Invest New Drugs (2013) 31:742–750
DOI 10.1007/s10637-012-9881-z

PHASE I STUDIES

A Phase 1 dose-escalation study of the safety and pharmacokinetics of once-daily oral foretinib, a multi-kinase inhibitor, in patients with solid tumors

Geoffrey I. Shapiro · Stewart McCallum · Laurel M. Adams · Laurie Sherman · Steve Weller · Suzanne Swann · Harold Keer · Dale Miles · Thomas Müller · Patricia LoRusso

Received: 10 July 2012 / Accepted: 18 September 2012 / Published online: 6 October 2012

Summary Foretinib is an oral multi-kinase inhibitor targeting MET, vascular endothelial growth factor receptor (VEGFR)-2, RON, KIT, and AXL kinases. In this Phase 1, open-label, non-randomized study, foretinib was administered once daily at doses of 60 mg, 80 mg, 100 mg, or 120 mg for 28 days. The primary objectives were to determine the maximum tolerated dose (MTD) and assess the safety and tolerability of the daily oral administration schedule. Secondary objectives included pharmacokinetics, pharmacodynamics, and assessment of tumor response. Patients had histologically confirmed metastatic or unresectable solid tumors for which no standard treatments existed and all received oral foretinib once daily. Dose escalation was planned as a conventional "3+3" design with an expansion at the MTD for collection of additional safety and pharmacokinetic information. Thirty-seven patients were treated across four dose levels. The MTD was established as 80 mg foretinib. Dose-limiting toxicities were hypertension, dehydration, and diarrhea. The most common adverse events included fatigue, hypertension, nausea, and diarrhea. Twenty-three of 31 patients (74 %) had a best response of stable disease. No patient had a confirmed partial or complete response. At the MTD, steady state was achieved by approximately 2 weeks, with average post-dose time to maximum concentration, peak concentration, and trough concentration of 4 h, 46 ng/mL, and 24 ng/mL, respectively. In patients treated at the MTD, soluble MET and VEGF-A plasma levels significantly increased ($P<0.003$) and soluble VEGFR2 plasma levels significantly decreased from baseline ($P<0.03$). The MTD of foretinib bisphosphate salt was determined to be 80 mg once daily.

Keywords Foretinib · Multi-kinase inhibitor · Solid tumors · GSK1363089 · XL880

Presented in part at ASCO 2007; Assays and Cellular Targets (ACT) 2007; AACR-NCI-EORTC 2007; AACR-NCI-EORTC 2009.

G. I. Shapiro
Dana-Farber Cancer Institute and Harvard Medical School,
Boston, MA, USA

S. McCallum · L. Sherman · S. Swann
GlaxoSmithKline,
Collegeville, PA, USA

L. M. Adams · S. Weller
GlaxoSmithKline,
Research Triangle Park,
Durham, NC, USA

H. Keer · D. Miles · T. Müller
Exelixis,
South San Francisco, CA, USA

P. LoRusso
Barbara Ann Karmanos Cancer Institute,
Detroit, MI, USA

L. M. Adams (✉)
Oncology Research and Development, GlaxoSmithKline,
Research Triangle Park,
Durham, NC, USA
e-mail: laurel.m.adams@gsk.com

Introduction

Aberrant signaling of MET, a tyrosine kinase receptor, is known to play an important role in the initiation and progression of several types of human cancers [1, 2]. The hepatocyte growth factor (HGF) is the only known ligand for MET and evidence supports roles for HGF/MET signaling in the regulation of cell proliferation, tissue invasion,

and metastasis [2–4]. This ligand:receptor complex is thought to mediate angiogenesis through down-regulation of thrombospondin-1, an inhibitor of angiogenesis and tumor growth, as well as up-regulation of vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis [5]. Furthermore, increased aggressiveness of tumors and poor prognosis in cancer patients is associated with overexpression of HGF and MET [5–11]. Preclinical data also suggest up-regulation of MET after treatment with a VEGF receptor (VEGFR) inhibitor could be a mechanism of resistance to anti-angiogenic therapies [12, 13].

Angiogenesis inhibitors that target VEGF signaling can prolong time to progression and, in some cases, overall survival of cancer patients, but, in many, the disease eventually progresses. One potential way to overcome therapeutic resistance to anti-VEGF therapy would be to combine inhibition of VEGFR signaling with inhibition of a different signal transduction pathway, such as the HGF/MET pathway. Preclinical evidence has demonstrated that combined HGF/MET and VEGF signaling increases the expression of VEGF-regulated genes and novel transcripts in endothelial cells [14], as well as prevents endothelial cell apoptosis, forms capillaries *in vivo*, and increases the microvessel density within tumors [5, 15]. Therefore, inhibition of both HGF/MET and VEGF/VEGFR could enhance the initial response to therapy and provide a potential solution to the expected compensatory hypoxic response [16–18]. The effectiveness of this dual inhibition has recently been demonstrated *in vivo* where XL184 (cabozantinib), a dual receptor tyrosine kinase inhibitor of both MET and VEGFR, was shown to be more effective in suppressing tumor growth, angiogenesis, and metastasis than inhibition of VEGF alone [13].

