ELECTRONIC SUPPLEMENTARY MATERIAL

Phase 1 study of the focal adhesion kinase inhibitor, BI 853520, in Asian patients with advanced or metastatic solid tumors

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1 Methods

1.1 Inclusion/exclusion criteria

Eligible patients were aged ≥20 years and had histologically or cytologically confirmed advanced, measurable or evaluable, non-resectable and/or metastatic solid tumors, that were progressive within 6 months prior to study entry as demonstrated by serial imaging and refractory to standard therapy, or for which no effective standard treatment was available. Patients were also required to: have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; have a life expectancy of ≥3 months as judged by the investigator; be recovered from the reversible toxicities (alopecia excluded) of prior anti-cancer treatment or prior surgery (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] grade <2); and have adequate hematologic, renal, and hepatic function (absolute neutrophil count [ANC] ≥1,500/mm^3, platelet count ≥100,000/mm^3, serum creatinine ≤1.5 x the institutional upper limit of normal [ULN], total bilirubin ≤1.5 x institutional ULN, aspartate amino transferase [AST] and alanine amino transferase [ALT] ≤3 x institutional ULN [≤5 x ULN if related to liver metastases); and have available tumor material (archived tissue or fresh biopsy) for determination of E-cadherin expression.

Patients were excluded if they had: serious concomitant non-oncologic disease/illness as judged by the investigator; New York Heart Association grade III–IV congestive heart failure, myocardial infarction within 6 months prior to study entry, or symptomatic coronary artery disease; known active infectious disease including HIV or active hepatitis B/C; second malignancy (not cured, or within the previous 5 years) except for adequately resected cervix carcinoma *in situ*, resected non-melanomatous skin cancers (including basal cell carcinoma and squamous cell cancer), and appropriately treated mucosal gastric cancer or mucosal colorectal cancer; treatment with cytotoxic anti-cancer therapies or investigational drugs within 4 weeks of the first dose of study drug (or shorter duration for patients treated with non-cytotoxic drugs, at the agreement of the principal investigator and sponsor); chronic diarrhea or other gastrointestinal disorder that may have interfered with the absorption of BI 853520, as judged by the investigator; active/symptomatic brain metastases (patients with a history of treated brain metastases had to have a stable or normal brain magnetic resonance imaging [MRI]/computed tomography [CT] scan

at screening with no radiation or surgery for brain metastases within the prior 4 weeks).

1.2 Dose-limiting toxicity (DLT) criteria

Drug-related adverse events meeting any of the following criteria were classified as DLTs:

- Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 non-hematological toxicity (except inadequately treated nausea, vomiting, diarrhea, or transient electrolyte abnormality).
- Persistent (≥7 days) CTCAE grade 2 nausea and/or vomiting (despite adequate treatment) that may cause an interruption of drug intake during these days.
- Any interruption of drug intake for ≥7 days (≥25%) due to toxicity.
- Any adverse event that prevents a patient starting cycle 2 within 14 days of completion of cycle 1.
- CTCAE grade 4 neutropenia lasting ≥7 days (in case it occurs, a control hematology test must be performed at least twice weekly until improvement to a lower grade) and/or complicated by infection.
- CTCAE grade 4 thrombocytopenia (in case it occurs, a control hematology test must be performed at least twice weekly until improvement to a lower grade), thrombocytopenic bleeding or any thrombocytopenia requiring platelet transfusion.
- Febrile neutropenia (absolute neutrophil count <1000/mm^3 and fever ≥38.5°C).

1.3 Criteria for dose reductions and discontinuations

Treatment with the study medication had to be discontinued temporarily in case of adverse events requiring a dose reduction according to investigator's judgment and/or dose-limiting toxicity (DLT). Patients with DLT or an adverse event requiring a dose reduction were allowed to continue therapy only after recovery from the event to Common Terminology Criteria for Adverse Events (CTCAE) levels of grade 1 that allowed further therapy and only with a reduced dose of BI 853520. The reduced dose was valid for all following treatment cycles for individual patients. A reduction of the dose was allowed twice for individual patients during the whole trial, but not to any dose below 50 mg, which was the starting dose of the study. In case a patient

experienced a third episode of DLT or an adverse event requiring a dose reduction, the treatment had to be discontinued. Likewise, the treatment had to be discontinued in case the event did not recover sufficiently (i.e., to grade 1 or less within 14 days).

