Phase I Safety, Pharmacokinetic, and Biomarker Study of BIBF 1120, an Oral Triple Tyrosine Kinase Inhibitor in Patients with Advanced Solid Tumors

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Abbreviations: VEGFR, vascular endothelial growth factor receptor; PDGF, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; TKI, tyrosine kinase inhibitor; BMD, bone marrow-derived; MTD, maximum tolerated dose; DLT, dose-limiting toxicity.

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Abstract

BIBF 1120 is an oral multitargeted tyrosine kinase inhibitor that blocks the activity of vascular endothelial growth factor (VEGF) and other growth factor receptors. We have now performed a phase I study to evaluate the safety, pharmacokinetics, and pharmacodynamic biomarkers of BIBF 1120. Patients with advanced refractory solid tumors were treated with BIBF 1120 at oral doses of 150 to 250 mg twice daily (bid). Drug safety and pharmacokinetics were evaluated, as were baseline and posttreatment levels of circulating CD117-positive bone marrow–derived (BMD) progenitor cells and plasma soluble VEGF receptor 2 (sVEGFR2) as potential biomarkers for BIBF 1120. Twenty-one patients were treated at BIBF 1120 doses of 150 mg bid (n = 3), 200 mg bid (n = 12), or 250 mg bid (n = 6). Dose-limiting toxicities of reversible grade 3/4 elevations of liver enzymes occurred in three of 12 patients at 200 mg bid and three of six patients at 250 mg bid. Stable disease was achieved in 16 (76.2%) patients, and median progression-free survival was 113 days (95% confidence interval, 77–119 days). Pharmacokinetic analysis indicated that the maximum plasma concentration and area under the curve for BIBF 1120 increased with dose within the dose range tested. Levels of CD117-positive BMD progenitors and sVEGFR2 decreased significantly during treatment over all BIBF 1120 dose cohorts. In conclusion, the maximum tolerated dose of BIBF 1120 in the current study was determined to be 200 mg bid, and our biomarker analysis indicated that this angiokinase inhibitor is biologically active.
Introduction

Angiogenesis, defined as the formation of new blood vessels from a preexisting vasculature, is essential for tumor growth and the spread of metastases (1, 2). Tyrosine kinase receptors, including vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and fibroblast growth factor receptors (FGFRs), together with their corresponding ligands, play key roles in angiogenesis (1). Antiangiogenic therapy that targets signaling by these receptor-ligand systems represents an important advance in clinical oncology (3). Given that most angiogenesis inhibitors are cytostatic, however, it has been difficult to assess their biological effects in early clinical trials. Validated biomarkers that allow monitoring of the biological activity of these agents are thus urgently needed (4, 5). The most intuitive approach to measurement of the biological activity of such targeted agents is evaluation of their effects on tumor cells or the vasculature. However, this invasive approach raises practical and ethical concerns (6, 7). Noninvasive, blood-based biomarkers that allow repetitive sampling throughout treatment and follow up are therefore preferred.

BIBF 1120 is an orally available triple tyrosine kinase inhibitor (TKI) that predominantly blocks VEGFR1 to -3, FGFR1 to -3, as well as PDGFRα and -β tyrosine kinases at nanomolar concentrations (Fig. 1) (8-10). In preclinical studies, BIBF 1120 has been shown to inhibit the growth of and to reduce vessel density in subcutaneously implanted human tumor xenografts in nude mice (8, 11). A previous phase I BIBF 1120 monotherapy study in patients with advanced and heavily pretreated malignancies demonstrated encouraging antitumor activity and a tolerable safety profile. The maximum tolerated dose (MTD) was determined as 250 mg twice daily (bid) (12). A further phase I
combination study demonstrated that BIBF 1120 at 200 mg bid can be combined with standard doses of paclitaxel and carboplatin (13). Several Phase II monotherapy trials have gone on to demonstrate promising signs of efficacy in patients with advanced non–small cell lung cancer (NSCLC) and ovarian cancer (14, 15).