Foretinib is a small-molecule receptor tyrosine kinase inhibitor that (i) targets abnormal signaling of the HGF/MET ligand:receptor complex and (ii) simultaneously targets receptor tyrosine kinases involved in tumor angiogenesis, such as VEGFR2. *In vitro* and *in vivo*, foretinib has low nanomolar inhibitory activity for MET and VEGFR2 and high *in vitro* affinity for the kinases RON, KIT, and AXL. Foretinib induces a conformational change with a mean cellular target residence time of >24 h by binding tightly to the adenosine triphosphate pocket of MET and VEGFR2 [19, 20]. Preclinical data have demonstrated the potential of foretinib [19]. Foretinib inhibited tumor cell migration and invasion *in vitro* and xenograft growth of B16F10 human melanoma *in vivo*. Peak plasma levels required for optimal efficacy were 1–3 μM, but associated trough levels were 0.02–0.1 μM (Exelixis, data on file), consistent with producing a prolonged biological effect [19].

In the recently published first-time-in-human (FTIH) study, foretinib was administered for 5 consecutive days every 14 days [21]. Dose escalation followed a conventional "3+3" design. Forty patients were treated in eight dose cohorts. The maximum tolerated dose (MTD) was determined to be 3.6 mg/kg foretinib bisphosphate salt, with a maximum administered dose of 4.5 mg/kg on this schedule. Dose-limiting toxicities (DLTs) were grade 3 elevated levels of aspartate aminotransferase and lipase, and central nervous system hemorrhage. Partial responses (PR) were observed in two patients with papillary renal cell cancer and one patient with medullary thyroid cancer, and stable disease (SD) was observed for 22 patients [21].

The primary objectives of this subsequent Phase 1 study were to determine the MTD and to assess the safety and tolerability of foretinib bisphosphate salt administered once daily in patients with solid tumors. Secondary objectives included evaluation of the pharmacokinetics (PK) and pharmacodynamics (PD) of once-daily oral administration of foretinib and assessment of tumor response.

Methods

Patient selection

Eligible patients were ≥18 years of age with an Eastern Cooperative Oncology Group performance status of ≤2 and histologically confirmed solid tumors that were metastatic or unresectable and for which effective treatments did not exist. Patients were excluded if they had received chemotherapy, radiotherapy, cytokines, or an investigational agent within 30 days of enrollment, had received radiation to ≥25 % of bone marrow, were pregnant or lactating, had known brain metastases, or had uncontrolled, intercurrent illness. The medical ethics committees at both participating institutions approved the study, and all patients gave written informed consent prior to participation.

Study design

Foretinib bisphosphate salt was administered orally once daily in this Phase 1, open-label, non-randomized study (MET111648, NCT00743067). During the study treatment period days 1–28, PK and PD blood samples were collected at specified times and DLTs for MTD determination were assessed. Patients could receive further treatment with foretinib in the treatment extension period for up to a total of 1 year at the discretion of the investigator and beyond 1 year with the agreement of the sponsor. A conventional "3+3" design was planned for the dose-escalation phase to determine the MTD. An additional nine patients were enrolled at the MTD to obtain further safety data, and a separate cohort of 13 patients was enrolled at the MTD to better characterize the PK profile of foretinib. The medical ethics committees at both participating institutions approved the study and it was conducted in accordance with Good Clinical Practice and all

applicable regulatory requirements and guiding principles of the Declaration of Helsinki.

Study medication

Foretinib was provided as 20 mg and 100 mg capsules, formulated as bisphosphate salt (molecular weight=828.64 Da; free-base molecular weight=632.66 Da) and was administered orally at doses of 60 mg, 80 mg, 100 mg, and 120 mg once daily (free-base doses of approximately 46 mg, 61 mg, 76 mg, and 92 mg once daily).

Safety assessments

Safety was assessed through standard clinical and laboratory tests and recording of clinical adverse events and serious adverse events. After an ocular safety signal (night blindness) was observed with foretinib a complete eye examination, which included best corrected visual acuity, Goldman or Humphrey visual field evaluation, measurement of intraocular pressure, slit lamp examination, and dilated funduscopic examination, was performed every 6 months. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0 was used for grading [22]. DLTs were defined as any foretinib-related event occurring during the study treatment period that met any of the following criteria: 1) non-hematologic toxicity grade ≥3 (including grade 3 nausea and/or vomiting and diarrhea despite treatment and grade 3 hypertension despite optimal anti-hypertensive therapy); 2) any of the grade 4 hematologic toxicities thrombocytopenia, neutropenia of >4 days duration, or neutropenia of any duration with fever or documented infection; or 3) an indication that further dose escalation would have exposed subsequent patients in higher dose cohorts to risk of irreversible medical harm. Patients were considered evaluable for safety analyses if they received at least one dose of study drug.

