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Phase I Study of the Angiogenesis Inhibitor BIBF 1120 in Patients with Advanced Solid Tumors

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Abstract

Purpose: BIBF 1120 is an oral, potent angiokinase inhibitor targeting receptors of the vascular endothelial growth factors, platelet-derived growth factors, and fibroblast growth factors. This phase I, accelerated titration study assessed the maximum tolerated dose, safety, pharmacokinetics, and pharmacodynamic effects of BIBF 1120.

Patients and Methods: Sixty-one patients with advanced cancers received BIBF 1120 in successive cohorts. Twenty-five received 50 to 450 mg once daily and 36 received 150 to 300 mg twice daily in 4-week treatment courses interspersed by 1 week of washout. Dynamic contrast-enhanced magnetic resonance imaging assessed antiangiogenic effect in 42 patients.

Results: Most frequent BIBF 1120–related adverse events were mostly mild to moderate (Common Toxicity Criteria grade 1-2) nausea (68.9%), vomiting (45.9%), and diarrhea (44.3%). The majority of dose-limiting adverse events of Common Toxicity Criteria grade 3 or 4 were reversible liver enzyme elevations. The maximum tolerated dose was 250 mg of BIBF 1120 for once and twice daily dosing. BIBF 1120 was absorbed moderately fast (t_{max} = 1-3 hours at steady state), with no deviation from dose linearity and no decrease of exposure over time. The gMean terminal half-life was from 13 to 19 hours. One complete and two partial responses occurred in patients with renal cell cancer (n = 2) and colorectal cancer (n = 1). Dynamic contrast-enhanced magnetic resonance imaging showed a significant reduction in tumor blood flow in 55% of evaluable patients.

Conclusions: BIBF 1120 dosed continuously displayed a favorable safety and pharmacokinetics profile, and first efficacy signals were observed. Twice daily dosing permitted increased drug exposure without additional toxicity. Two hundred milligrams BIBF 1120 twice daily is the recommended dose for phase II monotherapy studies. *Clin Cancer Res; 16(1); 311–9. ©2010 AACR.*

Angiogenesis is crucial for the growth of malignant tumors and metastases (1, 2). The degree of neovascularization in malignant tissues is a prognostic factor for many human solid tumors including breast, prostate, ovarian, and lung cancers (3, 4). Angiogenesis inhibitors offer a novel approach for cancer therapy (5). Vascular endothelial growth factor (VEGF) is one of the most important proangiogenic factors that can drive tumor angiogenesis (6, 7), although platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) also play an important role. PDGF receptor tyrosine kinases, expressed on the surface of pericytes and smooth muscle cells, contribute to the stability of blood vessel walls; PDGF signaling is important for pericyte survival and maintaining pericyte-endothelial cell contacts (8). FGF receptor (FGFR) tyrosine kinases are expressed on the surfaces of endothelial cells and smooth muscle cells. FGFR signaling pathways promote cell proliferation and survival, playing a role in the development and stabilization of blood vessels (9). PDGF and FGF may also be upregulated in tumors trying to escape from sustained VEGF inhibition (10, 11).

BIBF 1120 is a novel, orally available, potent triple angiokinase inhibitor that predominantly blocks the VEGF receptors 1 to 3, FGFR 1 to 3, and PDGF receptor α and β tyrosine kinases at nanomolar concentrations (12). BIBF 1120, an indolinone derivative, is thought to bind to the ATP binding pocket of the kinase domain, thereby interfering with the cross-autophosphorylation of the receptor homodimers

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Translational Relevance

This phase I, accelerated titration study investigated the maximum tolerated dose, safety, pharmacokinetic profile, and pharmacodynamics of BIBF 1120, a novel, orally available angiokinase inhibitor of vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor receptors, in 61 patients with advanced cancer. The MTD was 250 mg of BIBF 1120 for once and twice daily dosing; two daily administrations allowed an increase in total daily exposure without additional toxicity. Principal dose-limiting toxicities were reversible liver enzyme elevations. BIBF 1120 was well tolerated overall. Pharmacokinetic data showed no deviation from dose linearity and no decrease of exposure over time. Early signs of efficacy were observed: one complete response in a patient with renal cell cancer and two partial responses in patients with renal cell cancer and colorectal cancer. DCE-MRI results show an antiangiogenic effect of BIBF 1120 in a substantial number of patients, supporting clinical findings. Further investigation of BIBF 1120 in patients with solid tumors is warranted.

and blocking the signaling cascade responsible for tumor angiogenesis. BIBF 1120 inhibits protein kinase signaling pathways in three cell types contributing to angiogenesis, endothelial cells, pericytes, and smooth muscle cells, resulting in inhibition of cell proliferation and apoptosis (12). In different xenograft models, BIBF 1120 induced substantial tumor growth inhibition and regression of established tumors. BIBF 1120 also inhibits members of the Src kinase family such as Src, Lck, and Lyn, which are involved in the development and progression of human tumors (13).

