise.
*Includes bone sarcoma, cervix, esophagus, gall bladder ducts, kidney, oral cavity, ovary, prostate, rectum, and other.
†Twice daily.

Safety

The median duration of BGJ398 exposure was 7.1 weeks (range, 0.6 to 101.0 weeks; N = 132). Treatment-emergent AEs (TEAEs) were reported in 131 patients (99.2%), with most (95.5%) experiencing at least one AE suspected to be treatment related. Hyperphosphatemia (74.2%), constipation (40.2%), and decreased appetite (40.2%) were the most commonly reported TEAEs across all doses (Table 2). The most common AE suspected to be treatment related was asymptomatic hyperphosphatemia (72.7%); other frequent treatment-related AEs included stomatitis (36.4%), decreased appetite (28.8%), diarrhea (27.3%), fatigue (25.0%), alopecia (23.5%), and nausea (22.0%). Grade 3/4 TEAEs were reported in 69 patients (52.3%). Forty-one patients (31.1%) experienced a grade 3/4 AE suspected to be treatment related (Table 2). Seventy-eight patients (59.1%), primarily at ≥ 100-mg doses, experienced an AE requiring dose adjustment or interruption. Eighteen patients (13.6%) had an AE leading to discontinuation (eye related in six patients [4.5%]). Fifteen patients died while receiving treatment or within 28 days of the last BGJ398 dose (Appendix Table A3, online only); 11 were attributed to PD or to related AEs. One death was suspected to be BGJ398 related (Appendix Table A3).

DLTs, experienced by four of the 34 patients (11.8%) in the dose-determining set, included grade 3 increases in ALT/AST (n = 1 each at 100 and 150 mg), hyperphosphatemia (n = 1, 125 mg), and grade 1 corneal toxicity (n = 1, 150 mg). DLTs were reversible after BGJ398 interruption and/or concomitant medication. The BGJ398 MTD was determined as 125 mg once daily. Common AEs in patients treated at this dose and schedule (n = 57) included hyperphosphatemia (82.5%), constipation (50.9%), decreased appetite (45.6%), and stomatitis (45.6%). Dose adjustments/interruptions and AEs leading to discontinuations occurred in 73.7% and 10.5% of patients, respectively.

The DLT of hyperphosphatemia and the observation that most patients treated with doses ≥ 100 mg experienced AEs of hyperphosphatemia (Table 2) prompted the initiation of additional analyses to evaluate BGJ398 dose/schedule adjustment. Hyperphosphatemia was managed through dietary restrictions, phosphate-lowering therapy, and drug interruptions. Earlier data from 43 patients treated at 125 mg once daily revealed a median time to first dose interruption of 22 days and a median duration of interruption of 7 days. Considering these data and the properties of BGJ398 PK, an intermittent 3-weeks-on/1-week-off schedule of 125 mg once daily was introduced as a dose-expansion arm in a protocol amendment (Appendix Table A1).

The safety profile of BGJ398 125 mg in patients treated on the intermittent schedule was similar to that observed in patients treated continuously. Fewer patients experienced AEs requiring dose adjustment/interruption (50%), but the rate of AEs leading to

Table 2. TEAEs Occurring in > 10% of All Patients by Treatment

AE	BGJ398 5-60 mg Once Daily (n = 19)	BGJ398 100 mg Once Daily (n = 6)	BGJ398 125 mg Continuous Once Daily (n = 57)	BGJ398 125 mg Once Daily 3 Weeks On/1 Week Off (n = 40)	BGJ398 150 mg Once Daily (n = 6)	BGJ398 50 mg Twice Daily (n = 4)	All Patients (N = 132)	
							All Grades	Grade 3/4
Any TEAE	19 (100)	6 (100)	57 (100)	39 (97.5)	6 (100)	4 (100)	131 (99.2)	69 (52.3)
Grade 3/4 treatment-related AEs	3 (15.8)	3 (50.0)	18 (31.6)	14 (35.0)	2 (33.3)	1 (25.0)	—	41 (31.1)
TEAEs leading to dose adjustment or interruption	4 (21.1)	5 (83.3)	42 (73.7)	20 (50.0)	4 (66.7)	3 (75.0)	78 (59.1)	—
TEAEs leading to treatment discontinuation	4 (21.1)	2 (33.3)	6 (10.5)	5 (12.5)	1 (16.7)	0	18 (13.6)	—
Serious TEAEs	3 (15.8)	2 (33.3)	23 (40.4)	16 (40.0)	3 (50.0)	1 (25.0)	48 (36.4)	—
Eye-related TEAEs	6 (31.6)	4 (66.7)	27 (47.4)	19 (47.5)	2 (33.3)	2 (50.0)	60 (41.4)	4 (3.0)
TEAEs reported in > 10% of patients								
Hyperphosphatemia	5 (26.3)	6 (100)	47 (82.5)	31 (77.5)	5 (83.3)	4 (100)	98 (74.2)	7 (5.3)
Constipation	1 (5.3)	3 (50.0)	29 (50.9)	18 (45.0)	0	2 (50.0)	53 (40.2)	1 (0.8)
Appetite decreased	2 (10.5)	3 (50.0)	26 (45.6)	17 (42.5)	3 (50.0)	2 (50.0)	53 (40.2)	5 (3.8)
Stomatitis	0	4 (66.7)	26 (45.6)	15 (37.5)	2 (33.3)	1 (25.0)	48 (36.4)	3 (2.3)
Diarrhea	7 (36.8)	5 (83.3)	16 (28.1)	14 (35.0)	1 (16.7)	3 (75.0)	46 (34.8)	0
Nausea	6 (31.6)	4 (66.7)	16 (28.1)	13 (32.5)	3 (50.0)	3 (75.0)	45 (34.1)	2 (1.5)
Fatigue	6 (31.6)	0	16 (28.1)	18 (45.0)	1 (16.7)	2 (50.0)	43 (32.6)	4 (3.0)
Alopecia	0	2 (33.3)	16 (28.1)	13 (32.5)	1 (16.7)	0	32 (24.2)	1 (0.8)
Creatinine increased	1 (5.3)	1 (16.7)	15 (26.3)	9 (22.5)	1 (16.7)	0	27 (20.5)	0
Dry mouth	4 (21.1)	1 (16.7)	11 (19.3)	10 (25.0)	0	1 (25.0)	27 (20.5)	0
Dyspnea	2 (10.5)	2 (33.3)	11 (19.3)	10 (25.0)	1 (16.7)	1 (25.0)	27 (20.5)	7 (5.3)
Vomiting	2 (10.5)	1 (16.7)	13 (22.8)	10 (25.0)	0	1 (25.0)	27 (20.5)	3 (2.3)
Asthenia	1 (5.3)	2 (33.3)	11 (19.3)	8 (20.0)	1 (16.7)	2 (50.0)	25 (18.9)	1 (0.8)
Dry eye	1 (5.3)	2 (33.3)	9 (15.8)	10 (25.0)	1 (16.7)	0	23 (17.4)	1 (0.8)
Dyspepsia	3 (15.8)	2 (33.3)	9 (15.8)	5 (12.5)	2 (33.3)	2 (50.0)	23 (17.4)	0
Alanine aminotransferase increased	2 (10.5)	1 (16.7)	12 (21.1)	5 (12.5)	1 (16.7)	0	21 (15.9)	9 (6.8)
Abdominal pain	2 (10.5)	1 (16.7)	8 (14.0)	6 (15.0)	0	3 (75.0)	20 (15.2)	1 (0.8)
Aspartate aminotransferase increased	2 (10.5)	1 (16.7)	12 (21.1)	4 (10.0)	1 (16.7)	0	20 (15.2)	6 (4.5)
Dysgeusia	1 (5.3)	3 (50.0)	9 (15.8)	6 (15.0)	0	0	19 (14.4)	0
Back pain	4 (21.1)	0	5 (8.8)	5 (12.5)	2 (33.3)	2 (50.0)	18 (13.6)	0
Pyrexia	3 (15.8)	1 (16.7)	7 (12.3)	7 (17.5)	0	0	18 (13.6)	1 (0.8)
Anemia	1 (5.3)	2 (33.3)	6 (10.5)	8 (20.0)	0	0	17 (12.9)	0
Cough	3 (15.8)	1 (16.7)	6 (10.5)	5 (12.5)	1 (16.7)	0	16 (12.1)	0
Epistaxis	0	1 (16.7)	9 (15.8)	4 (10.0)	1 (16.7)	0	15 (11.4)	0
Lipase increased	3 (15.8)	1 (16.7)	6 (10.5)	4 (10.0)	0	1 (25.0)	15 (11.4)	7 (5.3)
Arthralgia	0	1 (16.7)	6 (10.5)	5 (12.5)	1 (16.7)	1 (25.0)	14 (10.6)	0
Hypercalcemia	2 (10.5)	0	6 (10.5)	5 (12.5)	0	1 (25.0)	14 (10.6)	3 (2.3)
Weight decreased	0	0	10 (17.5)	3 (7.5)	1 (16.7)	0	14 (10.6)	0

NOTE. Data are presented as No. (%).
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

discontinuation (12.5%) and the most common AEs were similar in the two schedules (Table 2). On the basis of these data, the RP2D for BGJ398 was chosen as 125 mg once daily administered in the 3-weeks-on/1-week-off schedule. With this regimen, the majority of patients achieved exposures above the threshold associated with preclinical evidence of FGFR pathway inhibition and in vivo efficacy (Fig 2).[20]

PK

BGJ398 mean plasma concentration time profiles and area under the plasma concentration-time curve by cohort, starting at dosages ≥ 20 mg once daily, are presented in Fig 2. Estimated PK parameters are reported in Appendix Table A4 (online only). Plasma concentrations for BGJ398 at dosages of 5 mg and 10 mg once daily were frequently below the lower limit of quantification (data not shown).