Pharmacokinetic sampling and analysis

During the study treatment period, plasma samples for PK analysis were obtained prior to dosing and post-dose at 30 min and 1, 2, 4, 8, and 12 h on Day 1, pre-dose on Days 2, 8, 15, 22, and 29, and 4 h post-dose on Day 8. For patients in the expanded PK cohort, additional PK samples were obtained on Day 22 at 30 min and 1, 2, 4, 8, and 12 h post-dose and pre-dose on Day 23 and urine was collected pre-dose on Day 1 and as a 24-h pool starting immediately after dosing on Day 22.

Blood samples (approximately 7 mL each) were collected into potassium (K3) EDTA or potassium (K2) EDTA as the anti-coagulant. Plasma was separated by centrifugation and stored frozen at approximately −20 °C until shipped. All samples were analyzed at Exelixis (South San Francisco, CA, USA). The concentration of foretinib was measured in each plasma sample using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method, with a linear range of 0.5–500 ng/mL. The sample volume was 0.1 mL. Urine samples were shipped on dry ice to Exelixis for analysis. The concentration of foretinib was measured in each sample using a validated LC/MS/MS method, with a linear range of 0.5–500 ng/mL. The sample volume was 0.1 mL.

PK analysis of foretinib plasma concentration-time data was performed using standard non-compartmental methods to obtain estimates of maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the concentration-time curve (AUC), elimination half-life ($t_{1/2}$), and apparent oral clearance (CL/F). For CL/F determination (equal to dose divided by AUC), the free-base dose amount was used.

Pharmacodynamics

Blood samples were collected pre-dose on Days 1, 8, 15, 22, and 29. Blood (approximately 7 mL) was collected into potassium (K2) EDTA as the anti-coagulant. Plasma was separated by centrifugation and stored frozen at approximately −70 °C. Plasma levels of soluble MET (sMET), HGF, soluble VEGFR2 (sVEGFR2), and VEGF-A were measured using enzyme-linked immunosorbent assay at Pathway Diagnostics, Malibu, California, USA (now Quest Diagnostics Biomarker Lab, Valencia, California, USA) and at Exelixis (for sMET).

Tumor response

For patients with measurable lesions, tumor assessments were performed no more than 21 days prior to the first dose and approximately every 8 weeks thereafter using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 version [23]. To be assigned a status of complete response (CR) or PR, changes in tumor measurements must have been confirmed by repeat assessment performed more than 30 days after the criteria for response were first met. For stable disease, follow-up measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks. Patients were considered evaluable for response if they had received at least one dose of foretinib and had a baseline and at least one post-baseline tumor assessment.

Statistical methods

Descriptive statistics were used to summarize baseline characteristics, safety assessments, PK variables, and tumor response. Duration of SD was summarized using Kaplan–Meier methods. For PD markers, change from baseline was analyzed at each time point using analysis of variance.

Results

Patient characteristics and MTD determination

Thirty-seven patients were treated at four different dose levels between August 2006 and September 2009. Baseline characteristics are shown in Table 1. A wide variety of solid tumors were represented and patients were heavily pretreated.

The starting dose was 60 mg foretinib, followed by escalation to 80 mg and 120 mg. DLTs of grade 3 hypertension and grade 3 dehydration were seen in two of three patients in the 120 mg cohort. Since recent data at the time regarding angiogenesis suggested the importance of pushing this class of agent to maximum dose, an intermediate dose of 100 mg was assessed instead of immediately dropping back to the 80 mg dose. At 100 mg foretinib, a DLT of grade 3 diarrhea and grade 3 fatigue was seen in one of three patients. Of the remaining 2 patients, one experienced elevated creatinine and the third had hematuria. At this point it was felt that the 100 mg/day dose would not likely be tolerated chronically and the cohort was not expanded. Therefore, the MTD was estimated to be 80 mg. None of the 25 patients who received 80 mg foretinib experienced a DLT.

Of the 37 patients, six (16 %) did not continue to receive foretinib after the study treatment period due to death not related to study drug (n=2), adverse event (n=1; hematuria considered related to study drug), progressive disease (n=1), investigator decision (n=1), or withdrawal of consent (n=1). Thirty-one patients (84 %) continued into the treatment extension period, with one patient continuing to receive treatment at the time the study was closed for analysis. Patients received foretinib for a mean of 147 days, with a range of 7–527 days.