The objectives of this study were to determine the maximum tolerated dose (MTD), evaluate the safety, and characterize the pharmacokinetics of continuous once or twice daily treatment with BIBF 1120 in patients with advanced solid cancers.

Patients and Methods

Eligibility. Eligible patients were adults with advanced, nonresectable and/or metastatic measurable solid tumors who had failed established treatment or for whom no therapy of proven efficacy existed, who presented with an Eastern Cooperative Oncology Group performance status of 0 to 2 and a life expectancy of ≥3 mo. Patients with significant cardiac, hematopoetic, hepatic, or renal dysfunction, gastrointestinal disorders thought to interfere with the absorption of the study drug, uncontrolled severe hypertension, active ulcers or infectious disease, injuries with incomplete wound healing, or brain metastases requiring therapy were excluded, as were those completing radiotherapy or major surgery or those treated with other investigational drugs within 4 weeks of the start of BIBF 1120 treatment. The medical ethics committee approved the protocol and all patients provided written informed consent according to Good Clinical Practice regulations.

Study design and treatments. This was an open label, phase I accelerated dose-escalation trial investigating first once and then twice daily dosing schedules of BIBF 1120. Every treatment cycle comprised 28 d of continuous daily treatment with BIBF 1120, followed by a 1-wk washout. For patients with clinical benefit and without dose limiting toxicity (DLT), subsequent treatment cycles were permitted. Patients received 50 or 200 mg capsules of BIBF 1120 (Boehringer Ingelheim Pharma GmbH & Co. KG) after food. Antiemetic prophylactic treatment was prohibited. Dose levels were as follows: once daily (morning) dosing—50, 100, 150, 200, 250, 300, 450 mg/d; twice daily dosing—2 × 150, 150 + 200 (evening dose), 2 × 200, 2 × 250, and 2 × 300 mg/d. The recommended starting dose of 50 mg was based on the results of 4-wk toxicology studies in rats and monkeys.

No intrapatient dose escalation was allowed. DLTs were defined as any drug-related toxicity with Common Toxicity Criteria (CTC) grade of ≥3 with the exception of alopecia and untreated vomiting. The dose was increased by 100% in the next cohort if no patients in an ongoing dose tier developed drug-related toxicity with CTC grade of greater than 1 during the initial treatment course. In case that one patient experienced toxicity of CTC grade of ≥2, the dose was increased by no greater than 50% of the preceding dose for each subsequent cohort. In the absence of grade 2 toxicity, only one patient needed to be treated per cohort. If grade 2 toxicity occurred, further dose escalation followed a standard 3+3 design.

Study assessments. The safety and tolerability of BIBF 1120 were assessed by changes in incidence and severity of adverse events, physical examination, vital signs (including 12-lead resting electrocardiogram), and laboratory examinations according to CTC. Hematologic status, coagulation parameters, and clinical chemistry were measured at screening and in weekly intervals. Phenotypic analysis of peripheral blood lymphocyte CD3, CD4, CD8, CD19, and CD56 subsets was undertaken at screening, and every 4 wk until end of trial visit. In the absence of treatment-related adverse events with a CTC grade greater than 1, measurement intervals were increased to a maximum of 4 wk after two complete treatment cycles. Tumor response was recorded by computed tomography or magnetic resonance imaging (MRI) scans according to the Response Evaluation Criteria in Solid Tumors.