We have now performed a phase I dose-escalation study to determine the MTD, tolerability, basic pharmacokinetics, and antitumor effect of BIBF 1120 given orally on a twice daily schedule in Japanese patients with advanced refractory solid tumors. To identify biomarkers that reflect the pharmacodynamics and dose-response relation of BIBF 1120, we further evaluated baseline (before BIBF 1120 treatment) and posttreatment levels of circulating CD117 (c-KIT)–positive bone marrow–derived (BMD) progenitor cell subsets as well as of plasma soluble VEGFR2 (sVEGFR2). We show that a subset of CD117+ BMD progenitors, immunophenotypically defined as CD45dimCD34+CD117+ cells, is a potential biomarker for guidance of optimal therapy with BIBF 1120.

Patients and Methods

Patient eligibility

Eligible patients were 20 years of age or older with a confirmed diagnosis of advanced solid tumors who had not responded to conventional treatment or for whom no therapy of proven efficacy was available. They were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of <2 and adequate organ function. Individuals were excluded if they had a brain tumor or brain metastases requiring therapy, gastrointestinal disorders that might interfere with absorption of the study drug, or serious illness or concomitant nononcologic disease that was difficult to control by medication.
Patients were also excluded if they had a history of obvious pulmonary fibrosis or interstitial pneumonitis, autoimmune disease, serious drug hypersensitivity, cardiac infarction, or congestive heart failure. All subjects received information regarding the nature and purpose of the study, and they provided written informed consent in accordance with institutional guidelines.

**Study design**

This study was designed as a single-center, open-label, dose-escalation, Phase I trial. The primary objectives of this dose-escalation trial were to determine if BIBF 1120 doses from 150 mg to 250 mg administered twice-daily on a continuous daily could be confirmed as safety and tolerable treatment and to collect overall safety data. The secondary objectives included the determination of the MTD, the pharmacokinetic parameters, pharmacodynamics and preliminary information regarding the antitumor activity and the efficacy on angiogenic peripheral blood biomarkers in this treatment population. The study was reviewed and approved by the Institutional Review Board.

Dose levels of BIBF 1120 were 150, 200, and 250 mg bid. Intra-patient dose escalation was not permitted. Each treatment course comprised 28 days of continuous daily treatment with BIBF 1120. If a patient experienced a drug-related dose-limiting toxicity (DLT), the treatment with BIBF 1120 had to be discontinued. If all DLTs had been recovered to baseline or below grade 1 according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 within 14 days of stopping treatment with BIBF 1120, treatment could be resumed at one dose lower level.

The dose escalation/reduction scheme was based on the occurrence of drug-related DLTs within the first treatment course. If a DLT was not observed in any of the first three
patients, the dose was escalated to the next level. If a DLT was observed in one of the first three patients, three additional patients were recruited to that dose level. If a DLT occurred in only one out of six patients, dose escalation was permitted. If two or more of six patients experienced a DLT, additional patients were recruited at one lower dose level for a total of at least six patients. In addition to this dose escalation/reduction scheme, if the investigators and independent data monitoring committee (IDMC) agreed that additional patients were necessary to confirm the dose escalation/reduction decision in the case when two or more patients experienced DLTs, which were not life-threatening and were reversible and manageable with or without medication, entering additional patients at that dose level was allowed. The MTD was defined as the highest dose level at which less than 33% of the patients would experience a DLT during the first treatment course. Once the MTD had been determined, that cohort was expanded to at least 12 patients in total, in order to more completely assess the safety and tolerability of the dose level.

Safety and efficacy assessments

The safety and tolerability of BIBF 1120 were assessed according to Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. The following AEs were defined as DLTs: drug-related AEs hematological or non-hematological toxicity of CTCAE grade 3 or 4 within the first treatment course with BIBF 1120. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (16).