The median time to reach maximum plasma concentration after a single dose was approximately 2 to 3 hours. The mean area under the plasma concentration-time curve from 0 to 24 hours on day 1 increased by approximately nine-fold, from 20 to 150 mg once daily. Despite the relatively short median terminal elimination half-life on day 1 for these doses (range, 2.69 to 5.90 hours), accumulation was observed with dosing of ≥ 60 mg once daily;

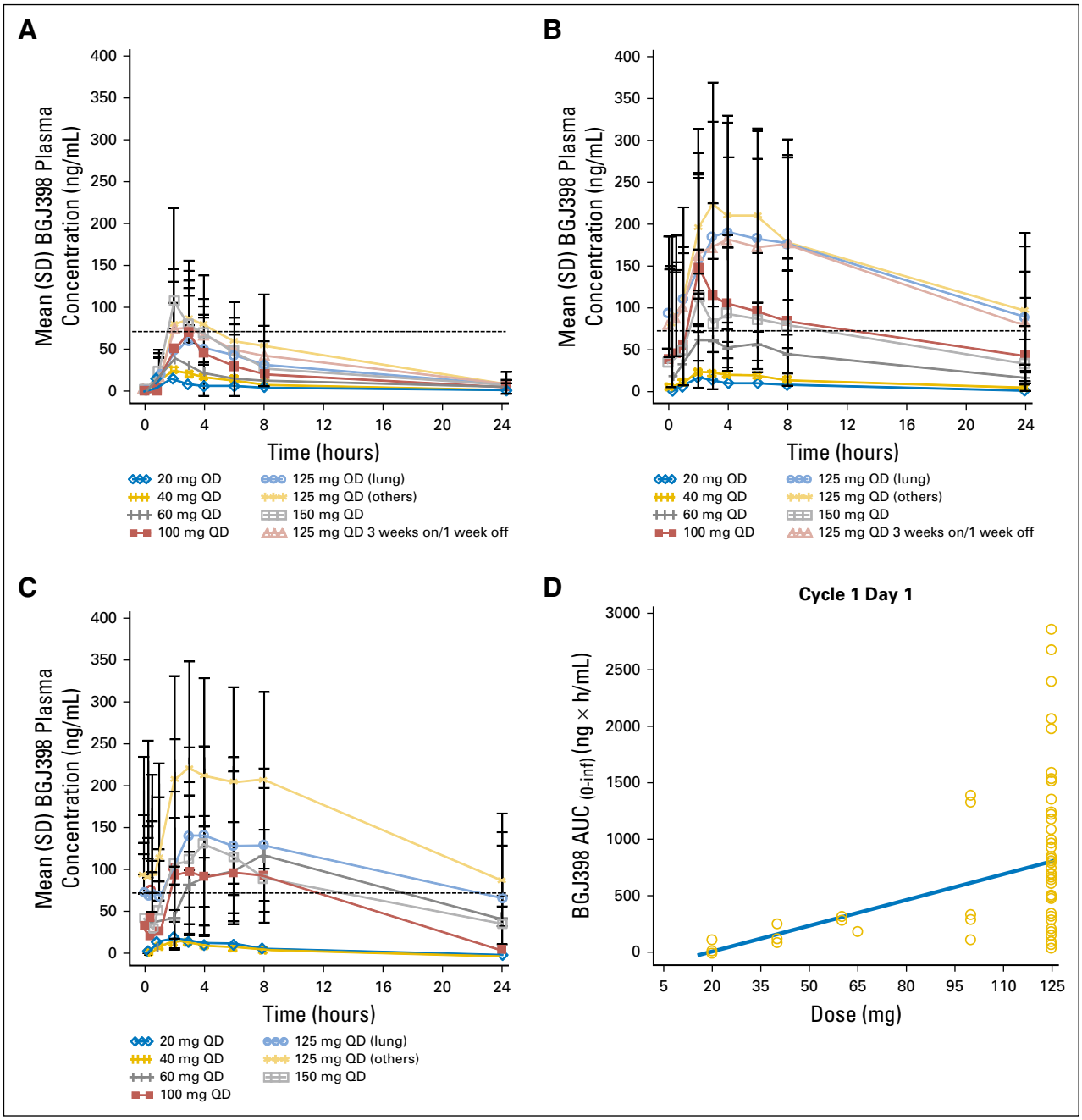

Fig 2. Pharmacokinetics of BGJ398. AUC, area under the plasma concentration-time curve; inf, infinity; QD, once daily; SD, standard deviation.

mean accumulation ratios ranged from 3.78 to 6.60 (day 15) and from 2.99 to 7.86 (day 28). After 125 mg once daily dosing, the unbound average steady-state BGJ398 concentration on day 28 of cycle 1 was 6.93 nM. Because dose interruptions occurred frequently after continuous once daily dosing, PK parameters on day 28 should be interpreted with caution.

Clinical Activity

Among all the patients treated with BGJ398 (N = 132), 42 had a BOR of SD, six achieved PR, and one achieved an unconfirmed PR (confirmatory scan performed 1 day early). Among the 85 patients treated at ≥ 100 mg with evaluable data, 28 (32.9%) had reduced tumor burden assessed as the best percentage change from baseline in the sum of the longest diameter in the target lesion or lesions (Fig 3).

The disease control rate (DCR: PR + SD) in 36 patients with *FGFR1*-amplified sqNSCLC treated at doses of ≥ 100 mg continuously was 50%; four patients (11.1%) achieved PRs (100 mg [n = 1], 125 mg [n = 3, 2 confirmed]) and 14 patients had SD. In the subset of 31 patients treated at 125 mg continuously, 12 continued to receive treatment for > 8 weeks, and one half of these patients continued to receive therapy for ≥ 16 weeks (Fig 4).

Twenty-seven of the 36 patients treated at ≥ 100 mg had pre- and post-treatment target lesion assessments; of these, 11 (40.7%) had reduced tumor burden (Fig 3; Appendix Table A5, online only). The responders remained on study for 39.9 to 76.6 weeks (confirmed PRs) and for 26.3 weeks (unconfirmed PR).

The DCR in eight patients with *FGFR3*-mutated bladder/urothelial cancer treated at doses ≥ 100 mg was 75%; three patients (37.5%) achieved PRs (125 mg continuously [n = 1], 125 mg 3-weeks-on/1-week-off [n = 2]) and three patients had SD. Five patients (62.5%) had reduced tumor burden and two of three with SD had reductions in tumor measurements nearing PR (27% to 28%; Fig 3). Of the six patients with disease control, the time receiving treatment ranged from 15.1 to ≥ 101 weeks, with one ongoing at data cutoff (Fig 4). One patient withdrew after 2 weeks; this patient had PD in an assessment performed 25 days after the last dose. Of note, one patient with *FGFR1*-amplified bladder cancer treated at 125 mg progressed rapidly in cycle 1 after 11 days of treatment.

Although no other PRs were observed at doses ≥ 100 mg, 10 of 32 patients (31%) with breast cancer treated at ≥ 100 mg had a best response of SD. Of 26 patients with breast cancer (*FGFR1/2* amplified [n = 25]; *FGFR3* mutant [n = 1]) with pre- and post-treatment target lesion measurements, four (15.4%) had reduced tumor burden. In addition, all three patients with *FGFR2*-altered (fusion [n = 2] or mutation [n = 1]) cholangiocarcinoma with pre- and post-treatment target lesion assessments had reduced tumor burden (Fig 3).

PD

BGJ398 treatment led to increased serum phosphate levels (Appendix Fig A1A, online only), as well as to dose- and exposure-related hyperphosphatemia, in most patients treated at doses ≥ 100 mg (Table 2). The median percentage change in FGF23 plasma levels ranged from approximately −25% to 80%, with a trend toward greater increases in patients treated at higher doses (Appendix Fig A1B).