Dynamic contrast-enhanced (DCE) MRI (DCE-MRI) assessment was done at baseline, on day 2 for once daily dosing and day 3 for twice daily dosing, and after the end of each treatment course for patients remaining in the trial. Tumor lesion size (bidimensional diameter) was assessed using standard MRI technique (14). All MRIs were acquired using a 1.5-Tesla whole-body magnetograph (Sonata, Siemens). DCE imaging was done on a coronal slice through one or more representative lesions. For DCE, a

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Table 1. Patient characteristics

Characteristics	BIBF 1120	
	Once daily	Twice daily
No. of patients	25	36
Gender		
Male (*n*)	15	31
Female (*n*)	10	5
Age	59 (41-74)	63 (34-83)
Median (range)		
ECOG performance status at baseline		
0	7	9
1	17	26
2	1	1
Prior therapy		
Surgery	23	33
Chemotherapy	24	29
Radiotherapy	9	15
Immunotherapy*	5	8
Hormonal therapy	1	4
Tumor type		
Colorectal	14	16
Kidney, ureter	1	9
Pleura	3	2
Prostate	0	3
Breast	2	0
Sarcoma, soft tissue	1	1
Head and neck	0	2
Lung	0	2
Pancreas	1	0
Liver, biliary tree	2	0
Cervix, vagina and vulva	1	0
Thyroid	0	1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Immunotherapy comprised, e.g., IFN, interleukin, levamisole.

T1-weighted Inversion Recovery TrueFISP sequence was used (15). The initial area under the curve ($iAUC_{60}$) was calculated as the area under the Gd concentration-time curve for the first 60 s after the onset of contrast agent uptake (16). The transfer constant (K_{trans}) was calculated based on a two-compartment model (17). Reductions of K_{trans} and $iAUC_{60}$ of >40% were considered a significant treatment effect of BIBF 1120. K_{trans} and $iAUC_{60}$ are given as median values of the whole region of interest histograms.

Pharmacokinetics. Blood samples (5 mL) were collected on days 1 to 2 and 29 to 30 at 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 h after first dosing. For the once-daily dose group, an additional pharmacokinetic sample was taken 48 h after the first dose to determine the terminal half-life of BIBF 1120. Predose blood samples to determine trough pharmacokinetic values and the attainment of steady state of BIBF 1120 were collected on days 3, 9, 16, 23, and 29. For pharmacokinetic reasons, BIBF 1120 was administered only once per day on days 1 and 29 in both dosing schedules. During repeated treatment courses, trough pharmacokinetic samples were taken on days 7, 14, 21, and 28. Plasma concentrations of BIBF 1120 were analyzed by validated high performance liquid chromatography tandem mass spectrometry. Standard noncompartmental methods were used to calculate pharmacokinetic parameters (WinNonlin version 4.1, Pharsight).

Results

Patient characteristics. In total, 61 patients were treated with escalating doses of BIBF 1120 once (n = 25; median age, 59 years; range, 41-74) or twice daily (n = 36; median age, 63 years; range, 34-83; Table 1). Median treatment duration was 96 days (1-653 days).

Safety. All patients were assessable for safety. Generally, adverse events were mild or moderate (CTC grade of ≤2) and mostly occurred during the first treatment course (n = 51, 83.6%) independent of dosing schedule. Six patients (9.8%) discontinued treatment due to drug-related adverse events. No treatment-related deaths were observed. Nausea, vomiting, diarrhea, fatigue, and dizziness were the most frequent drug-related adverse events across all treatment cycles (see Table 2). Most liver enzyme elevations in patients treated twice daily were observed after the first 28 days of treatment. CTC grade 3 gastrointestinal adverse events such as nausea, vomiting, and diarrhea were only observed in the twice-daily dosing group. Bilirubin elevations related to BIBF 1120 were not observed. Two patients had hypertension of CTC grade 1 with twice daily dosing, one patient suffered from hypertension of CTC grade 3, and another of CTC grade 2 with once daily dosing of BIBF 1120.

During the first cycle and across all doses tested, three patients (4.9%) developed a drug-related reduction of CD4+ lymphocytes of CTC grade 3. Across all treatment courses, six patients had drug-related CTC grade 3 CD4+ counts.

Dose limiting toxicity. The predominant DLT for once daily dosing of BIBF 1120 was an increase in hepatic enzyme levels, observed mostly during the first treatment cycle (Tables 2 and 3). Besides alanine aminotransferase and γ-GT elevation, CD4+ lymphocytopenia and gastrointestinal adverse events were the DLTs in the twice daily treatment group. After treatment discontinuation, all DLTs were fully reversible. As shown in Table 3, the MTD for once and twice daily dosing of BIBF 1120 was 250 mg once daily and 250 mg twice daily, respectively. Thus, splitting the total daily dose into two daily administrations allowed an increase in total daily exposure with favorable tolerability: at 450 mg once daily, 2 of 3 patients suffered from DLTs, whereas only 1 of 13 patients treated with 250 mg twice daily (total daily dose 500 mg) developed a dose limiting adverse event.