Pharmacokinetics

Blood samples (4 mL) were collected on Days 1–2 and 29–30 prior to and 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours after dosing. Predose blood samples to determine trough
pharmacokinetic values and the attainment of steady state of BIBF 1120 were collected on Days 8, 15, 22, and 29 in first treatment course. For pharmacokinetic reasons, BIBF 1120 was administered only once per day on Days 1 and 29 in first treatment course. During repeated treatment courses (2–6), trough pharmacokinetic samples were taken on Days 15 and 29. Plasma concentrations of BIBF 1120 were analyzed and pharmacokinetic parameters were calculated by same manner at the previously conducted Phase I study (12).

**Biomarker evaluation**

The concentration of sVEGFR2 in plasma were measured by enzyme-linked immunosorbent assay (ELISA) on Days 1, 2, 8 and 29 after BIBF 1120 treatment according to the manufacture’s instructions (R&D System, Mineapolis, MN).

CD117/c-KIT positive-BMD progenitor cell subsets were measured using flowcytometry. Peripheral blood was collected before starting and after 2, 8 and 29 days of BIBF 1120 treatment. The 800 uL of whole blood was supplemented with 4.5 mL of 0.2% Bovine serum albumin-phosphate buffered saline (BSA-PBS) and centrifuged for 5 minutes (1500 rpm). After the removal of supernatant by aspiration, 4.5 mL of 0.2% BSA-PBS was added and centrifuged. Cell pellet was mixed with 50 μL of human gamma-globulin. Antibodies (CD34-FITC, CD117-PE, and CD45-PerCP) were added and kept for 45 minutes at 4 °C. Hemolytic agent (4.5 mL) was added and incubated for 10 min. After centrifugation (1500 rpm, 5 minutes), supernatant was washed twice. Subsequently, 0.2% BSA-PBS (4.5mL) was added, supernatant was removed by centrifugation (1500rpm, 5 min). Cell pellet was filled up to 800 uL by BSA-PBS and analyzed by FACS Calibur flowcytometer (BD Biosciences). Cell surface markers of CD133 and CD117 were further
identified from the CD34+CD45dim cells in peripheral blood by using flow-cytometry (Fig 2A). The cell phenotype data of CD133+/− CD117+/- cells were calculated by the percentage of cell numbers of target quadrant/those of all quadrants (CD34+CD45+dim cells).

**Statistical analysis**

Student’s paired t test was used to compare plasma sVEGFR2 levels or circulating CD45dimCD34+CD117+ cell numbers between Day 8 and before treatment as well as between Day 29 and before treatment in order to evaluate the significance of changes induced by BIBF 1120 treatment (Microsoft Excel). A p value of <0.05 was considered statistically significant.

**Results**

**Patient demographics**

Twenty-one patients with advanced, refractory solid tumors were recruited between June 2006 and July 2007. Demographic and clinical characteristics of the patients are listed in Table 1. The median number of cycles administered per patient was three (range, 1–7 cycles) and 10 patients received at least 4 cycles.

**Dose escalation and MTD**

No DLT was observed at the starting dose of 150 mg bid in the first three patients (Table 2), dose escalation to the second dose level of 200 mg bid. Since one of the first three patients experienced a DLT of grade 3, an increase in alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (γ-GT) levels at 200 mg bid, three patients were additionally treated at this dose according to the protocol definition. Among the first six patients...
treated at 200 mg bid, two patients experienced a DLT of grade 3 (ALT and $\gamma$-GT increases in one patient, ALT increase in one patient). Given that these increases in hepatic enzyme levels were fully reversible, the investigators and IDMC agreed to add four more patients for confirming the judgment of dose escalation/reduction of the dose level. The four additional patients did not experience a DLT, and overall two of 10 patients at this dose level experienced a DLT, and therefore dose escalation proceeded to 250 mg bid. At this dose level, three of six patients showed DLTs [aspartate aminotransferase (AST) and ALT elevations of grade 3 in one patient, ALT elevation of grade 3 in one patient, and $\gamma$-GT elevation of grade 3 in one patient], and the MTD had been exceeded. The next lower dose of 200 mg bid was therefore identified as the MTD.