DISCUSSION

This global first-in-human study of the FGFR1-3 inhibitor BGJ398 demonstrated a tolerable safety profile in patients with advanced

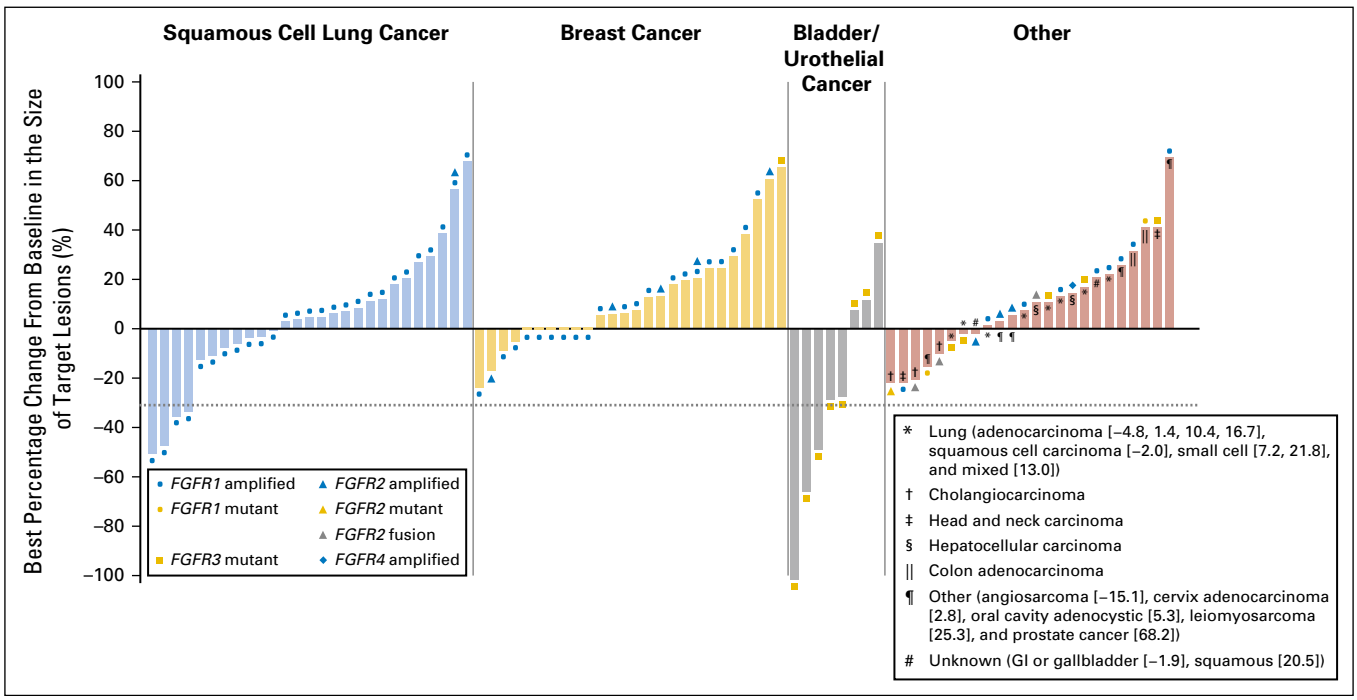

Fig 3. Waterfall plots of best change from baseline in the size of target lesions for patients treated at ≥ 100 mg BGJ398.

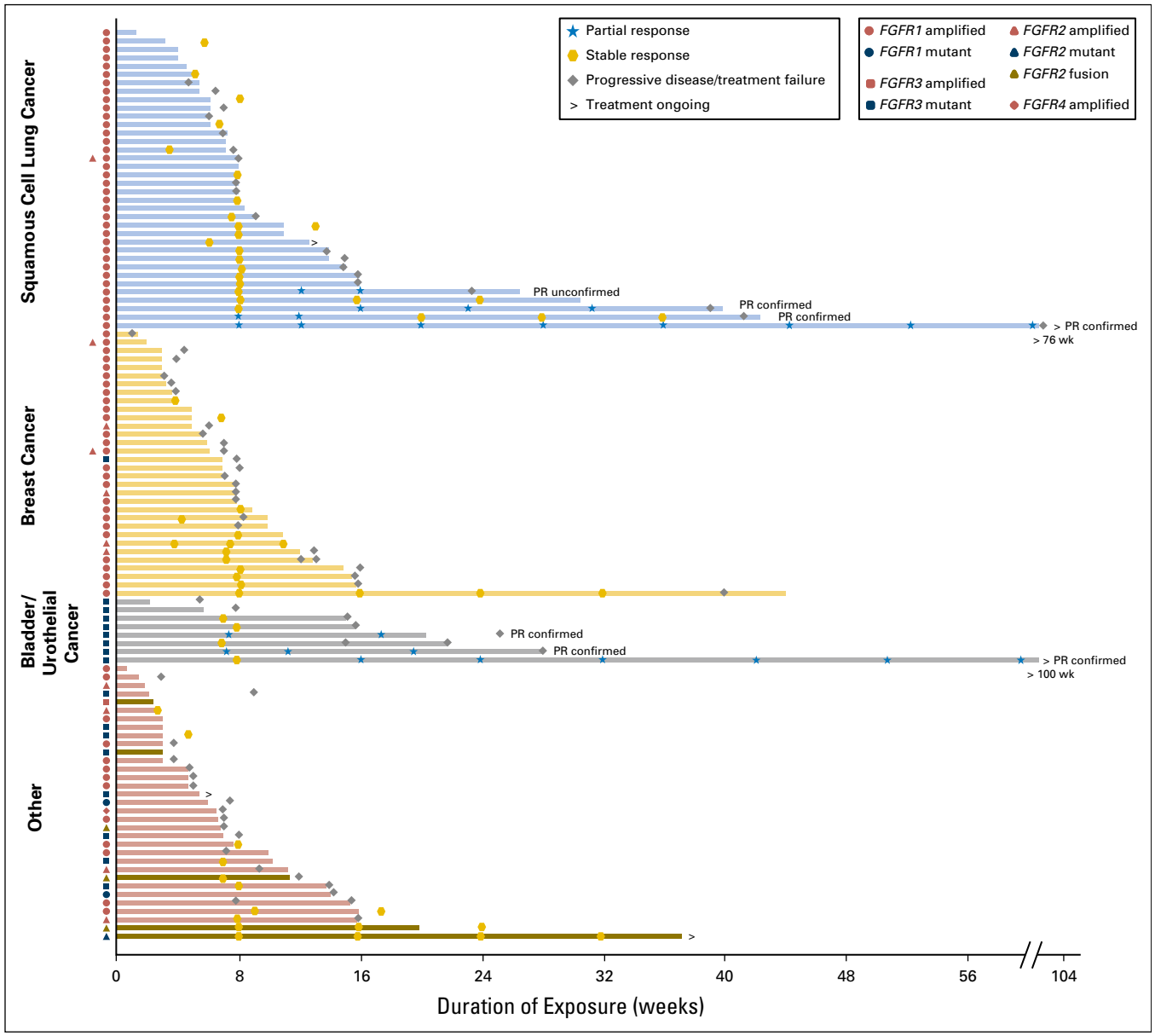

Fig 4. Response and duration of exposure in patients treated at BGJ398 doses ≥ 100 mg. Among the patients with other cancer types were five patients with cholangiocarcinoma (green bars). PR, partial response.

solid tumors bearing *FGFR* amplifications, mutations, or fusions. The BGJ398 MTD/RP2D was determined to be 125 mg daily; the recommended schedule at the RP2D was 3 weeks on/1 week off on the basis of DLTs observed in four patients treated at doses ≥ 100 mg, BGJ398 PK, and safety data in patients treated on the intermittent schedule. This BGJ398 dose resulted in an average unbound steady-state concentration of 6.93 nM, which is similar to the half maximal inhibitory concentration of BGJ398 in the RT112 human tumor-derived *FGFR* gene fusion bladder cancer cell line (4 nM).[25] Commonly reported AEs included hyperphosphatemia, constipation, decreased appetite, and stomatitis. A similar safety profile was observed with the pan-FGFR inhibitor JNJ-42756493.[26]

The FGFR pathway plays an important role in FGF23-mediated phosphate homeostasis.[6,7] Accordingly, hyperphosphatemia, the most common AE, was experienced by most patients receiving ≥ 100 mg BGJ398.[27] An intermittent dosing arm (125 mg once daily 3 weeks on/1 week off) was opened during dose expansion to manage hyperphosphatemia-related interruptions, resulting in fewer patients requiring an AE-related dose adjustment/interruption (50.0% *v* 73.7% [continuous]). Importantly, objective responses and reductions in tumor measurements were observed with both schedules, with similar overall safety profiles. Further exploration of BGJ398 dosing may be performed in the context of ongoing or future trials.

Because the FGF23/FGFR pathway mediates renal tubular phosphate secretion,[7] FGF23 levels were used initially as a biomarker for FGFR pathway inhibition. Median FGF23 levels increased by ≤ 80% in patients treated with BGJ398, with generally higher levels at higher doses. Elevated serum phosphate levels,

consistently observed with BGJ398 doses ≥ 100 mg, proved to be a sensitive, dose-dependent PD indicator of on-target activity and a key biomarker for FGFR pathway inhibition.

