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ORIGINAL RESEARCH ARTICLE

Phase I Study of the Focal Adhesion Kinase Inhibitor BI 853520 in Japanese and Taiwanese Patients with Advanced or Metastatic Solid Tumors

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Abstract

Background Focal adhesion kinase (FAK) inhibitors have demonstrated anti-tumor activity preclinically and are currently being evaluated in humans. A first-in-human study evaluating the novel FAK inhibitor BI 853520 in a predominantly Caucasian population with advanced or metastatic non-hematologic malignancies demonstrated acceptable tolerability and favorable pharmacokinetics.

Objective This study was undertaken to investigate the safety, tolerability, and maximum tolerated dose (MTD) of BI 853520 in Japanese and Taiwanese patients with advanced solid tumors.

Patients and Methods In this open-label, phase I, dose-finding study, BI 853520 was administered once daily (QD) in a continuous daily dosing regimen with 28-day cycles and escalating doses to sequential cohorts of patients. Twenty-one patients (62% male; median age 65 years) were treated at two sites in Japan and Taiwan.

Results The median duration of treatment was 1.2 months (range 0.2–7.7). As no dose-limiting toxicities were observed during cycle 1 in the 50, 100, or 200 mg cohorts, the MTD of BI 853520 was determined to be 200 mg QD. Drug-related adverse events were reported in 19 patients (90%), and all except one were of grade 1 or 2. Pharmacokinetic parameters were supportive of a once-daily dosing schedule. A confirmed objective response rate of 5% and disease control rate of 29% were achieved; median duration of disease control was 3.7 months.

Conclusions This trial demonstrated a manageable and acceptable safety profile, favorable pharmacokinetics, and potential anti-tumor activity of BI 853520 in pretreated Japanese and Taiwanese patients with advanced or metastatic solid tumors.

Clinical trials registration NCT01905111.

Key Points

In this study of BI 853520 in Japanese and Taiwanese patients with advanced solid tumors, no dose-limiting toxicities were observed, and a maximum tolerated dose of 200 mg was identified.

Pharmacokinetic parameters support once-daily dosing and potential anti-tumor activity was demonstrated in this setting.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11523-019-00620-0) contains supplementary material, which is available to authorized users.

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1 Introduction

Focal adhesion kinase (FAK)/protein tyrosine kinase 2 is a ubiquitous, non-receptor, cytoplasmic tyrosine kinase that localizes to areas of focal adhesion where the plasma membrane makes contact with the extracellular matrix [1–4]. FAK is a key regulator of integrin- and growth factor receptor-mediated signaling [5] and plays a pivotal role in modulating a variety of intracellular signaling pathways that govern fundamental processes in normal and cancer cells, including cell survival, proliferation, and motility [2–5].

Evidence suggests FAK may be a determinant of tumor development and metastasis. For example, increased FAK expression and activity occurs in primary and metastatic cancers of many tissue origins [6–12], and is often associated with poor clinical outcomes [3, 5, 13, 14]. In addition, FAK overexpression has been shown to mediate kinase-dependent growth of malignant cells [15]. Preclinical studies have demonstrated anti-tumor activity with FAK inhibition [16–20], and several FAK inhibitors are being evaluated in early-phase clinical studies [2, 3, 5, 21–23].

BI 853520 is a novel, potent, highly selective, adenosine triphosphate-competitive inhibitor of FAK that has demonstrated preclinical on-target activity and anti-tumor effects in various xenograft models [24]. A first-in-human (FIH) phase I study (ClinicalTrials.gov identifier NCT01335269) evaluating BI 853520 in a predominantly (92%) Caucasian population with advanced or metastatic non-hematologic malignancies defined a maximum tolerated dose (MTD) of 200 mg of BI 853520 once daily (QD) in a continuous dosing schedule (see the article by de Jonge et al. [25] in this issue of *Targeted Oncology*). At the MTD, BI 853520 was associated with acceptable tolerability and favorable pharmacokinetics. Common drug-related adverse events (DRAEs) reported for more than 10% of patients included gastrointestinal events (nausea, diarrhea, vomiting) and proteinuria. Pharmacokinetic analyses supported the oral bioavailability of BI 853520 and a QD dosing schedule, while pharmacodynamic analyses demonstrated on-target FAK modulation by BI 853520 at the MTD. Although no radiographic objective responses were reported in the FIH study, BI 853520 elicited disease control in 27% of patients.