Table 1 Patient characteristics at baseline

Characteristic	Total (N=37)
Age, years, mean (SD)	52.8 (15.42)
Sex, *n* (%)	
Female	12 (32.4)
Male	25 (67.6)
Race, *n* (%)	
Asian	1 (2.7)
Black or African American	5 (13.5)
White	31 (83.8)
Mean years since diagnosis (SD)	2.9 (2.95)
Mean years since metastasis (SD)	1.7 (1.75)
Prior antitumor therapy, *n* (%)	
Prior radiation *or* cancer therapy	35 (94.6)
Prior radiation *and* cancer therapy	16 (43.2)
Mean number of prior chemotherapy regimens (SD)	3.5 (2.12)
Primary site of tumor, *n* (%)	
Chest	4 (10.8)
Abdomen	2 (5.4)
Pelvis	1 (2.7)
Lymph nodes	1 (2.7)
Rectum	6 (16.2)
Colon	6 (16.2)
Other	17 (45.9)

Safety

Thirty-seven patients were included in the safety evaluation, all of whom (n=37; 100 %) reported adverse events. Fatigue and hypertension were the most commonly reported events (Table 2) and were generally considered related to study treatment. Most patients experienced grade 1 or 2 fatigue or hypertension that was adequately managed and did not lead to early withdrawal. Grade 1 or 2 proteinuria was experienced by 38 % of patients. Nausea, diarrhea, anorexia, vomiting, headache, and dehydration were also frequently reported adverse events, the majority of which were grade 1 or 2.

Serious adverse events related to study treatment were reported by five patients. Of the patients receiving foretinib 80 mg, one experienced left ventricular dysfunction (grade 3), one had a pulmonary embolism (grade 4), and one patient reported grade 3 diarrhea and grade 4 fatigue. Of the patients receiving foretinib 120 mg, one reported dehydration (grade 3) and one experienced elevated creatinine and hypertension (both grade 2). Dehydration and hypertension were considered DLTs. All drug-related serious adverse events resolved but the grade 3 left ventricular dysfunction, along with a non-serious grade 2 event of worsening (pre-existent) congestive heart failure, led to permanent discontinuation of study drug. Two patients died within 29 days of first dose, one due to acute respiratory failure (alveolar opacities were noted and bronchial pneumonia was a possibility) and the other due to progression of pancreatic adenocarcinoma. An additional 15 patients died due to progressive disease during the extension phase or in follow-up. No death was considered related to treatment with foretinib.

Adverse events usually resolved either spontaneously or upon an interruption or reduction in foretinib dose. The dose of foretinib was reduced for 15 patients and administration was delayed for 14 patients. Over the course of the study, adverse events led to permanent treatment discontinuation for seven patients (19 %). In addition to the two deaths described above, hematuria, hypocalcemia, and failure to thrive led to withdrawal of one patient each; a sixth withdrew due to congestive cardiac failure and left ventricular dysfunction (mentioned above) and the seventh withdrew due to decreased appetite, nausea, dyspnea, pleural effusion,

Table 2 Treatment-emergent adverse events with foretinib (overall and grade 3/4) reported by >25 % of patients

Treatment-emergent adverse event	Foretinib 60 mg (*N*=6) (%)	Foretinib 80 mg (*N*=12) *n* (%)	Foretinib PK cohort 80 mg (*N*=13) *n* (%)	Foretinib 100 mg (*N*=3) *n* (%)	Foretinib 120 mg (*N*=3) *n* (%)	Total (*N*=37) *n* (%)
Fatigue	4 (66.7)	7 (58.3)	10 (76.9)	1 (33.3)	3 (100)	25 (67.6)
Grade 3	0	1 (8.3 %)	4 (30.8)	1 (33.3)	0	6 (16.2)
Grade 4	0	1 (8.3 %)	0	0	0	1 (2.7)
Hypertension	4 (66.7)	9 (75.0)	7 (53.8)	3 (100)	2 (66.7)	25 (67.6)
Grade 3	2 (33.3)	2 (16.7)	2 (15.4)	2 (66.7 %)	1 (33.3)	9 (24.3)
Nausea	2 (33.3)	8 (66.7)	7 (53.8)	2 (66.7)	1 (33.3)	20 (54.1)
Grade 3	0	1 (8.3 %)	3 (23.1)	0	0	4 (10.8)
Diarrhea	1 (16.7)	9 (75.0)	6 (46.2)	2 (66.7)	1 (33.3)	19 (51.4)
Grade 3	0	1 (8.3 %)	2 (15.4)	1 (33.3)	0	4 (10.8)
Anorexia	0	4 (33.3)	6 (46.2)	3 (100)	1 (33.3)	14 (37.8)
Proteinuria	1 (16.7)	6 (50.0)	4 (30.8)	1 (33.3)	2 (66.7)	14 (37.8)
Vomiting	1 (16.7)	7 (58.3)	4 (30.8)	1 (33.3)	1 (33.3)	14 (37.8)
Grade 3	0	0	1 (7.7)	0	0	1 (2.7)
Dehydration	0	3 (25.0)	6 (46.2)	2 (66.7)	1 (33.3)	12 (32.4)
Grade 3	0	1 (8.3 %)	2 (15.4)	0	1 (33.3)	4 (10.8)
Blood lactate dehydrogenase increased	1 (16.7)	4 (33.3)	3 (23.1)	1 (33.3)	2 (66.7)	11 (29.7)
Edema peripheral	1 (16.7)	6 (50.0)	2 (15.4)	1 (33.3)	1 (33.3)	11 (29.7)
Grade 3	0	0	1 (7.7)	0	0	1 (2.7)
Headache	2 (33.3)	4 (33.3)	3 (23.1)	1 (33.3)	1 (33.3)	11 (29.7)
Abdominal pain	1 (16.7)	4 (33.3)	4 (30.8)	1 (33.3)	0	10 (27.0)
Grade 3	0	0	2 (15.4)	0	0	3 (8.1)
Insomnia	0	4 (33.3)	5 (38.5)	1 (33.3)	0	10 (27.0)