Tumor response. Twenty-three patients were assessable for tumor response in the once daily cohort and 35 patients in the twice daily cohort. Two confirmed partial responses were observed in patients suffering from

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Table 2. Number of patients with BIBF 1120–related adverse events occurring in >5% of patients

Adverse event*	Maximum grade (CTC)	BIBF 1120			
		Once daily		Twice daily	
		First, *n* (%)	All courses, *n* (%)	First, *n* (%)	All courses, *n* (%)
All patients	25	25	36	36	
Patients with adverse event	21 (84)	24 (96)	30 (83.3)	33 (91.7)	
Nausea	1	13 (52)	13 (52)	17 (47.2)	19 (52.8)
	2	4 (16)	5 (20)	2 (5.6)	3 (8.3)
	3	0	0	2 (5.6)	2 (5.6)
Vomiting	1	7 (28)	9 (36)	10 (27.8)	15 (41.7)
	2	3 (12)	3 (12)	0	0
	3	0	0	1 (2.8)	1 (2.8)
Diarrhea	1	6 (24)	6 (24)	9 (25)	13 (36.1)
	2	5 (20)	6 (24)	1 (2.8)	1 (2.8)
	3	0	0	0	1 (2.8)
Dyspepsia	1	2 (8)	2 (8)	0	2 (5.6)
Anorexia	1	0	2 (8)	0	0
Abdominal pain	2	2 (8)	2 (8)	0	0
Fatigue	1	2 (8)	3 (12)	4 (11.1)	4 (11.1)
	2	0	0	4 (11.1)	5 (13.9)
Dizziness	1	0	0	4 (11.1)	5 (13.9)
Pruritus	1	0	4 (16)	0	0
Urticaria	1	0	0	0	2 (5.6)
Hepatic enzyme elevation†‡	2	1 (4)	1 (4)	0	0
	3	3 (12)	3 (12)	0	0
	4	1 (4)	1 (4)	1 (2.8)	1 (2.8)
ALT increase†	2	0	0	1 (2.8)	1 (2.8)
	3	0	0	1 (2.8)	2 (5.6)
AST increase†	2	0	0	1 (2.8)	0
	3	1 (4)	2 (8)	1 (2.8)	1 (2.8)
γ-GT increase†	2	0	0	1 (2.8)	1 (2.8)
	3	1 (4)	1 (4)	1 (2.8)	2 (5.6)
CD4 lymphocytes decreased†	3	1 (4)	4 (16)	2 (5.6)	2 (5.6)
Hypertension†	1	0	0	0	2 (5.6)
	2	1 (4)	1 (4)	0	0
	3	0	1 (4)	0	0
Headache	1	0	2 (8)	2 (5.6)	2 (5.6)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ glutamyl transpeptidase.
*Preferred terms.
†Number of patients with adverse events occurring in >1% of patients. Presented is the highest ever reached CTC grade. The same patient may have experienced more than one event.
‡Hepatic enzyme elevation describes the following cases that were presented under the respective highest CTC grade. Twice daily cohort: one patient had AST of grade 4 and ALT + γGT grade 3. Once daily cohort: one patient had ALT+AST of grade 4 +γGT grade 3, one patient had ALT+γGT of grade 3, one patient had AST+γGT of grade 3, one patient had ALT+AST of grade 3 and one patient had ALT of grade 2.

colorectal and renal cell cancer, respectively, treated with BIBF 1120 twice daily (Fig. 1A). One confirmed complete response occurred in another patient with renal cell carcinoma whose lung metastases had disappeared after 2 months of treatment with BIBF 1120 at 200 mg once daily. Two of 10 patients with advanced renal cell cancer remained on therapy for >1 year (maximum of 648 days) and seven patients were treated for at least 5 months. One patient with hepatocellular cancer was stable for 653 days on treatment with 50 mg once daily of BIBF 1120. Thirty-seven patients (64%) had stable disease for at least two treatment cycles. The overall median time to tumor progression was 99 days (95% confidence interval, 64-145 days) for the once daily dosing cohort and 106 days (95% confidence interval, 64-172 days) for the twice daily dosing cohort.