Patient ethnicity can affect the pharmacokinetics and pharmacodynamics of a drug and, therefore, the safety profile and response to treatment [26]. The current phase I dose-finding study (NCT01905111) was undertaken to evaluate the safety and tolerability of BI 853520 monotherapy in Japanese and Taiwanese patients with advanced solid tumors and to determine the MTD in this population. The pharmacokinetics and preliminary anti-tumor activity of BI 853520 were also assessed.

2 Methods

2.1 Patients

Full inclusion and exclusion criteria are provided in the Electronic Supplementary Material. In brief, eligible patients had histologically or cytologically confirmed advanced, measurable or evaluable, non-resectable and/or metastatic solid tumors, which had progressed within 6 months prior to study entry; Eastern Cooperative Oncology Group performance status of 0 or 1; and life expectancy ≥ 3 months. Key exclusion criteria included inadequate hematologic, renal, and hepatic function; treatment with cytotoxic anti-cancer therapies or investigational drugs within 4 weeks of the first dose of the study drug; chronic diarrhea or other gastrointestinal disorders; and active/symptomatic brain metastases.

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, Good Clinical Practice guidelines, and applicable regulatory requirements (including International Conference on Harmonisation guidelines). Ethical approval for the study was given by the Institutional Review Board and the Research Ethics Committee in Japan and Taiwan, respectively. All patients provided written informed consent.

2.2 Study Design and Treatment

This was an open-label, phase I, dose-finding study to evaluate BI 853520 in Japanese and Taiwanese patients with advanced or metastatic solid tumors. The primary objective was to explore the safety and tolerability of BI 853520 monotherapy and determine the MTD. Secondary objectives included evaluation of the pharmacokinetics and preliminary anti-tumor activity of BI 853520.

BI 853520 was administered QD in a continuous daily dosing regimen with 28-day cycles. Sequential cohorts of three to six patients received escalating doses of BI 853520 in a standard 3 + 3 design to establish the MTD, with a starting dose of 50 mg QD. The starting dose was two dose levels below the MTD reported in the FIH study (see de Jonge et al. [25]), as neither 50 mg QD or 100 mg QD had resulted in dose-limiting toxicities (DLTs) or DRAEs of grade ≥ 2 in that study. Dose levels of 100 and 200 mg QD were planned, with allowance for exploration of intermediate dose levels if necessary. There was no pre-planned evaluation of doses exceeding 200 mg QD, and dose escalation proceeded according to the occurrence of DLT in cycle 1. The MTD was determined as the highest dose level at which none or one of six patients experienced DLT during cycle 1 (DLT criteria are listed in the Electronic Supplementary Material).

Following determination of the MTD, it was planned that an additional six patients would be treated and evaluable in

an expansion cohort for further evaluation of BI 853520 at the MTD. Criteria for dose reductions and discontinuations are listed in the Electronic Supplementary Material.

2.3 Endpoints and Assessments

2.3.1 Safety

The primary endpoint of the study was the MTD of BI 853520. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [27].

2.3.2 Pharmacokinetics

The pharmacokinetic profile of BI 853520 was determined from plasma and urine analysis after a single oral dose, and after repeated dosing in cycle 1 (steady state on day 28). Further details are provided in the Electronic Supplementary Material. BI 853520 concentrations were measured by a validated assay based on liquid chromatography and tandem mass spectrometry.