Occurrence of grade 3 or grade 4 adverse events are listed. If none are listed, all occurrences of adverse event were grade 1 or grade 2

pneumonia, and sinus tachycardia. Only hematuria and left ventricular dysfunction were considered by the investigator to be related to treatment with foretinib. Left ventricular dysfunction and dyspnea resolved upon treatment discontinuation.

Nine ocular events were reported for eight patients; these were blurred vision (*n*=4), night blindness (*n*=2), conjunctival hemorrhage (*n*=1), scotoma (*n*=1), and visual impairment (*n*=1). All ocular events were grade 1 or 2 and all resolved except for one case of blurred vision. Scotoma and blurred vision (*n*=1 each) were considered related to study drug.

Pharmacokinetics

Plasma concentrations were available for 36 patients; data from 35 patients were sufficient for non-compartmental PK analysis. Across all dose levels, the median t_{max} ranged 2–6 h, after which foretinib concentrations generally appeared to decrease monoexponentially (Fig. 1).

The dosing regimen, PK sampling scheme and the small number of patients in several cohorts did not permit accurate estimation of $t_{1/2}$ or dose proportionality. Of the 25 patients treated at the MTD dose (80 mg), 23 had data from Day 1 and 6 had data from Day 22 that were suitable for PK analysis. Foretinib mean values for plasma C_{max}, C_{min} and $AUC_{0\text{-}24}$ were 45.7 ng/mL, 23.9 ng/mL and 805 h*ng/mL, respectively, on Day 22 (Table 3). Moderate interpatient variability in C_{max} and $AUC_{0\text{-}24}$ was observed. Based on data from six patients with serial PK data on both Day 1 and Day 22, foretinib accumulated approximately 3.8-fold in plasma. Based on assessment of pre-dose concentrations obtained from Day 2 to Day 29, steady state was achieved by approximately Day 15.

The mean percentage of dose excreted in urine as intact foretinib on Day 22 was 0.88 % (range: 0.15–1.9 %). However, during the method validation, it was determined that foretinib could adsorb to the plastic collection jug unless the urine was acidified; therefore, it is possible that the measured urine concentrations of foretinib were underestimated.

Pharmacodynamics

In patients treated at the MTD (80 mg), sMET and VEGF-A plasma levels were significantly increased from baseline on Day 8 through Day 29, and sVEGFR2 plasma

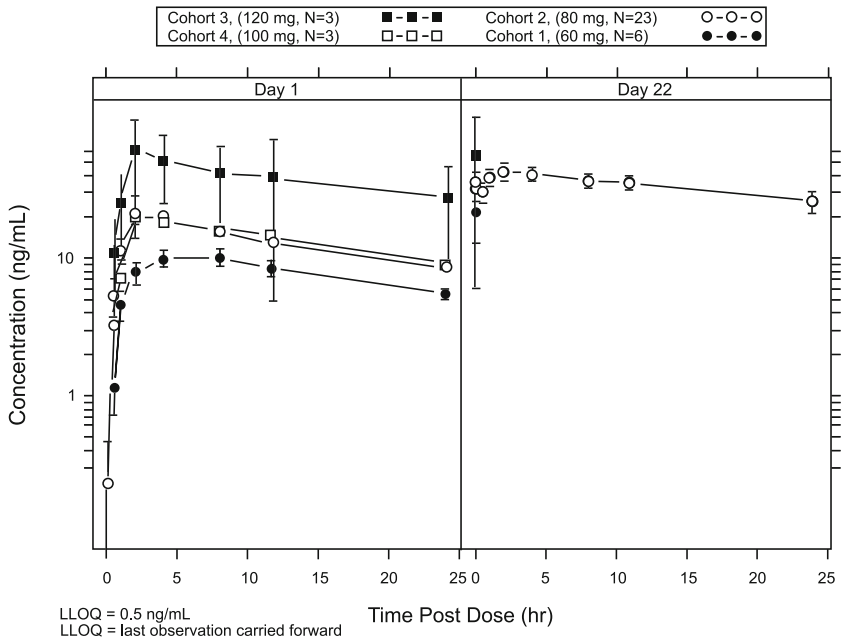

Fig. 1 Cohort mean (±SE) foretinib plasma concentrations

levels significantly decreased from baseline (Table 4). HGF plasma levels did not change significantly from baseline.