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Pharmacokinetics. Peak plasma levels were reached after 2 to 3 hours for once daily dosing and 1 to 3 hours for twice daily dosing after p.o. drug intake at steady state (Table 4; Fig. 2). Maximum plasma concentrations ($C_{max,ss}$) and exposure ($AUC_{\tau,ss}$) increased with doses and there was no indication for a deviation from dose linearity after single administration and in steady state (see Supplementary Fig. S1). At steady state, the AUC increased from 171 ng·h/mL (150 mg twice daily group) to 226 ng·h/mL (250 mg twice daily group) to 366 ng·h/mL (300 mg twice daily), which represents a dose-related linear increase of around 1.5-fold and 2.3-fold, respectively, of the AUC, in line with the expected AUC increase considering the large coefficient of variation. The apparent volume of distribution ranged from 10,100 liters (250 mg once daily dose) to 25,400 liters (250 mg twice daily group) at steady state (data not shown). The terminal half-life ($t_{1/2,ss}$) of BIBF 1120 ranged from 12.9 to 19 hours over all dose groups. There was no decrease of exposure over a 6-month treatment period with BIBF 1120 (data not shown). A moderate to high interpatient variability in all pharmacokinetic parameters over all dose groups was observed. The shape of the BIBF 1120 plasma concentration-time profiles was similar for the 150 and 250 mg twice daily dose groups after single dose administration and at steady state (Fig. 2), and exhibited at least biexponential disposition kinetics. There was a moderate accumulation of the AUC from single dose to steady state with a gMean accumulation ratio of 1.27 to 1.90 (see Supplementary Table S1), which was reached at the latest after 9 days.

DCE-MRI assessment. Forty-two patients were evaluable for DCE-MRI. A decrease of ≥40% in $iAUC_{60}$ was observed in 7 of 42 patients (16.7%) at day 2/3 after the start of treatment and in 7 of 37 patients (18.9%) at the end of the first course. At the end of course 2, 30% (9 of 30) of patients had decreases of ≥40% in $iAUC_{60}$; after the third treatment course, the proportion was 38.9% (9 of 18). A K_{trans} decrease of ≥40% was observed in 26.2% of patients (11 of 42) on day 2/3 after the start of BIBF 1120 treatment and in 27% (10 of 37) at the end of the first course. After 56 and after 84 days of treatment, 50% of patients (15 of 30 and 9 of 18, respectively), showed a decrease of ≥40% in K_{trans}.

In total, 17 patients (40.5%) had an $iAUC_{60}$ and 23 patients (54.8%) had a K_{trans} decrease of ≥40%. As shown in Fig. 1B, there was no difference between once or twice daily dosing or total daily BIBF 1120 dose in general with respect to changes in $iAUC_{60}$ of K_{trans} (data not shown) over time.

Logistic regression analysis with K_{trans} or $iAUC_{60}$ response as dependent and $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ at steady state as explanatory variables revealed a significant association of $AUC_{0\text{-}24,ss}$ ($P = 0.01$) and $C_{max,ss}$ ($P = 0.004$) with $iAUC_{60}$ response (data not shown). In addition, logistic regression analysis with K_{trans} or $iAUC_{60}$ response (decrease of ≥40% from baseline) as explanatory variable and absence of progression (stable disease, partial response, or complete response) as a dependent variable revealed a significant association between K_{trans} response and absence of progressive disease ($P = 0.004$). Patients with $AUC_{0\text{-}24,ss}$ above 800 ng h/mL and $C_{max,ss}$ above 60 ng/mL were more likely to show a DCE-MRI response. No association between liver enzyme elevations and maximal concentration (C_{max}) or exposure (AUC) was found during logistic regression analyses.

Discussion

The aim of this study was to determine the MTD for once and twice daily dosing of BIBF 1120, which was 250 mg; splitting the total daily dose into two daily administrations allowed to increase the total daily exposure without additional toxicity.