2.3.3 Efficacy

The following efficacy endpoints were assessed: (1) investigator-assessed objective response rate (complete response [CR] or partial response [PR]) according to Response Evaluation Criteria In Solid Tumors version 1.1 [28]; (2) disease control rate (CR, PR, or stable disease [SD]); (3) duration of disease control; and (4) tumor shrinkage. Tumors were assessed by computed tomography/magnetic resonance imaging scan at screening (baseline), at the end of cycle 2, and every two cycles thereafter until the end of treatment. Patients with baseline and at least one post-baseline tumor response assessment were evaluable for response.

2.4 Statistical Analyses

All analyses were based on the treated set, defined as all patients who received at least one dose of study drug. All statistical analyses were descriptive.

3 Results

3.1 Patients

Between July 2013 and August 2014, 23 patients provided informed consent and 21 patients were treated at two clinical sites in Japan and Taiwan. The median age was 65 years (range 35–77), 62% of patients were male, and 52% were from Taiwan (Table 1). The most common solid tumor types were stomach cancer (19%), colorectal cancer (14%), and soft tissue sarcoma (14%). All but one patient had received prior anti-cancer chemotherapy, while 14 (67%) had received at least three prior chemotherapy regimens. At the time of database lock (17 October 2014), all 21 patients had discontinued treatment (reasons: progressive disease [PD], $n=14$; AEs, $n=4$; study withdrawal, $n=3$).

Table 1 Patient demographics and baseline characteristics ($N=21$)

Characteristic	N (%)[a]
Median age, years (range)	65 (35–77)
Male/female	13 (62)/8 (38)
Country	
Japan/Taiwan	10 (48)/11 (52)
ECOG PS 0/1	11 (52)/10 (48)
Tumor type	
Stomach	4 (19)
Colorectal	3 (14)
Soft tissue sarcoma	3 (14)
Other[b]	11 (52)
Median time since histological diagnosis, months (range)	32.5 (15.4–178.0)
Prior anti-cancer therapies[c]	
Chemotherapy	20 (95)
≥3 chemotherapy regimens	14 (67)
Surgery	17 (81)
Radiotherapy	6 (29)
Other	6 (29)

ECOG PS Eastern Cooperative Oncology Group performance status

[a]Unless otherwise stated

[b]Biliary tree ($n=2$), bladder ($n=2$), esophageal ($n=2$), other ($n=2$), liver ($n=1$), melanoma ($n=1$), prostate ($n=1$)

[c]Patients could have received more than one type of prior therapy

3.2 Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose

Fourteen patients were included in the dose-escalation part of the study (50 mg QD, $n=3$; 100 mg QD, $n=3$; 200 mg QD, $n=8$), with all but two in the 200 mg dose cohort being evaluable for DLT. As no DLTs were observed during cycle 1 in the 50, 100, or 200 mg cohorts, the MTD of BI 853520 was determined to be 200 mg QD. This dose was further evaluated in the expansion cohort, which comprised seven further patients with no selection for tumor types. All but one of these patients were evaluable for DLT.

Overall, DLTs were reported in three of 21 patients treated during the study. In the 100 mg QD cohort, one patient had drug-related grade 2 Dupuytren's contracture during cycles 5 and 6, which was managed through dose interruption lasting > 7 days. In the 200 mg QD expansion cohort, one patient had drug-related grade 3 proteinuria

during cycle 2; this patient continued treatment at a reduced dose of 100 mg QD until PD. A second patient in the 200 mg QD expansion cohort had isolated drug-related grade 2 increased blood bilirubin during cycle 1. Treatment was eventually discontinued permanently in this patient due to dose interruption lasting > 14 days.