Tumor response

Of the 31 evaluable patients, 23 (74 %) had a best response of SD (Table 5). No patient had a confirmed PR or CR. The incidence of SD did not appear to be dose related and was not substantially different among cohorts. For patients whose disease was not progressive at data cut-off, SD was censored at the date of last available tumor assessment. The overall median for duration of SD was 6.37 months (range: 0.79–18.04 months). In the 80 mg cohorts, 10 patients had SD for 6 months or longer. Of these 10 patients, two had thyroid cancer, two had papillary renal cell cancer, two had

Table 3 Plasma pharmacokinetic parameters for patients receiving the maximum tolerated dose of foretinib (80 mg once daily)

Plasma PK parameter	Mean (CV%)
t_{max}, h	
Day 1 (*n*=23)	4.4 (64)
Day 22 (*n*=6)	3.6 (99)
C_{max}, ng/mL	
Day 1 (*n*=23)	24.5 (51)
Day 22 (*n*=6)	45.7 (28)
C_{min}, ng/mL	
Day 22 (*n*=6)	23.9 (44)
$AUC_{0–24}$, h•ng/mL	
Day 1 (*n*=20)	303 (32)
Day 22 (*n*=6)	805 (33)
CL/F, L/h	
Day 22 (*n*=6)	83.4 (33)

CV coefficient of variance

Table 4 Change from baseline in pharmocodynamic markers for patients receiving the maximum tolerated dose of foretinib (80 mg)

Marker	Day	n	Median value	Percent change[a]	*P*-value
sMET, ng/mL	1	20	190.25	–	–
	8	18	229.74	21	<0.0001
	15	18	213.66	12	0.0003
	22	15	227.2	19	0.0013
	29	14	213.96	12	0.0028
VEGF-A, pg/mL	1	20	30.72	–	–
	8	18	70.22	129	<0.0001
	15	18	86.39	181	<0.0001
	22	15	84.37	175	<0.0001
	29	14	63.2	106	<0.0001
sVEGFR2, pg/mL	1	20	18254.16	–	–
	8	18	14500.07	−21	0.0205
	15	18	12387.78	−32	0.0003
	22	15	12503.9	−32	<0.0001
	29	14	10914.42	−40	<0.0001
HGF, pg/mL	1	20	1217.76	–	–
	8	18	709.59	−42	0.3145
	15	18	1051.6	−14	0.819
	22	15	1081.83	−11	0.624
	29	14	876.52	−28	0.9998

[a] Changes from pre-dose baseline were measured on Days 1 and 8 at 4 h post-dose and from pre-dose Day 1 baseline for all other time points

HGF hepatocyte growth factor; *sMET* soluble MET; *sVEGFR2* soluble vascular endothelial growth factor receptor 2; *VEGF-A* vascular endothelial growth factor A

Table 5 Tumor response of patients receiving foretinib

Variable	Foretinib 60 mg (*N*=5)	Foretinib 80 mg (*N*=11)	Foretinib PK cohort 80 mg (*N*=9)	Foretinib 100 mg (*N*=3)	Foretinib 120 mg (*N*=3)	Total (*N*=31)
Best overall response, *n* (%)						
Complete response	0	0	0	0	0	0
Partial response	0	0	0	0	0	0
Stable disease	4 (80.0)	8 (72.7)	7 (77.8)	2 (66.7)	2 (66.7)	23 (74.2)
Disease progression	1 (20.0)	3 (27.3)	2 (22.2)	1 (33.3)	1 (33.3)	8 (25.8)
Duration of stable disease (months)						
N	4	8	7	2	2	23
Median	4.27	11.10	6.85	NA	4.35	6.37
Min, Max	1.81+, 5.95	3.06, 18.04	0.79+, 14.75+	2.10, 5.52+	3.91, 4.80	0.79+, 18.04
Progression-free survival (months)						
Median	4.21	9.31	2.86	2.11	3.91	3.91
Min, Max	1.45, 5.95	0.95, 18.06	1.64, 15.23+	1.55, 7.93	1.18, 4.80	0.95, 18.06

Min minimum; *Max* maximum; *NA* not applicable; + censored observation

Denominators for percentages are *N*, the total number of patients evaluable at each dose level

Best overall response was assessed by the investigator per the Response Evaluation Criteria in Solid Tumors

alveolar of soft parts sarcoma (left thigh and retroorbital), and colon, liver, thymus, and appendiceal cancers were reported in one patient each.

Discussion

Foretinib is a small-molecule kinase inhibitor that targets members of the MET and VEGFR tyrosine kinase families (including MET, RON, and VEGFR2 kinases), with additional inhibitory activity toward AXL, KIT, Flt-3, PDGFR-β, and Tie-2 [19]. This Phase 1, dose-escalation study identified an oral dose of 80 mg foretinib bisphosphate salt as the MTD when administered once daily.

DLTs were hypertension, dehydration, and diarrhea. The most common adverse events observed were hypertension, fatigue, diarrhea, and vomiting. These events were generally grade 1 or 2 and resolved following dose delay or dose reduction. Two of the adverse events observed during the treatment period, hypertension and proteinuria, are thought to be linked to inhibition of VEGF-mediated signaling [24]. Personalized management of hypertension proved to be effective without disrupting drug administration.