1.4 Pharmacokinetic assessments

The pharmacokinetic profile of BI 853520 was determined from plasma and urine analysis after a single oral dose and after repeated dosing (steady state).

Blood samples for plasma pharmacokinetic analyses were acquired during cycle 1 on day 1–2 (prior to dosing, then 30 min, 1, 2, 3, 4, 6, 8, 10, and 24 hours post-dosing), days 3, 8, 15, and 22 (prior to dosing), and day 28 (prior to dosing, then 30 min, 1, 2, 3, 4, 6, 8, and 10 hours post-dosing), and during cycles 2–4 on days 1 and 15 (prior to dosing). All urine voided prior to dosing on day 1 of cycle 1 and during sampling intervals 0–4, 4–10, 10–24, and 24–48 following administration on days 1 and 28 of cycle 1, was collected (24–48 hour sample was only taken following the day 1 administration).

Plasma and urine concentrations of BI 853520 were measured by validated assay based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). The lower limit of detection for the assay was 1 nmol/L for plasma and 10 nmol/L for urine.

Pharmacokinetic parameters were estimated by non-compartmental analysis using WinNonlin® version 5.2 (Pharsight Corp., Mountain View, CA, USA) and outputs were generated using SAS® version 9.2.

2 Results

Table 1

Pharmacokinetic parameters of BI 853520 after single-dose and multiple-dose oral administration of 200 mg QD in cycle 1 in Japanese and Taiwanese patients.

Parameter	Japanese (*N* = 6)		Taiwanese (*N* = 9)	
Single dose	Geometric mean	Geometric CV, %	Geometric mean	Geometric CV, %
$AUC_{\tau,1}$, nmol·h/L	16,700	52.4	14,500	51.9
$AUC_{0-\infty}$, nmol·h/L	29,000	62.1	24,700	54.1
C_{max}, nmol/L	1640	42.0	1530	42.3
t_{max}, h[a]	2.95	1.95–2.98	2.00	1.00–3.00
$t_{1/2}$, h	21.5	15.4	20.4	37.8
fe_{0-24}, %	5.78[b]	24.9[b]	5.52	38.8
	Japanese (*N* = 5)		Taiwanese (*N* = 5)	
Multiple dose	Geometric mean	Geometric CV, %	Geometric mean	Geometric CV, %
$AUC_{\tau,ss}$, nmol·h/L	43,700	93.7	30,900	104
$C_{max,ss}$, nmol/L	2960	64.3	2560	100
$t_{max,ss}$, h[a]	2.95	1.98–7.93	2.00	1.00–3.00
$t_{1/2,ss}$, h	22.0[b]	38.6[b]	19.0	6.99
$R_{A,AUC}$	2.38	77.2	1.94	42.8

$R_{A,Cmax}$	1.71	63.9	1.53	57.1
$fe_{0-24,ss}$, %	8.50	39.3	9.23	22.5

$AUC_{\tau,1}$, area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose; $AUC_{\tau,ss}$, area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ; $AUC_{0-\infty}$, area under the concentration-time curve of the analyte in plasma over the time interval 0-infinity; C_{max}, maximum measured concentration of the analyte in plasma; $C_{max,ss}$; maximum measured concentration of the analyte in plasma at steady state; fe_{0-24}, fraction of the analyte excreted in urine within the time interval 0 to 24 hours in % of dose; $fe_{0-24,ss}$, fraction of analyte eliminated in urine at steady state from 0 to 24 hours; $R_{A,AUC}$, accumulation ratio of the analyte in plasma 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 of the analyte in plasma over the dosing interval τ at steady state, expressed as ratio of C_{max} at steady state and after single dose; t_{max}, time from dosing to maximum measured concentration of the analyte in plasma; $t_{max,ss}$, time from (last) dosing to the maximum concentration of the analyte in plasma at steady state; $t_{1/2}$, terminal half-life of the analyte in plasma; $t_{1/2,ss}$, terminal half-life of the analyte in plasma at steady state

[a] Shown as median and range.

[b] Data available for four patients.