3.3 Safety

The median duration of treatment with BI 853520 was 1.2 months (range 0.2–7.7), and three patients (14%) had at least six treatment cycles initiated. DRAEs were reported in 19 patients (90%), of which the most frequent (> 10% of patients) were proteinuria (48%), diarrhea (38%), nausea (29%), and vomiting (19%) (Table 2). All DRAEs were grade 1 or 2, except for the DLT of grade 3 proteinuria.

Serious AEs (SAEs) were reported in five patients (24%), as follows: malignant neoplasm progression (n=2), decreased appetite (n=1), dehydration (n=1), arthralgia (n=1), pain in extremity (n=1), and ankle fracture (n=1). None of the SAEs was considered drug-related. Four patients (19%) discontinued treatment due to AEs, including one patient in the 100 mg QD cohort (drug-related Dupuytren's contracture), and three patients in the 200 mg QD cohort (one case each of drug-related proteinuria, drug-related increased blood bilirubin, and non-drug-related increased blood bilirubin). Two patients in the 200 mg QD cohort died from malignant neoplasm progression during the post-treatment period, although neither death was considered to be drug related. No other notable clinical findings with regard to laboratory assessments (except for proteinuria [drug related in 48% of patients]) or vital signs were observed.

Table 2 Drug-related adverse events reported by investigator

AEs (N = 21[a,b])	N (%)
Any drug-related AE[c]	19 (90)
Proteinuria	10 (48)
Diarrhea	8 (38)
Nausea	6 (29)
Vomiting	4 (19)
Decreased appetite	2 (10)
Dupuytren's contracture	2 (10)
Rash, maculo-papular	2 (10)
Abdominal pain upper	1 (5)
Anemia	1 (5)
AST increased	1 (5)
Back pain	1 (5)
Blood bilirubin increased	1 (5)
Blood creatinine increased	1 (5)
Dehydration	1 (5)
Erectile dysfunction	1 (5)
Fatigue	1 (5)
Inguinal hernia	1 (5)

AE adverse event, *AST* aspartate aminotransferase

[a]Safety was evaluated in all patients who had received at least one dose of BI 853520

[b]Includes patients in the BI 853520 200 mg expansion cohort

[c]Drug-related AEs were all of grade 1 or 2 severity, except for one case of grade 3 proteinuria in a patient in the 200 mg expansion cohort

3.4 Pharmacokinetics

Plasma concentration–time profiles for BI 853520 after single- and multiple-dose administration in cycle 1 are shown in Fig. 1. Due to the small number of evaluable patients in the 50 mg QD (n = 3) and 100 mg QD (n = 2) dose cohorts, data from the 200 mg QD cohort (n=15) were considered representative of the pharmacokinetics of BI 853520 in this study (Table 3).

The maximum plasma concentration (C_{max}) of BI 853520 was achieved at 2.0 and 2.9 h following single- or multiple-dose administration, respectively, and declined with geometric mean terminal half-life ($t_{½}$) of 20.9 and 20.3 h, respectively. Geometric mean values for the accumulation ratio based on area under the plasma concentration–time curve (AUC) and C_{max} were 2.15 and 1.62, respectively. The cumulative fraction of BI 853520 excreted in urine was less than 9%. An exploratory comparison of pharmacokinetic findings in patients who experienced grade 2 proteinuria with those who did not experience proteinuria indicated that proteinuria tended to correlate with higher AUC and C_{max} levels.

An exploratory comparison of the pharmacokinetics of BI 853520 in Japanese patients (n = 6) and Taiwanese patients (n = 9) in the 200 mg QD cohort was also conducted and the data are summarized in the Electronic Supplementary Material (Supplementary Table 1). The geometric mean values of exposure (AUC and C_{max}) to BI 853520 200 mg QD in Japanese patients were similar to or slightly higher than those in Taiwanese patients. Individual values of exposure showed similarity between Japanese and Taiwanese patients and there were no substantial differences in other pharmacokinetic parameters. Pharmacokinetic parameters at steady state were also obtained from Japanese patients (n=5) and Taiwanese patients (n=5).