According to the protocol definition, two additional patients were further evaluated at the MTD cohort. Among the total of 12 patients who received 200 mg bid, three patients experienced a reversible grade 3 or 4 AST, ALT, and $\gamma$-GT elevation, that were correspond to DLT, and 200 mg bid BIBF 1120 was thus confirmed as the MTD.

**Safety**

Twenty-one patients received at least one dose of study treatment and were evaluated for safety. As shown in Table 3, the most frequent BIBF 1120-related side-effects were increased hepatic enzymes (ALT [61.9% of patients], AST [57.1%], and $\gamma$-GT [57.1%]), vomiting (57.1%), anorexia (52.4%), fatigue (52.4%), alkaline phosphatase (ALP) increase (42.9%), nausea (38.1%), and diarrhea (33.3%). Most of these events were of mild to moderate intensity and of CTCAE grade 1 or 2, fully reversible and clinically manageable over all doses. The predominant CTCAE grade 3 and 4 AEs were reversible liver enzyme elevations occurring at BIBF 1120 200 mg bid and BIBF 1120 250 mg bid in
a total of eight patients. Except for one patient with combined grade 4 AST and ALT elevations, all elevations were of grade 3 intensity. One patient in the BIBF 1120 150 mg bid cohort reported grade 3 hypertension and another patient in the BIBF 1120 250 mg bid cohort reported grade 3 fatigue. Drug-related increases in hepatic enzymes occurred within the first week after treatment initiation and were fully reversible on cessation of treatment. There were no bleeding events or clinically relevant hematological toxicities during all treatment courses throughout the study. Due to AEs or DLTs, four patients in the BIBF 1120 200 mg bid and three patients in the BIBF 1120 250 mg bid dose cohorts required dose reduction.

**Pharmacokinetics**

Pharmacokinetic parameters following a single oral dose and multiple oral doses of BIBF 1120 (150–250 mg, bid) are shown in Table 4. Maximum plasma concentrations ($C_{\text{max, (ss)}}$) were reached at 2 to 3 hours after dosing after single and multiple dosing of BIBF 1120 (Fig 2A and B and Table 4). After attaining $C_{\text{max}}$, the plasma concentration declined in an apparent biexponential manner with the terminal half-life of approximately 10 hours. Of note, the terminal half-life of BIBF 1120 was calculated from samples obtained during the first 24 hours post-dose. After multiple dosing of BIBF 1120, maximal plasma concentrations were reached at 2 to 3 hours after dosing (Fig 2B and Table 4). The accumulation ratio (Rac) values based on AUC were 1.42 to 1.7, and accumulation was consistent with the terminal half-life observed after single doses. Steady-state plasma concentrations were attained at least on Day 8 of repeated twice-daily oral dosing based on visual inspection of the trough plasma concentration. In general, $C_{\text{max}}$ and area under the curve (AUC) were increased with increasing dose. Trough plasma concentrations of BIBF
1120 during repeated treatment courses were almost at the same level within each dose group. The range of geometric mean of trough concentration was 14.4 to 38.4 nM for 150 mg bid group and 28.2 to 84.6 nM for 200 mg bid group. In the 250 mg bid group, the number of trough concentrations collected during repeated treatment courses was very limited due to the occurrence of dose reduction in this group.