Table 3. Number of patients with DLT within the first course of BIBF 1120 treatment

Total daily dose (mg)	Once daily		Twice daily	
	All patients	Patients with DLT	All patients	Patients with DLT
50	2	0	—	—
100	1	0	—	—
150	—	—	6	0
150 + 200	—	—	6	0
200	8	1 (12.5) AST+γGT increased	6	1 (16.7) CD4 lymphocytes decreased
250	6	1 (16.7) CD4 lymphocytes decreased	13	1 (7.7) nausea
300	5	2 (40) AST+γGT (1), ALT+AST (1)	5	4 (80) nausea+vomiting (1), ALT+AST increased (1), ALT+AST+γGT (1), CD4 lymphocytes decreased + γGT, increased (1)
450	3	2 (66.7) ALT+AST+γGT (1), ALT+γGT (1)	—	—

NOTE: DLT was defined as any CTC grade 3 or 4 hematologic or nonhematologic toxicity.

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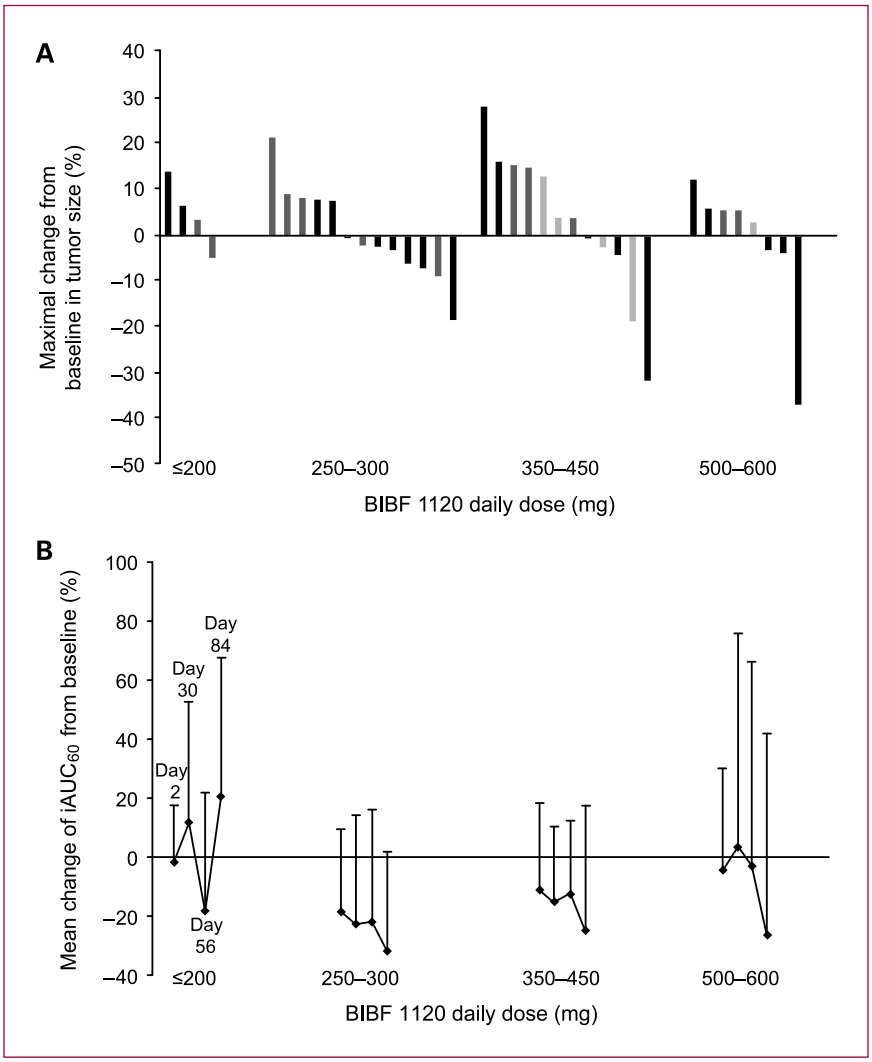

Fig. 1. *A,* maximum change from baseline in tumor size per daily dose group. All patients evaluable for iAUC change and MRI imaging; *black columns*, patients with colorectal cancer; *light gray columns*, patients with kidney/ureter cancer. *B,* mean change and SEM in $iAUC_{60}$ from baseline at day 2, day 30, day 56, and day 84 by daily dose group.

In general, adverse events were mild or moderate. The most frequently reported drug-related adverse events were gastrointestinal events (nausea, vomiting, and diarrhea) during the first treatment cycle, with only a minimal increase in subsequent cycles. Two patients discontinued treatment due to gastrointestinal adverse events; both related to tumor progression. Overall, the gastrointestinal events observed during this phase I study were comparable with those observed with other angiogenesis inhibitors (18–21) and could be readily prevented or controlled with timely administration of appropriate medication.