3.5 Anti-Tumor Activity

Eighteen of 21 patients (86%) were evaluable for best confirmed response. Six patients (29%) achieved disease control and 12 (57%) had PD (Table 4). Among the six patients with disease control, one patient with gastric cancer in the 100 mg QD cohort achieved a confirmed objective PR and the remaining five patients had SD (one each

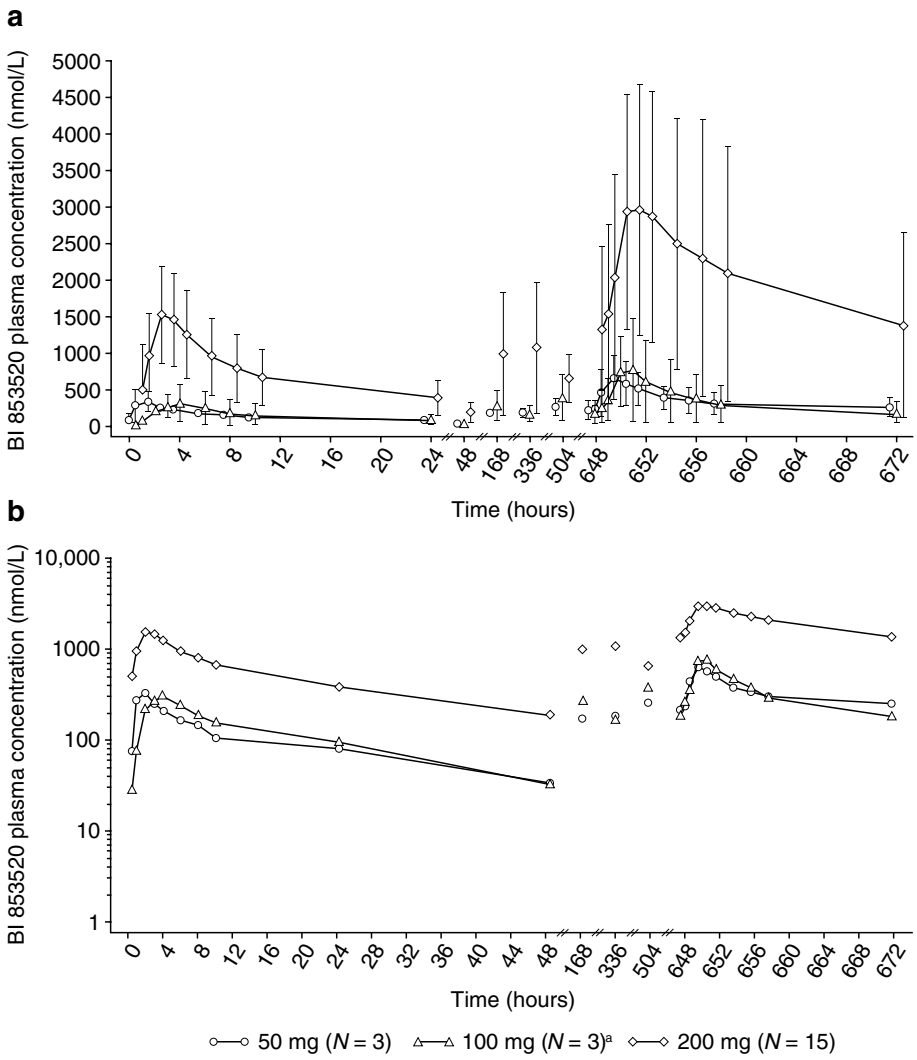

Fig. 1 Arithmetic mean plasma concentration–time profiles of BI 853520 after single-dose and multiple-dose oral administration of 50, 100, and 200 mg once daily of BI 853520 in cycle 1: **a** linear scale (error bars represent standard deviation); and **b** logarithmic scale. [a] One patient was not evaluable for pharmacokinetic parameters due to incomplete data