BGJ398 treatment provided disease control in 49 of 132 patients across all doses, with PRs observed in patients with *FGFR1*-amplified sqNSCLC (n = 4) and *FGFR3*-mutant bladder/urothelial cancer (n = 3). The clinical activity observed in *FGFR1*-amplified sqNSCLC (11% overall response rate, 50% DCR) is notable given the unfavorable prognosis for patients who relapse after chemotherapy.[28] Moreover, the duration on study for responding patients (6.1 to 17.7 months) is comparable to that achieved with nivolumab, an anti–PD-1 antibody approved in metastatic sqNSCLC after failure of platinum-based chemotherapy.[29-32] To date, no oncogenic driver-targeted drug has shown activity as a monotherapy, raising the possibility of a molecularly definable sqNSCLC subtype sensitive to FGFR inhibition. Despite preselecting for *FGFR1* amplification, the response rate was lower than expected on the basis of preclinical data, suggesting that *FGFR1* amplification may not function as a sole biomarker predicting clinical benefit.[11] Although the basis for this discrepancy (eg, tumor heterogeneity, different amplification parameters, and/or presence of required cofactors)[33,34] remains unknown, BGJ398 use as a personalized treatment approach in sqNSCLC warrants further investigation. Future whole genome analyses may help define the exploitable molecular differences between responders and nonresponders,[34] providing further insight into additional oncogenic drivers in sqNSCLC.

Responses observed in *FGFR3*-mutant bladder/urothelial cancer after failure of platinum-based chemotherapy (38% overall response rate, 75% DCR) strongly support a role for *FGFR3* mutations as driver alterations in this molecular subgroup and the potent inhibitory function of BGJ398. In light of the < 1-year overall survival for patients with metastatic urothelial/bladder cancer after relapse after first-line chemotherapy,[35] BGJ398-targeted treatment warrants further investigation. To this end, a fourth expansion arm was opened to further evaluate BGJ398 activity in patients with urothelial cancer harboring an *FGFR3* mutation or fusion.

SD with reduced tumor burden was also observed in patients with cholangiocarcinoma (*FGFR2* fusions [n = 2], *FGFR2* mutation [n = 1]) and *FGFR1*-amplified squamous head and neck cancer. The disease control observed in cholangiocarcinoma is notable given the limited treatment options available for patients who progress after chemotherapy.[36,37] Of interest, another patient with cholangiocarcinoma who was enrolled with a presumed *FGFR3* mutation progressed rapidly and was later identified to be wild type for *FGFR* but as having a mutation in *KRAS*, a negative predictor (preclinically) for BGJ398 sensitivity.[20] A phase II study exploring BGJ398 as a second-line or later therapy in patients with *FGFR2*-altered advanced/metastatic cholangiocarcinoma is ongoing (ClinicalTrials.gov identifier NCT02150967).

The lack of objective responses and the limited disease control observed with BGJ398 in patients with breast cancer challenge the idea of *FGFR* amplification as a sole oncogenic driver in this disease; however, BGJ398 may prove more effective against advanced breast cancer when combined with other endocrine or targeted agents. Certain *FGFR* alterations (eg, *FGFR3* mutations/gene fusions in bladder/urothelial carcinoma and *FGFR2* gene fusions in cholangiocarcinoma) are dominant oncogenic drivers and confer sensitivity to BGJ398-mediated FGFR inhibition, whereas *FGFR1* amplification, observed in a number of tumor types including sqNSCLC and breast cancer, may not be sufficient to identify a BGJ398-sensitive population. It is unclear whether alternative or additional biomarkers (eg, FGFR1 protein levels or FGFR pathway activity) would better predict responders, or whether FGFR signaling is less essential for tumor growth in breast cancer.

When this study was initiated in 2009, predictors of FGFR inhibitor sensitivity were limited. As the knowledge of FGFR biology and driver genetic alterations increased and assays for patient selection became available over the 6-year enrollment period, patient inclusion criteria were amended accordingly (Appendix Table A1). This study allowed the clinical evaluation of multiple preclinical hypotheses related to BGJ398-mediated FGFR pathway sensitivity and established which patient populations were likely to benefit from treatment with an FGFR-selective inhibitor.

Taken together, treatment with BGJ398 in patients with advanced solid tumors bearing *FGFR* alterations was tolerable, with manageable toxicity. The MTD/RP2D was determined to be 125 mg once daily on a 3-weeks-on/1-week-off schedule. BGJ398 demonstrated antitumor activity in *FGFR1*-amplified sqNSCLC, *FGFR3*-mutant bladder/urothelial cancer, and *FGFR2*-gene fusion/mutant cholangiocarcinoma, strongly supporting further biologic and clinical investigation. BGJ398 clinical development is ongoing, including adding a fourth expansion arm to this study for patients with urothelial carcinoma and *FGFR3* mutation/gene fusion and a phase II study in cholangiocarcinoma with *FGFR2* gene fusion/other *FGFR* genetic alterations.[38,39]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

Conception and design: Jose Manuel Perez Garcia, Manuel Hidalgo, Jan H.M. Schellens, D. Ross Camidge, Howard Burris, Somesh Choudhury, Francois Ringeisen, Randi Isaacs, Reinhard Buettner, Jürgen Wolf
Administrative support: Martin Schuler
Provision of study materials or patients: Lucia Nogova; Lecia V. Sequist, Manuel Hidalgo, D. Ross Camidge, Martin Schuler, Ulka Vaishampayan, Howard Burris, G. Gary Tian, Geoffrey I. Shapiro, Jürgen Wolf
Collection and assembly of data: Lucia Nogova, Lecia V. Sequist, Jean-Pierre Delord, Jan H.M. Schellens, D. Ross Camidge, Martin Schuler, Ulka Vaishampayan, Howard Burris, G. Gary Tian, Mario Campone, Wan-Teck Lim, Patricia LoRusso, Geoffrey I. Shapiro, Katie Parker, Somesh Choudhury, Francois Ringeisen, Randi Isaacs, Reinhard Buettner, Jürgen Wolf
Data analysis and interpretation: Lucia Nogova, Lecia V. Sequist, Fabrice Andre, Manuel Hidalgo, Jan H.M. Schellens, Philippe A. Cassier, D. Ross Camidge, Ulka Vaishampayan, Howard Burris, Zev A. Wainberg, Wan-Teck Lim, Patricia LoRusso, Geoffrey I. Shapiro, Katie Parker, Xueying Chen, Somesh Choudhury, Francois Ringeisen, Diana Graus-Porta, Dale Porter, Randi Isaacs, Reinhard Buettner, Jürgen Wolf
Manuscript writing: All authors
Final approval of manuscript: All authors

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Affiliations

Lucia Nogova, **Reinhard Buettner**, and **Jürgen Wolf**, University Hospital Cologne, Cologne; **Martin Schuler**, University Hospital Essen, and German Cancer Consortium (DKTK), Essen, Germany; **Lecia V. Sequist**, Massachusetts General Hospital; **Geoffrey I. Shapiro**, Dana-Farber Cancer Institute, Boston, MA; **Jose Manuel Perez Garcia**, Vall d'Hebron Institut d'Oncologia, Barcelona; **Manuel Hidalgo**, START Madrid; **Manuel Hidalgo**, Spanish National Cancer Research Centre, Madrid, Spain; **Fabrice Andre**, Gustave Roussy, Villejuif; **Jean-Pierre Delord**, Institute Universitaire du Cancer de Toulouse, Toulouse; **Philippe A. Cassier**, Centre Regional Leon-Berard, Lyon; **Mario Campone**, Institute de Cancerologie de l'Ouest-René Gauducheau, Nantes, France; **Jan H.M. Schellens**, Netherlands Cancer Institute, Amsterdam, and Utrecht University, Utrecht, the Netherlands; **D. Ross Camidge**, University of Colorado, Aurora, CO; **Ulka Vaishampayan**, Barbara Ann Karmanos Cancer Institute, Detroit, MI; **Howard Burris**, Sarah Cannon Research Institute, Nashville; **G. Gary Tian**, The West Clinic, Memphis, TN; **Zev A. Wainberg**, UCLA School of Medicine, Los Angeles, CA; **Wan-Teck Lim**, National Cancer Centre, Singapore; **Patricia LoRusso**, Yale Cancer Center, New Haven, CT; **Katie Parker**, **Xueying Chen**, **Somesh Choudhury**, and **Randi Isaacs**, Novartis Pharmaceuticals Corporation, East Hanover, NJ; **Dale Porter**, Novartis Institutes for Biomedical Research, Cambridge, MA; **Francois Ringeisen**, Novartis Pharma AG; and **Diana Graus-Porta**, Novartis Institutes for Biomedical Research, Basel, Switzerland.