**Tumor response**

Twenty patients were evaluated for tumor response. Although no complete or partial responses were observed, 16 (76.2%) patients had stable disease for at least two treatment courses (56 days). The disease stabilization was observed across the all tested doses: BIBF 1120 150 mg, all patients (100%) of three; 200 mg, nine (75%) of twelve; 250 mg, four (67%) of six. Median progression-free survival (PFS) for all patients was 113 days (95% confidence interval [CI]: 77–119 days)

**Plasma levels of sVEGFR2 during treatment with BIBF 1120**

At baseline, the mean plasma level of sVEGFR2 obtained from 15 patients (150 mg bid (n=3), 200 mg bid (n=9) and 250 mg bid (n=3)) was 7.7 ± 1.7 ng/mL (range, 5.3–11.0 ng/mL). Plasma concentrations of sVEGFR2 decreased significantly over the first 4 weeks of treatment to a level of 5.8 ± 1.3 ng/mL (range, 3.2–8.8, p<0.001, t-test) (Fig. 3A). The decreases in sVEGFR2 levels were seen across all doses tested. As shown in Figure 3B, the decrease in sVEGFR2 showed an inverse linear correlation with the trough plasma drug levels of BIBF 1120 (correlation coefficient: r= –0.46).

**Levels of circulating CD117/C-KIT⁺-BMD progenitors during treatment with BIBF 1120**

Subsets of CD117 positive-BMD progenitor cells were measured in progenitor-enriched
(CD45$^{\text{dim}}$CD34$^+$) whole blood of 15 patients (150 mg bid (n=3), 200 mg bid (n=9) and 250 mg bid (n=3)). CD117 was expressed in the CD45$^{\text{dim}}$CD34$^+$ subset with a level of 60-80% and representative data are shown in Figure 4A. CD45$^{\text{dim}}$CD34$^-$CD117$^+$ cells significantly decreased over all BIBF 1120 dose cohorts during the first cycle of therapy (p=0.009 on Day 8 and p=0.004 on Day 29, t-test) (Fig. 4B).

**Discussion**

This Phase I study showed that BIBF 1120 can be safely administered to Japanese patients with advanced solid tumors, and the MTD was determined as 200 mg bid, which was one dose lower than Caucasian patients (12). Biomarker investigations revealed that the plasma concentration levels of the soluble VEGFR2 and the CD45$^{\text{dim}}$CD34$^+$ CD117$^+$ cells significantly decreased over the first 4 weeks of treatment with BIBF 1120.

As has been observed in previous Phase I and Phase II studies with BIBF 1120, gastrointestinal side-effects such as vomiting, fatigue, nausea and diarrhea were the most frequent AEs (12, 15) and have also been observed with other VEGFR inhibitors such as sorafenib or sunitinib (4, 5, 17). These side-effects of mostly of mild or moderate intensity occurred predominantly at the MTD of BIBF 1120 or at higher doses and were easy to monitor and manageable with standard supportive treatment. Hypertension has also been reported with several other VEGF and VEGFR inhibitors (4, 5), and was observed in three patients in this study. All cases were controllable with appropriate antihypertensive treatment.

The pharmacokinetic analysis revealed that there was a dose linear increase for $C_{\text{max}}$ and AUC. $C_{\text{max}}$ values have been reached within 3 hours after administration and
steady state was reached at least on Day 8. All pharmacokinetic parameters displayed a moderate to high variability as expected for an oral compound. In addition, different patients with various different anticancer pretreatments have been enrolled into this study, thus differences in pretreatment and other intrinsic factors, such as age and status, might have influenced the variability of these parameters too. Overall, there was no difference in the pharmacokinetic behavior of BIBF 1120 between Japanese and Caucasian patients (12, 18). Based on the trough plasma concentrations for BIBF 1120 at dose levels of 150 mg bid and above, sufficient exposure has been reached to block the target structures of the molecule according to the IC_{50} values (8, 11).