with urachus cancer and esophageal cancer in the 50 mg QD cohort, and one each with meningioma, gastric cardiac cancer, and intrahepatic bile duct cancer in the 200 mg QD cohort). The median duration of confirmed disease control was 3.7 months (interquartile range 1.8–5.8). In total, 17 of 21 patients (81%) were evaluable for tumor shrinkage assessment. Median tumor shrinkage (change from baseline in the sum of the longest diameters of target lesions) was +5.0 mm (range −6.2 to +46.0). The median best percentage change from baseline in the sum of longest diameters of target lesions was +10.4% (−31.3 to +70.2).

4 Discussion

This phase I, open-label study in Japanese and Taiwanese patients with advanced or metastatic solid tumors identified the MTD of BI 853520 as 200 mg QD in a continuous dosing schedule. This was consistent with the FIH study of BI 853520 in a predominantly Caucasian population (see de Jonge et al. [25]). In addition, BI 853520 demonstrated an acceptable safety profile that was consistent with observations in the FIH study (see de Jonge et al. [25]). Only two of 15 evaluable patients treated at the MTD (200 mg QD) experienced DLT, neither of which occurred during cycle 1 (one occurred in cycle 2 and one occurred in the expansion cohort). One patient experienced DLT in the 100 mg QD cohort. This patient had drug-related grade 2 Dupuytren's contracture during cycles 5 and 6, which may be indicative of the role FAK signaling has been shown to play in regulating cell realignment and differentiation in response to mechanical stretch [29].

The most common DRAE was proteinuria, which was grade 1/2 and required no dose modification or interruption in all but one case. The one case of grade 3 proteinuria, which was the only grade > 2 DRAE, occurred in a patient in the 200 mg QD expansion cohort. It was managed through dose reduction to 100 mg QD. Grade 3 proteinuria

Table 3 Pharmacokinetic parameters of BI 853520 after single- and multiple-dose administration in cycle 1 (200 mg once daily cohort)

Parameter	BI 853520 200 mg QD	
	Geometric mean	Geometric CV, %
Single dose ($N=15$)		
$AUC_{\tau,1}$, nmol·h/L	15,300	50.6
$AUC_{0-\infty}$, nmol·h/L	26,300	55.6
C_{max}, nmol/L	1570	40.7
t_{max}, h[a]	2.00	1.00–3.00
$t_{½}$, h	20.9	29.9
MRT_{po}, h	28.0	30.2
CL/*F*, mL/min	216	55.6
V_z/F, L	391	53.1
fe_{0-24}, %	5.60[b]	33.9[b]
$CL_{R,0-24}$, mL/min	21.7[b]	47.7[b]
Multiple dose ($N=10$)		
$AUC_{\tau,ss}$, nmol·h/L	36,800	94.6
$C_{max,ss}$, nmol/L	2750	77.3
$t_{max,ss}$, h[a]	2.94	1.00–7.93
$t_{½,ss}$, h	20.3[c]	24.9[c]
$MRT_{po,ss}$, h	28.3[c]	23.2[c]
CL/F_{ss}, mL/min	155	94.6
V_z/F_{ss}, L	311[c]	87.1[c]
$R_{A,AUC}$	2.15	58.4
$R_{A,C_{max}}$	1.62	56.9
$fe_{0-24,ss}$, %	8.86	30.3
$CL_{R,0-24,ss}$, mL/min	13.7	71.1