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Lucia Nogova
Honoraria: Pfizer
Consulting or Advisory Role: Boehringer Ingelheim, Roche
Research Funding: Pfizer
Travel, Accommodations, Expenses: Novartis, Pfizer

Lecia V. Sequist
Honoraria: AstraZeneca
Consulting or Advisory Role: Clovis Oncology, Novartis, Merrimack, AstraZeneca, ARIAD Pharmaceuticals, Genentech
Research Funding: Boehringer Ingelheim (Inst), Clovis Oncology (Inst), Genentech (Inst), Merrimack (Inst), ArQule (Inst), Novartis (Inst), AstraZeneca (Inst), Johnson & Johnson (Inst), Eli Lilly (Inst), Merck (Inst), Taiho Pharmaceutical (Inst)

Jose Manuel Perez Garcia
No relationship to disclose

Fabrice Andre
Research Funding: AstraZeneca (Inst), Novartis (Inst), Pfizer (Inst), Eli Lilly (Inst)

Jean-Pierre Delord
No relationship to disclose

Manuel Hidalgo
Stock or Other Ownership: Champions Oncology
Honoraria: Pfizer, Novartis, Merck Sharp & Dohme, Celgene
Consulting or Advisory Role: Novartis, Pfizer, Celgene, Merck, Eli Lilly/ImClone Systems
Research Funding: Pfizer, Celgene, Merck Serono
Travel, Accommodations, Expenses: Pfizer, Celgene, Merck

Jan H.M. Schellens
No relationship to disclose

Philippe A. Cassier
Honoraria: Novartis
Research Funding: Novartis (Inst)
Travel, Accommodations, Expenses: PharmaMar

D. Ross Camidge
Honoraria: Novartis

Martin Schuler
Honoraria: Alexion Pharmaceuticals, Boehringer Ingelheim, Celgene, Eli Lilly, Novartis, Pfizer, Bristol-Myers Squibb
Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Novartis
Research Funding: Boehringer Ingelheim (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst)
Patents, Royalties, Other Intellectual Property: University of Duisburg-Essen
Travel, Accommodations, Expenses: Merck Sharp & Dohme

Ulka Vaishampayan
Honoraria: Astellas Pharma, Pfizer, Janssen Pharmaceuticals, Novartis, Bayer AG, Sanofi, Bristol-Myers Squibb
Consulting or Advisory Role: Pfizer, Novartis, Astellas Pharma, Sanofi, Bristol-Myers Squibb
Speakers' Bureau: Pfizer, Novartis, Astellas Pharma, Bayer AG, Bristol-Myers Squibb
Research Funding: Astellas Pharma, Novartis, Exelixis, Pfizer

Howard Burris
No relationship to disclose

G. Gary Tian
Consulting or Advisory Role: Cardinal Health, Merrimack
Travel, Accommodations, Expenses: Cardinal Health

Mario Campone
Honoraria: Novartis, Servier, Menarini
Consulting or Advisory Role: Novartis, Servier, Menarini, Cellgen
Speakers' Bureau: Novartis, Amgen
Research Funding: Novartis (Inst)
Travel, Accommodations, Expenses: Novartis

Zev A. Wainberg
Consulting or Advisory Role: Taiho Pharmaceutical, Sirtex Medical, Amgen
Speakers' Bureau: Genentech
Research Funding: Novartis (Inst), Plexxikon (Inst), Pfizer (Inst), Biomarin (Inst), Merck (Inst)
Travel, Accommodations, Expenses: Genentech, Eli Lilly, Amgen

Wan-Teck Lim
Consulting or Advisory Role: Boehringer Ingelheim, Bristol-Myers Squibb, Novartis
Travel, Accommodations, Expenses: Boehringer Ingelheim, Roche

Patricia LoRusso
Consulting or Advisory Role: Astex Pharmaceuticals, Novartis, Astellas Pharma, Genentech, ARIAD Pharmaceuticals, Alexion Pharmaceuticals, Celgene
Research Funding: Genentech (Inst), Novartis (Inst), Merrimack (Inst), Immunogen (Inst), Tensha Therapeutics (Inst), Taiho Pharmaceutical (Inst), Roche (Inst), Incyte (Inst)

Geoffrey I. Shapiro
Consulting or Advisory Role: Vertex, Chugai Pharmaceutical, G1 Therapeutics, Eli Lilly, EMD Serono, Takeda Pharmaceuticals, Tesaro
Research Funding: Pfizer (Inst), Genentech (Inst), Bayer AG (Inst), Immune Design (Inst), Vertex (Inst), Millennium Pharmaceuticals (Inst), Puma Biotechnology (Inst), Tensha Therapeutics (Inst), Covidien (Inst), Novartis (Inst), Cellceutix (Inst), Sanofi (Inst), Cyclacel (Inst), Mirati Therapeutics (Inst), AstraZeneca (Inst), GlaxoSmithKline (Inst), Eli Lilly, Aileron (Inst), PharmaMar (Inst), PTC Therapeutics (Inst)

Katie Parker
Employment: Novartis
Stock or Other Ownership: Novartis (stock options)

Xueying Chen
Employment: Novartis

Somesh Choudhury
Employment: Novartis
Stock or Other Ownership: Novartis
Travel, Accommodations, Expenses: Novartis

Francois Ringeisen
Employment: Novartis
Stock or Other Ownership: Novartis

Diana Graus-Porta
Employment: Novartis
Stock or Other Ownership: Novartis

Dale Porter
Employment: Novartis
Stock or Other Ownership: Novartis
Patents, Royalties, Other Intellectual Property: Novartis

Randi Isaacs
Employment: Novartis
Stock or Other Ownership: Novartis
Patents, Royalties, Other Intellectual Property: Use patent for a particular drug in a specific indication

Reinhard Buettner
Stock or Other Ownership: Targos Molecular Pathology
Speakers' Bureau: Roche, Boehringer Ingelheim, Novartis, Pfizer, Merck Sharp & Dohme, Merck, Bristol-Myers Squibb, QIAGEN, Eli Lilly

Jürgen Wolf
Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Clovis Oncology, Novartis, Pfizer, Roche
Consulting or Advisory Role: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Clovis Oncology, Novartis, Pfizer, Roche
Research Funding: Novartis (Inst), Pfizer (Inst), Roche (Inst), Bristol-Myers Squibb (Inst)

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Appendix

Methods

Molecular Prescreening. Molecular prescreening to assess *FGFR* genetic alteration status was implemented after a protocol amendment and before enrollment of cohort 4 during the dose-escalation phase (BGJ398 40 mg once daily). Patient eligibility was determined on the basis of *FGFR* alteration status as assessed centrally or locally using fresh and/or archival tumor samples. Data on the number of patients prescreened versus the number of patients enrolled are not available, because this information was not reported by study sites that performed local assessment of eligibility.

Patients were eligible for enrollment if one of the following genetic alteration criteria was met: (1) *FGFR1* or *FGFR2* amplification was identified using fluorescence in situ hybridization (defined as a ratio of the respective FGFR to chromosome enumeration probe 8 [*FGFR1*] or chromosome enumeration probe 10 [*FGFR2*] of ≥ 2.2 or an average *FGFR* copy number of six or more signals/nucleus in ≥ 20 contiguous cells from two tumor areas); chromogenic or silver-enhanced in situ hybridization (defined as an average respective *FGFR* copy number of six or more signals/nucleus or a large gene cluster in $\geq 30\%$ of tumor cells from ≥ 100 contiguous cells from two tumor areas); or quantitative polymerase chain reaction (defined as a respective *FGFR* copy number of at least six); (2) *FGFR3* mutations were detected in exon 7 (R248C, S249C), exon 10 (G372C, A393E, Y375C), or exon 15 (K652M/T, K652E/Q); or (3) other *FGFR* genetic alterations, including gene fusions, were identified.

Alterations other than those described above were reviewed against public databases (eg, COSMIC and dbSNP), and enrollment was approved by study personnel for appropriate alterations (eg, to exclude known single-nucleotide polymorphisms and synonymous substitutions, or to include more recently identified somatic missense mutations). The intent of including unspecified *FGFR* alterations, such as fusions, in the prescreening evaluation was to adapt to the rapidly evolving understanding of the role of *FGFR* in various cancer types and to allow the enrollment of patients with previously unknown activating *FGFR* alterations (Appendix Table A1).

Additional Patient Enrollment Criteria. Patients were required to have adequate bone marrow (absolute neutrophil count $\geq 1{,}500/\mu L$ [$\geq 1.5 \times 10^9/L$]; platelets $\geq 75{,}000/\mu L$ [$\geq 75 \times 10^9/L$]; and hemoglobin ≥ 10 mg/dL [≥ 100 g/L]) and renal and hepatic function (serum creatinine $\leq 1.5 \times$ the upper limit of normal [ULN]; calculated or measured creatinine clearance $> 75\%$ lower limit of normal; and proteinuria grade ≤ 1, total bilirubin $\leq 1.5 \times$ ULN, AST and ALT $\leq 2.5 \times$ ULN, and serum albumin is greater than or equal to the lower limit of normal). Further requirements for inclusion included balanced calcium-phosphate homeostasis and adequate cardiovascular function, including a heart rate–corrected QT interval ≤ 470 ms and blood pressure within the normal range.