The principal DLTs observed during treatment with BIBF 1120 were liver enzymes elevations (alanine aminotransferase, aspartate aminotransferase, and γ-GT-elevations with CTC grade of ≥3). These liver enzyme elevations were fully reversible, and responded rapidly within 2 weeks to treatment discontinuation or dose reduction indicating reversible liver toxicity. Aspartate aminotransferase/alanine aminotransferase elevations of ≥grade 3 occurred mostly in patients who received BIBF 1120 above the MTD dose level, suggesting a dose threshold for this particular side effect. Importantly, no concurrent increase of bilirubin or alkaline phosphatase was observed.

Unlike some other angiogenesis inhibitors (19, 21), BIBF 1120 did not seem to cause relevant skin abnormalities and hypertension was a rare event in this study (18–20), although promising signs of efficacy in renal cell and colorectal cancer patients were observed indicative of appropriate BIBF 1120 drug exposure. Considering the relatively low incidence of fatigue, findings indicate that BIBF 1120 has a comparatively favorable safety profile overall (22).

Due to inhibition of kinases of the Src family (Src, Lck, and Lyn), BIBF 1120 may interfere with lymphocyte proliferation and function. However, the changes in CD4 counts during treatment were inconsistent, in some patients decreasing, in others increasing. In five of the eight patients with grade of ≥3 CD4 counts during treatment (reported as drug related in six patients), baseline counts already showed a decrease of grade 2 severity, and five of

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Table 4. Pharmacokinetic parameters of BIBF 1120 at steady state (day 29) in the first treatment course

BIBF 1120 dose (mg)	No. of patients	$C_{max,ss}$ ng/mL (gCV%)	$AUC_{\tau,ss}$ ng·h/mL (gCV%)	$t_{max,ss}$* h (range)	$t_{1/2,ss}$ h (gCV%)
Once daily					
50	1	8.22	32.1	3.07	14.7
100	1	40.8	207	2.00	11.8
200	8	35.4 (31.0)	223 (40.3)	1.98 (0.50-4.03)	15.3 (46.8)
250	6	58.6 (38.8)	479 (49.1)	2.53 (1.03-6.00)	13.7 (11.9)†
300	3	50.5 (137)	482 (128)	3.00 (2.92-4.03)	14.1 (35.7)
Twice daily					
150	6	34.8 (49.0)	171 (56.2)	1.03 (0.517-3.17)	16.3 (10.4)‡
150+200	6	48.0 (70.0)	260 (57.3)	2.13 (1.00-4.03)	15.6 (36.6)
200	6	44.9 (80.5)	303 (81.2)	2.72 (1.00-7.92)	19.0 (60.0)
250	11	44.2 (54.3)	226 (55.6)	2.08 (0.517-4.08)	16.7 (35.2)§
300	3	68.6 (20.6)	366 (9.57)	2.00 (1.05-2.22)	12.9 (37.1)

NOTE: Presented is geometric mean. $AUC_{\tau,ss}$ for once daily $\tau = 24$ h; for twice daily $\tau = 12$ h. No steady-state pharmacokinetic data could be collected for the 450 mg cohort due to drop out of the patients.
Abbreviation: gCV, geometric mean of the coefficient of variation.
*Median.
†$n = 5$.
‡$n = 4$.
§$n = 10$.

these patients also received concomitant steroid medication. None of the patients with CTC grade of ≥3 drug-related decrease in CD4 cell counts had an infection at onset or developed opportunistic infections. Five of the six patients had an Eastern Cooperative Oncology Group score of 1 at study entry, one of 0. The duration of the respective drug-related CD4 cell decrease for three patients ranged between 8 to 141 days and all the patients recovered from the event. For the other three patients, the duration and outcome remained unknown. In this heavily chemotherapy-pretreated population, the functional reserve of the bone marrow was likely reduced. Thus, the fluctuations observed for CD4 cell counts may not reflect an effect of BIBF 1120. Overall, the exclusion of the CD4 cell depletion from the DLT definition would not have changed the overall MTD conclusion.