$AUC_{\tau,1}$ area under the plamsa concentration–time curve over a uniform dosing interval τ after administration of the first dose, $AUC_{\tau,ss}$ area under the plasma concentration-time curve at steady state over a uniform dosing interval τ, $AUC_{0-\infty}$ area under the plasma concentration–time curve extrapolated from time zero to infinity, *CL/F* apparent clearance, CL/F_{ss} apparent clearance at steady state, $CL_{R,0-24}$ renal clearance from time zero to 24 h, $CL_{R,0-24,ss}$ renal clearance from time zero to 24 h at steady state, C_{max} maximum plasma concentration, $C_{max,ss}$ maximum plasma concentration at steady state, *CV* coefficient of variation, fe_{0-24} fraction excreted in urine from time zero to 24 h, $fe_{0-24,ss}$ fraction excreted in urine from time zero to 24 h at steady state, MRT_{po} mean residence time following oral administration, $MRT_{po,ss}$ mean residence time following oral administration at steady state, *QD* once daily, $R_{A,AUC}$ accumulation ratio over the dosing interval τ at steady state, expressed as ratio of AUC at steady state and after single dose, $R_{A,Cmax}$ accumulation ratio over the dosing interval τ at steady state, expressed as ratio of C_{max} at steady state and after single dose, $t_{½}$ terminal half-life, t_{max} time to maximum plasma concentration, V_z/F apparent volume of distribution, V_z/F_{ss} apparent volume of distribution at steady state

[a]Shown as median and range

[b]Data available for 13 patients

[c]Data available for nine patients

Table 4 Investigator-assessed best confirmed response, by Response Evaluation Criteria In Solid Tumors version 1.1 ($N=21$)

Response category	*N* (%)
Disease control[a]	6 (29)
Objective response[b]	1 (5)
Complete response	0
Partial response	1 (5)[c]
Stable disease	5 (24)[d]
Progressive disease	12 (57)
Not evaluable	1 (5)
Missing	2 (10)

[a]Disease control defined as complete response, partial response, or stable disease

[b]Objective response defined as complete response or partial response

[c]Patient with gastric cancer (100 mg cohort)

[d]Patients with urachus cancer ($n=1$), esophageal cancer ($n=1$) in the 50 mg cohort, and patients with meningioma ($n=1$), gastric cardia cancer ($n=1$), and intrahepatic bile duct cancer ($n=1$) in the 200 mg cohort

was observed in 21% of patients in the dose expansion phase of the FIH study (see de Jonge et al. [25]). Kidney biopsies from two affected patients revealed dysjunction of podocytes from the glomerular basement membrane and moderate-to-marked podocyte effacement. It is known that FAK is present in the cytoplasm and nuclei of glomerular podocytes, and studies suggest that proteinuria may be related to activation of FAK in the glomerulus [30, 31]. However, the underlying mechanism of proteinuria upon FAK activation remains unclear and requires further investigation. In preclinical toxicology studies of BI 853520 in rats and dogs, the principal toxicological target organs were the gastrointestinal tract and liver [32]. Consistent with these preclinical toxicology data and observations in the FIH study (see de Jonge et al. [25]), other DRAEs included diarrhea, nausea, and vomiting. There were no serious DRAEs, including deaths.

The observed pharmacokinetic parameters are supportive of a QD dosing schedule. The plasma concentration of BI 853520 reached a maximum at 2.0 h after a single dose and 2.9 h at steady state and declined with a geometric mean $t_{½}$ of 20.9 and 20.3 h, respectively, while BI 853520 trough plasma concentrations were stable from day 8 to day 28. In the preclinical setting, data from a MiaPaCa2 xenograft model indicated that BI 853520 is active at a dose of 12.5 mg/kg QD [24].

There was no apparent difference in the pharmacokinetics of BI 853520 200 mg between Japanese and Taiwanese patients. This finding, together with the consistency between the results of this study and the phase I FIH trial conducted in a predominantly Caucasian population (see de Jonge et al. [25]), indicate that BI 853520 pharmacokinetics are consistent across different ethnicities. Further, two pharmacokinetic substudies (see the article by Verheijen et al. [33] in this issue of *Targeted Oncology*) suggest that neither formulation

(liquid dispersion vs. tablet) nor administration with/without a high-calorie meal have notable impact on the pharmacokinetics of BI 853520.