Patients with primary CNS tumors or CNS tumor involvement were not eligible for enrollment, unless clinically stable. Concomitant therapies prolonging the QT interval or associated with a risk of torsades de pointes were not permitted.

Study Design Rationale. During dose escalation, sequential patient cohorts received BGJ398 5 (starting dose), 10, 20, 40, 60, 100, 125, and 150 mg once daily in continuous 28-day cycles. Fifty milligrams twice daily was also investigated after the maximum tolerated dose (MTD)/recommended phase II dose was established. Patients treated at 100 mg once daily had drug exposures approaching the predicted efficacious level (unbound BGJ398 concentration of 70 ng/mL) on the basis of preclinical data[20]; however, a high degree of variability in exposure among patients was observed, and one patient experienced a dose-limiting toxicity of reversible grade 3 AST/ALT that resulted in dose interruption and modification during cycle 1. This variability in exposure was not observed at 60 mg once daily. These data supported further exploration of alternative dosing schedules for BGJ398, and the twice daily dose cohort was added in Amendment 5 (Jan 2012; Appendix Table A1). Enrollment in the 50 mg twice daily cohort began after the MTD was established, and was completed before patients were treated in expansion arms 1 and 2. The twice daily dosing schedule was not investigated further, because variability in exposure was also observed with this schedule, and suboptimal concentrations were achieved relative to predicted levels associated with preclinical efficacy.

Tumor Evaluations. Tumors were evaluated, using chest and abdomen computed tomography and, in patients with a history of brain metastases, cranial computed tomography or brain magnetic resonance imaging, at baseline and within 14 days of every second treatment cycle until discontinuation.

Pharmacokinetic Assessments. Serial blood samples were collected predose and up to 24 hours postdose on days 1, 15, and 28 of cycle 1. Samples were processed, and plasma was frozen at ≤ -60°C until analysis.

BGJ398 plasma concentrations were measured using a validated liquid chromatography–tandem mass spectrometry method with a 1.0 ng/mL lower limit of quantification. Pharmacokinetic (PK) parameters, including maximum plasma concentration, area under the plasma concentration-time curve, time to reach maximum plasma concentration, and half-life, were calculated using noncompartmental methods with Phoenix (Pharsight, Mountain View, CA). Descriptive statistics (mean, median, and standard deviation) were estimated for PK parameters in each cohort. Median values and ranges were provided for half-life and maximum plasma concentration.

Pharmacodynamic Assessments. Blood samples for determination of fibroblast growth factor (FGF) 23 levels were collected predose on days 1, 2, and 15 of cycle 1 and day 1 on cycles 2 and 3, as well as 4 and 8 hours postdose on day 1. Fibroblast growth factor 23 levels were assessed using standard methods. Median percentage changes in fibroblast growth factor 23 levels from baseline were plotted by dose.

Specific Dose-Limiting Toxicities. Specific dose-limiting toxicities modeled in the second adaptive Bayesian logistic regression model included corneal opacity, ectopic mineralization/calcification, or elevated serum creatinine (grade 1 for > 7 consecutive days) and serum ionized phosphorus (Pi) > 5.5 mg/dL and/or total serum calcium $\times$ Pi > 55 mg^2/dL^2 despite Pi-lowering therapy for ≥ 14 days.

Hyperphosphatemia Grading, Management, and Prevention. Because grading for hyperphosphatemia is not defined in the Common Terminology Criteria for Adverse Events (version 3) guidelines,[24] hyperphosphatemia was defined in this study as any value above the ULN, and severity was based on investigator discretion; severe hyperphosphatemia was considered grade 3. During dose escalation, treatment with phosphate binders was initiated when serum phosphate levels exceeded 5.5 mg/dL, with the goal of maintaining levels at ≤ 7 mg/dL. Prophylactic use of phosphate binders was instituted after the MTD determination and was used routinely in the dose expansion cohorts. Dose interruption was indicated when phosphate levels remained > 7 mg/dL despite the use of phosphate binders for ≥ 14 days.

Results

The BGJ398 125-mg dose level was determined to be the MTD on the basis of clinical safety and PK data and was supported quantitatively by the Bayesian logistic regression models used in this study. The 3-weeks-on/1-week-off intermittent schedule was investigated on the basis of the observation that the majority of patients being treated with the 125 mg once daily dosing schedule required dose interruptions by day 22 to control hyperphosphatemia, with interruptions lasting 7 days (median). The 3-weeks-on/1-week-off schedule was evaluated in an attempt to establish a regimen that allowed control of hyperphosphatemia over the course of the cycle. In addition, although exposure was variable, the majority of patients treated at 125 mg once daily achieved BGJ398 exposures above the threshold associated with preclinical evidence of fibroblast growth factor receptor pathway inhibition and in vivo efficacy.[20] Although the data are limited, this was not the case for patients treated at the 100 mg once daily dosage. It was recognized that many patients required dose reduction over the course of their therapy for the management of chronic toxicities; however, given the fact that patients with *FGFR* alterations are rare and are not easily identified, we chose to initiate treatment with a dose most likely to provide clinical benefit. Moreover, the rate of hyperphosphatemia and the overall safety profile between the 100-mg and 125-mg dose levels was not substantially different; therefore, 125 mg once daily 3 weeks on/1 week off was selected as the optimal BGJ398 dose and schedule for further exploration.

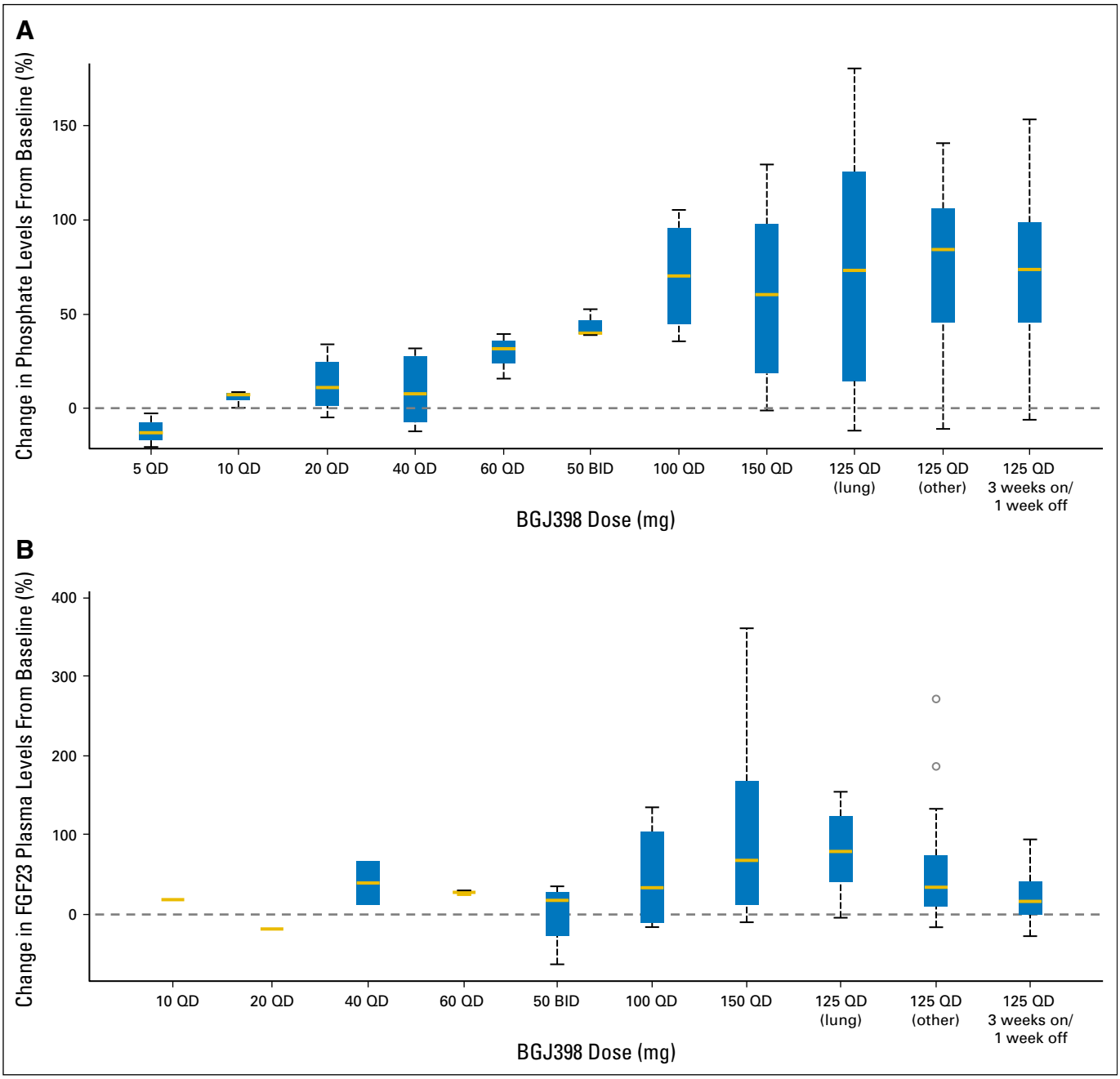

Fig A1. Pharmacodynamics of BGJ398. Percentage change from baseline in (A) phosphate and (B) FGF23 plasma levels on cycle 1 day 15 by dose. Median values are shown as box plots. BID, twice daily; FGF, fibroblast growth factor; QD, once daily.