All DLTs observed in this study were liver enzyme elevations (grade 3 or 4 ALT, AST, and γ-GT). These liver enzyme elevations were fully reversible, responded within two weeks to treatment discontinuation or dose reduction indicating reversible liver side effects and were not accompanied by an increase of bilirubin. However, at 200 mg bid of BIBF 1120 in Caucasian patients, no such liver enzyme elevations were observed in a previous phase I study (12). We cannot exclude the possibility of ethnic differences although there were no pharmacokinetic differences between Japanese and Caucasian patients. By the exploratory data evaluation, the body weight of all three patients, who experienced DLTs at the 200 mg bid as MTD, were below 50 kg, whereas the remaining nine patients 50 kg and over treated without DLTs. This finding suggested that body size such as body weight or body surface area, might confer liver enzyme elevations on BIBF 1120, with further investigation of possible dose dependency being warranted.

Evaluation of novel targeted agents, such as VEGF signaling inhibitors, may be supported by the identification of suitable biomarkers of biological activity. The most
intuitive method to measure the effect of any anticancer drug is to evaluate the tumor tissue. Tumor biopsy strategies provide a way to thoroughly characterize tumor histology and molecular processes with immunohistochemistry, DNA microarray, and proteomics analyses. Indeed, several considerable biomarkers of angiogenesis such as microvessel density or tumor VEGF expression have extensively investigated using tumor tissue specimens. On the other hand, identifying circulating biomarkers of angiogenesis would have the advantage of being minimally invasive allowing repetitive sampling throughout treatment without the ethical and technical complications of multiple biopsy. Circulating levels of sVEGFR2 was previously found to be decreased by other VEGFR2 inhibitors that directly target this receptor such as AZD2171 (8) and SU11248 (9), although the mechanism behind the consistent decrease in sVEGFR2 levels is not entirely understood (4, 5, 19-21). In the present study, plasma sVEGFR2 levels showed time-dependent decrease at all dose levels studied and the changes in sVEGFR2 were inversely associated with trough plasma concentration of BIBF 1120 suggesting that sVEGFR2 is a useful pharmacodynamic marker of drug exposure, with similar findings reported for other agents.

Circulating endothelial cells (CECs) have emerged as a potentially useful surrogate marker of antiangiogenic drug activity (4, 10, 19-21). CECs comprise two distinct populations: mature CECs which originate from vessel walls and have a limited growth capability and BMD CECs which are responsible for most endothelial proliferative potential. Circulating BMD endothelial progenitors have been reported to contribute to tumor vasculogenesis in animal models as well as in humans (18, 21-23). However, the variable degrees of incorporation of CECs shown in different tumor models have led to
controversy about the extent of their actual involvement in tumor vascularization.

Identification of CEC is highly complex and has been hampered by the overlapping antigenic similarities with a lack of consensus about the definition of these endothelial cells (4, 24). The pan-hematopoietic marker CD45 has been widely used to first exclude hematopoietic cells (22). CD34 was chosen as a co-label because it is reported to be present on endothelial progenitors, and CD34<sup>+</sup> cells alone can repopulate bone marrow in vivo (23). This present study reported the first quantitative analysis of subset of circulating CD117-BMD progenitor cells, characterized as CD45<sup>dim</sup>CD34<sup>+</sup>CD117<sup>+</sup>, after treatment with BIBF 1120. Results show that levels of circulating CD117-BMD progenitor cells were significantly decreased after BIBF 1120 treatment in time-dependent fashion. One possible explanation for the BIBF 1120-induced decrease in CD117-BMD progenitor cells is that CD117/C-KIT<sup>+</sup> is one of the target receptors of BIBF 1120 as well as many other VEGFR TKIs, resulting in the impaired growth of CD117/C-KIT<sup>+</sup> cells or inhibitory effects of differentiation/mobilization to peripheral blood. This study further demonstrated that the patients who responded (SD) to BIBF 1120 had a larger decrease in CD117-BMD progenitor cells after the initial 4 weeks of the study treatment compared with patients who did not (PD) (Supplementary Figure S1), although given the sample size, there was a limited power to detect a significant difference. This observation suggests that a reduction in CD117-BMD progenitor cells would be associated with a higher degree of target inhibition and greater clinical efficacy after BIBF 1120 treatment. This is the first study to show evidence of decreased levels of circulating CD117-BMD progenitor cells during treatment with antiangiogenic agents. Meanwhile, the main limitation, in evaluating the circulating endothelial progenitor cells for surrogate biomarker, are “Non-standardized.
protocols” or “Labor intensive”. Further investigation to validate whether it will be useful for monitoring the response to antiangiogenic therapy is warranted.