In this study, treatment with BI 853520 produced a confirmed objective response rate of 5% and a disease control rate of 29% in heavily pretreated patients. The median duration of disease control was 3.7 months. These data are similar to those observed in the FIH study (disease control rate of 27% with median duration of 3.3 months). As expected in this heavily pretreated population, the majority of patients had disease progression without disease control, with 12 patients (57%) showing disease progression by the end of cycle 2. Further evaluation of the anti-tumor activity of BI 853520 in a larger patient population, incorporating analysis of potential selection biomarkers, is warranted.

Preclinical investigations in murine adenocarcinoma xenograft models indicate that enhanced sensitivity to BI 853520 is linked to a mesenchymal tumor phenotype, defined by low E-cadherin messenger RNA (mRNA) and protein levels and low expression of hsa-miR-200c-3p, an epithelial-specific microRNA that promotes E-cadherin expression [24, 34]. A preliminary biomarker analysis was carried out as part of the FIH study by de Jonge et al. [25]; however, the potential predictive value of E-cadherin could not be determined. Additional studies are needed to further investigate the value of E-cadherin, hsa-miR-200c-3p, and/or other potential biomarkers to guide patient selection for FAK inhibitor treatment.

Similar anti-tumor activity and AEs have been reported in phase I studies of other FAK inhibitors. VS-6063, GSK2256098, and PF-00562271 were also tested in mixed populations of patients with advanced solid tumors, with evidence of disease stabilization [21–23, 35], metabolic responses [21], and, rarely, minimal objective response [23]. Like BI 853520, these agents are commonly associated with nausea, vomiting, diarrhea, and decreased appetite, as well as fatigue and headache [21–23, 35]. Proteinuria has been reported with GSK2256098 and PF-00562271, albeit at lesser frequency [21, 23], which could indicate a class effect. Reflecting differing pharmacokinetic properties to BI 853520, other FAK inhibitors require twice-daily, rather than QD, oral dosing [21, 23].

5 Conclusion

The findings from this phase I trial demonstrate the manageable and acceptable safety profile, favorable pharmacokinetics, and potential anti-tumor activity of BI 853520 in heavily pretreated Japanese and Taiwanese patients with advanced or metastatic solid tumors. The data are consistent with findings from the FIH study of BI 853520 in a predominantly Caucasian population and support further clinical evaluation of BI 853520. In addition, the combination of BI 853520 with other compounds [36, 37] should be considered for further clinical development.

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Compliance with Ethical Standards

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Conflict of interest James Chih-Hsin Yang has consulted for and received honoraria from Eli Lilly, Boehringer Ingelheim, Bayer, Roche/Genentech, Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceutical Co., Ltd., Daiichi Sankyo, AstraZeneca, Takeda, and Hansoh Pharmaceuticals. Kohei Shitara has consulted for or received honoraria from Astellas Pharma, Lilly, BMS, Takeda, Pfizer, Ono Pharmaceutical Co., Ltd., Novartis, AbbVie, and Yakult, and also reports research funding from Lilly, Ono Pharmaceutical Co., Ltd., Dainippon Sumoitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, and MSD. Ann-Lii Cheng has consulted for or received honoraria from Bayer, BMS, Eisai, MSD, Merck, Novartis, BeiGene, and Ono Pharmaceutical Co., Ltd. Akiko Sarashina and Yoshito Takeuchi are employees of Nippon Boehringer Ingelheim Co., Ltd. Linda C. Pronk is an employee of Boehringer Ingelheim. Toshihiko Doi, Yoichi Naito, and Chia-Chi Lin declare that they have no conflicts of interest. This trial was sponsored by Nippon Boehringer Ingelheim. Co., Ltd. in Japan, and Boehringer Ingelheim Taiwan Ltd. in Taiwan. This work was supported by Boehringer Ingelheim, Ingelheim am Rhein, Germany. BI 853520 is an asset of Boehringer Ingelheim.

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