Pharmacokinetic analyses of BIBF 1120 revealed moderately fast absorption with a terminal half-life suitable for once or twice daily dosing. Maximum plasma concentrations and exposure increased with doses, both after single administration and at steady state. There was no indication of deviation from "dose-linear pharmacokinetic" behavior of BIBF 1120 detectable after single dose and at steady state, which represents the therapeutically relevant systemic exposure for chronic anticancer therapy with BIBF 1120. Although it should be noted that no formal dose

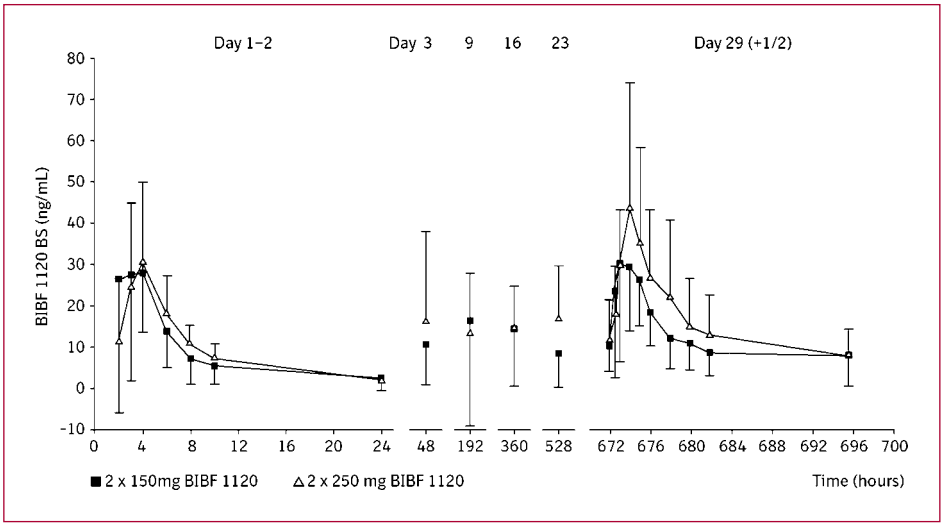

Fig. 2. Arithmetic mean plasma concentration-time profiles of BIBF 1120 after single and multiple administrations of 150 and 250 mg BIBF 1120 twice daily over 29 (+1/–2) days (±SD).

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proportionality analysis was conducted due to the small patient numbers. All pharmacokinetic parameters displayed moderate to high variability after single doses and at steady state, in line with phase I findings with other tyrosine kinase inhibitors (23–25). Moreover, the mixed study population with varied prior anticancer therapies, or comedications, could also have had some influence on the variability of the pharmacokinetics of BIBF 1120. At the MTD of 250 mg once or twice daily, maximum plasma concentrations were higher than the minimum concentrations required to inhibit VEGF receptor, FGFR, or PDGF receptor phosphorylation *in vitro* (12).

Antiangiogenic treatment was shown to be effective in patients with hepatocellular, renal cell, and colorectal cancer, and one patient with a previously progressive hepatocellular cancer presented with disease stabilization for almost 2 years at the BIBF 1120 dose of 50 mg qd. Two patients with renal cell cancer experienced a complete and a partial response, and the majority of the other eight patients suffering from renal cell cancer experienced a prolonged disease stabilization. Across the whole population, 64% of patients remained stable until at least 10 weeks after start of therapy and the median time to tumor progression was about 100 days. Regarding the DCE-MRI investigations, the frequency of $iAUC_{60}$ and K_{trans} decreases of ≥40%, which is a significant reduction, indicated an antiangiogenic effect of BIBF 1120 in a substantial number of patients. Overall, 17 of 42 evaluable patients had significant reductions in $iAUC_{60}$ and 23 patients had significant reduction in K_{trans} during the course of the study. These results further confirm that the changes to the tumor vasculature expected during effective antiangiogenic therapy can indeed be observed in BIBF 1120–treated patients.

In conclusion, BIBF 1120 showed a favorable safety profile in this advanced cancer patient population. Twice daily dosing permitted an increase in total dose without additional toxicity. Clinically important signs of efficacy were observed with single-agent BIBF 1120, including one complete response in a patient with renal cell carcinoma. These results indicate that further exploration of BIBF 1120 in cancer patients is warranted.

Disclosure of Potential Conflicts of Interest

R. Kaiser, L. de Rossi, M. Stefanic, B. Gaschler-Markefski, and P. Stopfer are employees of Boehringer Ingelheim; K. Mross received research funding from Boehringer Ingelheim. The other authors disclosed no potential conflicts of interests.

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