PK data demonstrated that foretinib accumulated approximately 3.8-fold on Day 22 compared with Day 1. Steady state was achieved by Day 15 on a once-daily dosing schedule. Although $t_{1/2}$ could not be estimated in this study, these results suggest that foretinib $t_{1/2}$ averaged approximately 2 days, a value that is generally consistent with the 40.5-h half-life estimated in the FTIH study during which foretinib was administered orally for 5 consecutive days in a 14-daycycle [21]. For the MTD dose of 80 mg once daily, the mean repeat dose trough concentration of 23.9 ng/mL (0.038 uM) was within the range of 0.02 to 0.1 uM associated with efficacy from preclinical investigations.

Circulating sMET and VEGF-A plasma levels were significantly increased from baseline upon treatment with foretinib, and sVEGFR2 plasma levels decreased from baseline. Changes in VEGF-A and sVEGFR2 were consistent with changes observed during treatment with anti-angiogenic agents. sMET is a potential biomarker of MET inhibition, and the changes seen suggest that foretinib demonstrates on-target activity for MET. These findings support earlier data demonstrating PD activity of foretinib on its targets, cell proliferation and apoptosis, in tumor biopsies obtained in the FTIH study [21].

The majority of patients (74.2 %) had an overall best response of SD ranging 1–18 months (median: 6.4 months), slightly longer than the mean of 4 months observed in 22 patients who experienced SD in the FTIH study. No CRs or PRs were observed in this study, which is in contrast to the three PRs observed in the FTIH study [21].

In conclusion, the safety profile in this Phase 1 study and that reported from the FTIH study supported plans for the evaluation of both schedules in a variety of tumor types in which HGF or MET overexpression and/or angiogenesis have been shown to be important for tumor cell proliferation and/or metastases. Phase 2 studies with intermittent and daily schedules have been completed in papillary renal carcinoma (PRC) and refractory gastric cancer, and with an intermittent schedule in squamous cell carcinoma of the head and neck cancer (SCCHN). Gastric cancer was selected as a tumor type with a high chance for response given that alterations in the MET receptor have frequently been

described in these tumors. Unfortunately, the patients recruited to the foretinib gastric cancer trial did not replicate the *MET* amplification levels reported in the literature previously, and no CRs or PRs were observed [25]. While the single agent foretinib study in SCCHN showed that foretinib was safe, with tumor reductions up to 21 %, there were no PRs or CR in the first 11 patients and the study was stopped for futility [26]. The PRC study including patients with both germline and somatic MET mutations as well as patients with *MET* amplifications has shown an overall confirmed PR rate of 13.5 % [27]. Phase 2 studies with the daily schedule are currently underway in several other tumor types, including hepatocellular carcinoma [28], non-small cell lung cancer, and breast cancer.

Acknowledgments We thank the patients, their families, and caregivers, and all of the personnel who contributed to the patient care and data collection for study MET111648. Funding for this study was provided by GlaxoSmithKline (NCT00743067) and Exelixis Inc. Editorial support in the form of assembling the first draft, collating author comments, copyediting, and fact checking was provided by Susannah Chang at WynneWords, LLC (Wynnewood, PA); final formatting, review, and submission assistance was provided by MediTech Media, UK and was funded by GlaxoSmithKline

Author contributions All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

Conflicts of interest Geoffrey I. Shapiro and Patricia LoRusso received research funding from GlaxoSmithKline and Exelixis for the study. Stewart McCallum, Laurel M. Adams, Laurie Sherman, Steve Weller, and Suzanne Swann are all compensated employees of GlaxoSmithKline and own company stock. Dale Miles is a compensated employee of Exelixis and owns company stock. At the time of the study Harold Keer and Thomas Müller were compensated employees of Exelixis and still own company stock.