Table A1. Study Protocol Amendments and Patient Molecular Screening

Protocol/Amendment	Date Released	Patient Prescreening/Molecular Eligibility	Rationale for Protocol Amendment/ Reference(s)
Original protocol	Aug 2009	No molecular preselection	
Amendment 1	Feb 2010	No molecular preselection	
Amendment 2	May 2010	With the availability of new clinical biomarker tests, enrollment was limited to patients with advanced solid tumors harboring *FGFR1* or *FGFR2* gene amplification or *FGFR3* gene mutation. The molecular selection criteria were implemented before enrollment of patients at the 40-mg dose level during dose escalation.	This amendment allowed for an earlier readout of pharmacodynamic markers in the patient population harboring genetic alterations in the FGFR pathway, made feasible by the clinical availability of biomarker tests and emerging epidemiology of the different subpopulations. The state of understanding at that time regarding the genetic basis of sensitivity to BGJ398 was described by Guagnano et al,[20] with evidence of BGJ398 sensitivity in preclinical models of *FGFR* amplification in breast and lung cancer and hotspot mutations in bladder cancer.
Amendment 3	Apr 2011	An option was added for central laboratory evaluation to detect *FGFR1* amplification in squamous cell lung cancer. Before the amendment, patients with squamous cell lung cancer with *FGFR1* amplification were eligible for enrollment on the basis of a molecular analysis performed by a local laboratory at an individual study site.	This amendment was implemented to improve enrollment, because local laboratory testing was not available at some study sites. Both local and central laboratories used stringent guidelines to define amplification, as described in the Appendix.
Amendment 4	Sep 2011	This amendment allowed the opening of a dedicated expansion arm at the MTD/RP2D for patients with squamous cell carcinoma harboring *FGFR1* amplification. Quantitative PCR was added as a methodology for detection of *FGFR1* amplification.	On the basis of newly published evidence,[11,12] this amendment allowed probing for early signs of activity in a specific population of patients with squamous cell lung cancer and *FGFR1* amplification. Quantitative PCR was added to the approved study methodologies to expand the ability of study sites to perform local testing.
Amendment 5	Jan 2012	This amendment introduced an alternative twice daily BGJ398 dosing schedule (50 mg).	With exposure levels in the predicted efficacious range at 100 mg once daily but also variable PK parameters, the PK profile achieved with an alternative twice daily schedule was compared with the PK profile after 100 mg once daily dosing.
Amendment 6	Jun 2012	This amendment allowed the enrollment of patients with any *FGFR* genetic alteration. The change also allowed patients to be enrolled on the basis of *FGFR* amplification identified using methods other than fluorescence in situ hybridization, chromogenic in situ hybridization, silver-enhanced in situ hybridization, or reverse transcriptase PCR.	To address the evolving understanding of *FGFR* contributions to human cancer, this change allowed exploration of potential BGJ398 activity in patients with advanced tumors carrying *FGFR* amplification or other *FGFR* genetic alterations that are potentially oncogenic drivers to be enrolled. Patients with *FGFR* gene fusions were also permitted to be enrolled on the basis of a report of *FGFR3-TACC* fusions in patients with glioblastoma published later in 2012* and personal communications in advance of a 2013 publication† regarding the use of MiOncoseq to identify *FGFR2* fusions in patients with cholangiocarcinoma. The underlying mechanism of previously observed sensitivity of bladder cancer cell lines to BGJ398[20] was later explained by a publication in early 2013 reporting *FGFR3* gene fusions in human bladder cancer.[10] In addition, patient enrollment was enhanced by allowing additional options for genetic screening.

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Table A1. Study Protocol Amendments and Patient Molecular Screening (continued)

Protocol/Amendment	Date Released	Patient Prescreening/Molecular Eligibility	Rationale for Protocol Amendment/ Reference(s)
Amendment 7	Jun 2013	This amendment allowed the opening of an expansion arm (arm 3), which used an alternative BGJ398 dosing schedule of 125 mg once daily 3 weeks on/1 week off for patients with advanced solid tumors harboring any *FGFR* genetic alteration (including gene amplification, mutation, or fusion).	Initiated a new expansion arm using an alternative dosing schedule implemented to aid management of hyperphosphatemia.
Amendment 8	Apr 2014	This amendment allowed the opening of an expansion arm (arm 4) dedicated to evaluating BGJ398 in patients with advanced or metastatic urothelial carcinoma with an *FGFR3* gene mutation or fusion.	Expansion arm 4 specifically evaluated BGJ398 in a patient population deemed sensitive on the basis of phase I study results as detailed in this article. With this amendment, new study sites were opened in current countries and in an additional eight countries, bringing the total number of study sites to 57 and enabling patient enrollment in an *FGFR3*-altered urothelial carcinoma study arm.
Amendment 9	Apr 2015	This amendment made no change to molecular screening/eligibility.	

Abbreviations: *FGFR*, fibroblast growth factor receptor. MTD, maximum tolerated dose; PCR, polymerase chain reaction; PK, pharmacokinetics; RP2D, recommended phase II dose.
*Singh D, et al: Science 337:1231-1235, 2012.
†Wu, et al: Cancer Discov 3:636-647, 2013.

Table A2. Patient Disposition

Treatment Status	BGJ398 Daily Dose					BGJ398 50 mg Twice Daily (n = 4)	All Patients (N = 132)
	5-60 mg (n = 19)	100 mg (n = 6)	125 mg Continuous (n = 57)	125 mg 3 Weeks On/ 1 Week Off (n = 40)	150 mg (n = 6)		
Treatment ongoing	19 (100)	6 (100)	55 (96.5)	37 (92.5)	6 (100)	4 (100)	127 (96.2)
Treatment discontinued	0	0	2 (3.5)	3 (7.5)	0	0	5 (3.8)
Primary reason for discontinuation							
Disease progression	13 (68.4)	4 (66.7)	36 (63.2)	29 (72.5)	4 (66.7)	3 (75.0)	89 (67.4)
Adverse event	4 (21.1)	2 (33.3)	6 (10.5)	4 (10.0)	1 (16.7)	0	17 (12.9)
Patient decision	2 (10.5)	0	8 (14.0)	3 (7.5)	1 (16.7)	0	14 (10.6)
Death	0	0	3 (5.3)	1 (2.5)	0	1 (25.0)	5 (3.8)
Protocol deviation	0	0	1 (1.8)	0	0	0	1 (0.8)
Administrative problem	0	0	1 (1.8)	0	0	0	1 (0.8)

NOTE. Data are presented as No. (%).

Table A3. Deaths

Patient	Tumor Type	Dose (mg once daily)	Study Day of Last Dose	Study Day of Death	Primary Cause of Death
1	Lung	125	27	29	Sepsis
2	Lung	125	50	51	Cardiac arrest*
3	Lung	125	7	10	Sepsis
4	Lung	125	96	114	Respiratory failure secondary to progressive disease
5	Lung	125	64	77	Squamous cell carcinoma
6	Lung	125	57	75	Lung cancer
7	Squamous cell carcinoma	125	110	114	Squamous cell carcinoma
8	Anal	125†	21	31	Respiratory failure
9	Breast	125†	14	27	Breast cancer
10	Esophageal	125†	14	42	Tumor progression
11	Bladder	125†	155	171	Bladder cancer
12	Renal	125†	11	39	Respiratory failure caused by progressive disease
13	Prostate/urothelial	125†	21	32	Urothelial cancer
14	Lung	150	104	115	Tumor progression
15	Lung	50‡	29	34	Not reported (unknown disease-related event)

*This 75-year-old male with advanced non–small-cell lung cancer died as a result of cardiac arrest 1 day after the last dose of the study drug. The patient had no clinical symptoms for myocardial infarction. Disease progression was suspected to be the cause; however, in the absence of a follow-up computed tomography scan to confirm, and without any other clear cause of death, this patient's death was reported as suspected to be related to BGJ398 treatment.
†Three weeks on/1 week off.
‡Twice daily.