In conclusion, BIBF 1120 shows an acceptable profile for Japanese patients suffering from advanced solid tumors at dose up to 200 mg bid. The preliminary evaluation of biologic activity of BIBF 1120 using plasma (sVEGFR2) and cellular (CD117-BMD progenitor cells) markers and disease stabilization data demonstrate that this agent is biologically active. BIBF 1120 is currently being investigated in a range of tumor types, and recruitment to a series of randomized, double-blind Phase II and III trials is ongoing.
References


sustained receptor blockade and good anti-tumor efficacy Cancer Research 2008;68: 4774-82.


Figure Legends

Figure 1. Structure of BIBF 1120

Figure 2. Mean (± SD) plasma concentration–time profiles of BIBF 1120 after single (Day 1) and multiple (Day 29) administration of 150, 200 and 250 mg BIBF 1120 twice-daily

Figure 3. sVEGFR2 levels in plasma after BIBF 1120 treatment.
A, plasma sVEGFR2 levels decreased during the 4-week treatment period. B, the decrease in sVEGFR2 at Cycle 1, Day 29 showed a modest inverse correlation with trough plasma drug levels of BIBF 1120 (R = −0.46).

Figure 4. Levels of circulating CD117-BMD progenitor cells after BIBF 1120 treatment.
A, Representative flow cytometric analysis for determining the number of CD117 positive-BMD progenitor cells defined as CD45dimCD34+CD117+. B, circulating levels of CD45dimCD34+CD117+ cells decreased during the 4-week treatment period.
Table 1. Patient characteristics

<table>
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<tr>
<th>Characteristic</th>
<th>No. of patients</th>
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<tr>
<td>Median (range) age (years)</td>
<td>62 (41–81)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (48%)</td>
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<td>Performance status (ECOG)</td>
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<td>5 (24%)</td>
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<tr>
<td>1</td>
<td>16 (76%)</td>
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<tr>
<td>Previous therapy</td>
<td></td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Chemotherapy</td>
<td>19 (91%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
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<tr>
<td>Tumor types</td>
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<tr>
<td>Small-cell lung cancer</td>
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<tr>
<td>Esophagus sarcoma</td>
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<tr>
<td>Adrenal carcinoma</td>
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<tr>
<td>Renal cell carcinoma</td>
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<tr>
<td>Adenoid cystic carcinoma</td>
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<tr>
<td>Unknown primary site</td>
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ECOG, Eastern Cooperative Oncology Group
### Table 2. Dose-escalation scheme and DLT

<table>
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<tr>
<th>BIBF 1120 Dose (mg bid)</th>
<th>No. of patients</th>
<th>DLT in first course</th>
<th>DLTs</th>
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<td>150</td>
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<tr>
<td>200</td>
<td>12</td>
<td>3</td>
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<tr>
<td>250</td>
<td>6</td>
<td>3</td>
<td>AST and ALT increase, ALT increase, γ-GT increase</td>
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</table>

DLTs, dose-limiting toxicities; ALT, alanine aminotransferase; AST, aspartate aminotransferase

γ-GT, gamma-glutamyl transferase
Table 3. Adverse events (≥10% incidence) related to BIBF 1120 in all treatment courses