References

1. Trusolino L, Comoglio PM (2002) Scatter-factor and semaphorin receptors: cell signalling for invasive growth. Nat Rev Cancer 2:289–300
2. Thiery JP (2002) Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2:442–454
3. Derksen PW, de Gorter HP, Meijer HP et al (2003) The hepatocyte growth factor/Met pathway controls proliferation and apoptosis in multiple myeloma. Leukemia 17:764–774
4. Zhang YW, Vande Woude GF (2003) HGF/SF-met signaling in the control of branching morphogenesis and invasion. J Cell Biochem 88:408–417
5. Zhang YW, Su Y, Volpert OV et al (2003) Hepatocyte growth factor/scatter factor mediates angiogenesis through positive VEGF and negative thrombospondin 1 regulation. Proc Natl Acad Sci U S A 100:12718–12723
6. Birchmeier C, Birchmeier W, Gherardi E et al (2003) Met, metastasis, motility and more. Nat Rev Mol Cell Biol 4:915–925
7. Yamashita J, Ogawa M, Yamashita S et al (1994) Immunoreactive hepatocyte growth factor is a strong and independent predictor of recurrence and survival in human breast cancer. Cancer Res 54:1630–1633
8. Ghoussoub RA, Dillon DA, D'Aquila T et al (1998) Expression of c-met is a strong independent prognostic factor in breast carcinoma. Cancer 82:1513–1520
9. Ueki T, Fujimoto J, Suzuki T et al (1997) Expression of hepatocyte growth factor and its receptor, the c-met proto-oncogene, in hepatocellular carcinoma. Hepatology 25:619–623
10. Daveau M, Scotte M, Francois A et al (2003) Hepatocyte growth factor, transforming growth factor alpha, and their receptors as combined markers of prognosis in hepatocellular carcinoma. Mol Carcinog 36:130–141
11. Boccaccio C, Comoglio PM (2006) Invasive growth: a MET-driven genetic programme for cancer and stem cells. Nat Rev Cancer 6:637–645
12. Sennino B, Naylor RM, Tabruyn SP et al (2009) Reduction of tumor invasiveness and metastasis and prolongation of survival of RIP-TAG2 mice after inhibition of VEGFR plus C-MET by XL 184. Mol Cancer Ther 8: Abstract 13
13. Sennino B, Ishiguro-Oonuma T, Wei Y (2012) Suppression of tumor invasion and metastasis by concurrent inhibition of c-Met and VEGF signaling in pancreatic neuroendocrine tumors. Cancer Discov 2:270–287
14. Gerritsen ME, Tomlinson JE, Zlot C et al (2003) Using gene expression profiling to identify the molecular basis of the synergistic actions of hepatocyte growth factor and vascular endothelial growth factor in human endothelial cells. Br J Pharmacol 140:595–610
15. Xin X, Yang S, Ingle G et al (2001) Hepatocyte growth factor enhances vascular endothelial growth factor-induced angiogenesis in vitro and in vivo. Am J Pathol 158:1111–1120
16. Pouyssegur J, Dayan F, Mazure NM (2006) Hypoxia signaling in cancer and approaches to enforce tumour regression. Nature 441:437–443
17. Vaupel P (2008) Hypoxia and aggressive tumor phenotype: implications for therapy and prognosis. Oncologist 13(Suppl 3):21–26
18. Ye X, Li Y, Stawicki S et al (2010) An anti-Axl monoclonal antibody attenuates xenograft tumor growth and enhances the effect of multiple anticancer therapies. Oncogene 29:5254–5264
19. Qian F, Engst S, Yamaguchi K et al (2009) Inhibition of tumor cell growth, invasion, and metastasis by EXEL-2880 (XL880, GSK1363089), a novel inhibitor of HGF and VEGF receptor tyrosine kinases. Cancer Res 69:8009–8016
20. Copeland RA, Pompliano DL, Meek TD (2006) Drug-target residence time and its implications for lead optimization. Nat Rev Drug Discov 5:730–739
21. Eder JP, Shapiro GI, Appleman LJ et al (2010) A phase I study of foretinib, a multi-targeted inhibitor of c-Met and vascular endothelial growth factor receptor 2. Clin Cancer Res 16:3507–3516
22. National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available online at: http://ctep.cancer.gov/reporting/ctc.html (last accessed 21 March 2009)
23. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
24. van Heeckeren WJ, Ortiz J, Cooney MM et al (2007) Hypertension, proteinuria, and antagonism of vascular endothelial growth factor signaling: clinical toxicity, therapeutic target, or novel biomarker? J Clin Oncol 25:2993–2995
25. Jhawer M, Kindler HL, Wainberg Z et al (2009) GSK1363089 (GSK089), a dual MET/VEGFR2 inhibitor, in metastatic gastric cancer (GC): Interim results of a multicenter Phase II study. ASCO

(2009) American Society of Clinical Oncology 45th Annual Meeting. Abstract #4502
26. Seiwert T, Swann S, Kurz H, Bonate P, McCallum S, Sarantopoulos J (2009) A Phase II study of the efficacy and safety of foretinib, a novel receptor tyrosine kinase inhibitor, given on an intermittent five days on nine days off (5/9) schedule in patients with recurrent or metastatic squamous cell cancer of the head and neck (SCCHN). Molec Cancer Ther 8 Suppl 1:Abstract #B6. Doi:10.1158/1535-7163. TARG-090B6.
27. Srinivasan R, Linehan M, Vaishampayan U et al (2009) A Phase II Study of 2 dosing regimens of foretinib (GSK 1363089), a dual MET/VEGFR2 inhibitor, in patients (pts) with papillary renal carcinoma (PRC). J Clin Oncol 27 Suppl 15s: Abstract #5103.
28. Yau T, Sukeepaisarnjaroen W, Chao Y et al (2012) A phase I/II study of foretinib, an oral multikinase inhibitor targeting MET, RON, AXL, TIE-2, and VEGFR in advanced hepatocellular carcinoma (HCC). J Clin Oncol 30 Suppl:Abstract #4108