Table A4. BGJ398 Pharmacokinetic Parameters (once daily doses)

BGJ398 Once Daily Dose/Parameter	$AUC_{(0\text{-}24\ h)}$ (h × ng/mL)	$AUC_{(0\text{-}inf)}$ (h × ng/mL)	C_{max} (ng/mL)	T_{max} (hours)	$T_{1/2}$ (hours)	R_{acc}
Cycle 1 day 1						
20 mg (n = 4)						
No.	3	3	4	4	3	—
Mean (SD)	71.79 (38.29)	78.30 (48.35)	15.80 (3.71)	—	—	—
Median	58.84	60.05	16.00	2.04	2.69	—
40 mg (n = 6)						
No.	5	4	6	6	4	—
Mean (SD)	167.39 (61.57)	185.97 (71.66)	27.22 (11.83)	—	—	—
Median	159.96	179.23	25.10	2.08	4.15	—
60 mg (n = 3)						
No.	3	2	3	3	2	—
Mean (SD)	255.18 (74.95)	310.79 (32.37)	42.37 (25.92)	—	—	—
Median	277.66	310.79	53.10	2.00	5.61	—
100 mg (n = 6)						
No.	6	5	6	6	6	—
Mean (SD)	473.05 (445.10)	469.35 (527.10)	76.42 (82.66)	—	—	—
Median	320.30	318.50	54.10	3.00	5.71	—
125 mg lung (n = 30)						
No.	23	18	29	29	22	—
Mean (SD)	581.35 (481.59)	660.88 (566.64)	71.59 (60.76)	—	—	—
Median	495.59	568.39	51.40	3.00	5.05	—
125 mg other (n = 26)						
No.	22	16	26	26	19	—
Mean (SD)	938.47 (603.45)	1057.38 (683.66)	115.98 (75.00)	—	—	—
Median	810.28	929.43	121.50	3.00	5.90	—
125 mg 3 weeks on/1 week off (n = 39)						
No.	33	27	36	36	30	—
Mean (SD)	846.50 (658.44)	788.55 (606.72)	92.81 (58.43)	—	—	—
Median	708.74	669.10	71.90	3.00	4.88	—
150 mg (n = 6)						
No.	6	6	6	6	6	—
Mean (SD)	677.90 (343.78)	706.82 (353.33)	118.65 (105.74)	—	—	—
Median	710.07	726.87	91.05	2.63	5.20	—
Cycle 1 Day 15						
20 mg (n = 4)						
No.	4	3	4	4	4	3
Mean (SD)	212.58 (210.41)	115.14 (47.99)	20.85 (4.28)	—	—	2.82 (1.59)
Median	133.18	131.51	19.35	1.99	5.91	2.45

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Table A4. BGJ398 Pharmacokinetic Parameters (once daily doses) (continued)

BGJ398 Once Daily Dose/Parameter	$AUC_{(0\text{-}24\ h)}$ (h × ng/mL)	$AUC_{(0\text{-}inf)}$ (h × ng/mL)	C_{max} (ng/mL)	T_{max} (hours)	$T_{1/2}$ (hours)	R_{acc}
40 mg (n = 6)						
No.	4	2	5	5	3	3
Mean (SD)	183.48 (113.07)	229.95 (144.09)	30.24 (18.64)	—	—	0.82 (0.50)
Median	191.98	229.95	28.00	2.07	6.17	0.91
60 mg (n = 3)						
No.	3	2	3	3	2	3
Mean (SD)	1,007.57 (477.30)	1,081.47 (749.36)	80.37 (44.54)	—	—	4.37 (2.86)
Median	1260.03	1081.47	85.70	2.08	9.84	4.13
100 mg (n = 6)						
No.	4	2	5	5	4	4
Mean (SD)	1,375.03 (1,244.19)	685.42 (600.48)	136.70 (104.59)	—	—	5.65 (3.51)
Median	1,045.91	685.42	93.70	3.00	7.89	5.75
125 mg lung (n = 30)						
No.	15	4	23	23	12	11
Mean (SD)	3,483.83 (2,991.54)	732.88 (549.51)	209.14 (137.37)	—	—	8.18 (5.43)
Median	3,240.82	708.11	219.00	4.00	15.43	6.60
125 mg other (n = 26)						
No.	19	2	22	22	12	16
Mean (SD)	3,902.68 (2,261.84)	2,950.53 (450.98)	261.44 (137.80)	—	—	5.88 (4.67)
Median	3,442.56	2950.53	235.00	3.54	11.12	4.49
125 mg 3 weeks on/1 week off (n = 39)						
No.	23	2	29	29	12	20
Mean (SD)	3,296.27 (1,998.18)	900.93 (440.79)	212.68 (115.07)	—	—	7.63 (6.85)
Median	3,183.30	900.93	244.00	4.12	11.55	4.78
150 mg (n = 6)						
No.	4	2	4	4	3	3
Mean (SD)	1,565.50 (1,671.84)	757.30 (727.61)	133.98 (139.23)	—	—	3.38 (2.92)
Median	1,025.44	757.30	85.30	3.00	9.34	3.78
Cycle 1 Day 28						
20 mg (n = 4)						
No.	3	2	3	3	2	2
Mean (SD)	146.81 (46.90)	133.59 (66.45)	22.80 (2.41)	—	—	2.52
Median	163.67	133.59	22.60	2.00	5.30	2.52
40 mg (n = 6)						
No.	3	3	4	4	3	2
Mean (SD)	179.03 (160.81)	201.66 (209.85)	18.35 (11.59)	—	—	1.35 (0.02)
Median	158.37	139.61	19.25	3.02	2.76	1.35
60 mg (n = 3)						
No.	1	0	2	2	1	1
Mean (SD)	2,192.88	—	113.95 (49.57)	—	—	6.93
Median	2,192.88	—	113.95	4.09	12.46	6.93
100 mg (n = 6)						
No.	4	1	5	5	3	3
Mean (SD)	1,977.52 (1,475.18)	438.58	117.90 (82.26)	—	—	6.37 (5.95)
Median	1,765.09	438.58	112.00	3.08	20.14	2.99
125 mg lung (n = 30)						
No.	18	2	19	19	13	13
Mean (SD)	2,427.38 (1,934.85)	202.81 (80.69)	153.53 (107.66)	—	—	10.00 (13.76)
Median	2,286.07	202.81	153.00	3.20	17.62	6.23
125 mg other (n = 26)						
No.	13	1	17	17	10	6
Mean (SD)	3,405.44 (1,819.50)	4,093.22	273.63 (137.04)	—	—	4.98 (1.66)
Median	4,091.88	4,093.22	274.00	4.00	15.88	5.43
150 mg (n = 6)						
No.	4	1	4	4	2	2
Mean (SD)	1,835.90 (581.88)	1,909.96	146.75 (19.67)	—	—	7.86 (8.79)
Median	1,784.66	1,909.96	151.50	2.99	12.44	7.86

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; R_{acc}, accumulation ratio; $T_{1/2}$, terminal elimination half-life; T_{max}, time to reach maximum plasma concentration

Table A5. *FGFR* Mutations and Fusions

Best Percentage Change in Tumor	Tumor Type	*FGFR* Genetic Alteration
−15.1	Angiosarcoma	*FGFR1* S125L mutation
−100	Bladder/urothelial carcinoma	*FGFR3* S249C mutation
−65.0	Bladder/urothelial carcinoma	*FGFR3* S249C mutation
−48.2	Bladder/urothelial carcinoma	*FGFR3* S249C mutation
−28.2	Bladder/urothelial carcinoma	*FGFR3* S249C mutation
11.4	Bladder/urothelial carcinoma	*FGFR3* S249C mutation
−27.3	Bladder/urothelial carcinoma	*FGFR3* K652E mutation
7.3	Bladder/urothelial carcinoma	*FGFR3* K652E mutation
34.2	Bladder/urothelial carcinoma	*FGFR3* Y373C mutation
64.3	Breast	*FGFR3* F384L mutation
−21.7	Cholangiocarcinoma	*FGFR2* N549S mutation
−20.2	Cholangiocarcinoma	*FGFR2* 10Q26.13 fusion (partner unknown)
−9.8	Cholangiocarcinoma	*FGFR2* BICC1 fusion
40.4	Colon adenocarcinoma	*FGFR1* S125L mutation
40.4	Head and neck carcinoma	*FGFR3* R248C mutation
10.4	Hepatocellular carcinoma	*FGFR2* BICC1 fusion
−4.8	Lung adenocarcinoma	*FGFR3* F384L mutation
16.7	Lung adenocarcinoma	*FGFR3* F384L mutation
10.4	Lung adenocarcinoma	*FGFR3* F386L mutation
−2.0	Lung squamous cell carcinoma	*FGFR3* S249C mutation

NOTE. Table includes patients treated at ≥ 100 mg and who had an *FGFR* mutation or fusion noted by any methodology and were included in the evaluation of best change from baseline in the sum of longest diameters in target lesion(s).
Abbreviation: FGFR, fibroblast growth factor receptor.