<table>
<thead>
<tr>
<th>BIBF 1120 Dose</th>
<th>150 bid (N=3)</th>
<th>200 bid (N=12)</th>
<th>250 bid (N=6)</th>
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<td>CTCAE grade</td>
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<td>4 4</td>
<td>3 2</td>
<td>13 61.9</td>
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<td>3 1</td>
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<tr>
<td>γ-GT increased</td>
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<td>2 2</td>
<td>12 57.1</td>
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<td>Vomiting</td>
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<td>9 0</td>
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<td>3 0</td>
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<td>2 0</td>
<td>8 38.1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 0</td>
<td>5 0</td>
<td>2 0</td>
<td>7 33.3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 0</td>
<td>3 0</td>
<td>0 0</td>
<td>4 19.0</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1 0</td>
<td>1 0</td>
<td>2 0</td>
<td>4 19.0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0 0</td>
<td>4 0</td>
<td>0 0</td>
<td>4 19.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 0</td>
<td>2 0</td>
<td>0 0</td>
<td>3 14.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 1</td>
<td>1 0</td>
<td>0 0</td>
<td>3 14.3</td>
</tr>
<tr>
<td>Rash</td>
<td>0 0</td>
<td>2 0</td>
<td>1 0</td>
<td>3 14.3</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 0</td>
<td>2 0</td>
<td>0 0</td>
<td>3 14.3</td>
</tr>
<tr>
<td>LDH increased</td>
<td>0 0</td>
<td>2 0</td>
<td>1 0</td>
<td>3 14.3</td>
</tr>
</tbody>
</table>

Presented is the highest ever reached CTCAE grade. One patient may have experienced more than one event.

CTCAE, Common Terminology Criteria for Adverse Events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyl transferase; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase

[Type text]
**Table 4.** Pharmacokinetic parameter of BIBF 1120 after a single dose (Day 1) and multiple dosing for 29 days

<table>
<thead>
<tr>
<th></th>
<th>BIBF 1120 Dose (mg)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 (N=3)</td>
<td>200 (N=12)</td>
<td>250 (N=6)</td>
<td></td>
</tr>
<tr>
<td><strong>Single dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>28.9 (61.5)</td>
<td>52.0 (64.3)</td>
<td>99.8 (70.3)</td>
<td></td>
</tr>
<tr>
<td>$t_{\text{max}}$, hours</td>
<td>2.00 (1.00–6.00)</td>
<td>2.98 (1.98–4.00)</td>
<td>2.98 (1.00–4.07)</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$, hours</td>
<td>10.3 (15.8)</td>
<td>10.2 (30.4)</td>
<td>9.53 (10.8) b)</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-12}$, ng·h/mL</td>
<td>145 (88.3)</td>
<td>233 (40.9)</td>
<td>399 (64.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple dosing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max,ss}}$, ng/mL</td>
<td>38.8 (107)</td>
<td>67.6 (74.3)</td>
<td>62.9 (14.4)</td>
<td></td>
</tr>
<tr>
<td>$t_{\text{max,ss}}$, hours</td>
<td>2.00 (1.98–4.00)</td>
<td>2.97 (1.98–3.98)</td>
<td>2.00 (1.00–4.00)</td>
<td></td>
</tr>
<tr>
<td>$t_{1/2,ss}$, hours</td>
<td>20.4 (55.3)</td>
<td>19.9 (75.5) c)</td>
<td>23.8 (39.4) d)</td>
<td></td>
</tr>
<tr>
<td>$AUC_{ss}$, ng·h/mL</td>
<td>207 (135)</td>
<td>423 (66.2)</td>
<td>411 (9.15)</td>
<td></td>
</tr>
<tr>
<td>Rac</td>
<td>1.42 (35.4)</td>
<td>1.70 (40.9)</td>
<td>1.50 (79.0)</td>
<td></td>
</tr>
</tbody>
</table>

geometric mean (geometric coefficient of variation %)

a) median (range)
b) N=5
c) N=6
d) N=2

[Type text]
Figure 1
Figure 2

![Graph showing BIBF1120 plasma concentration over time for Day 1 and Day 29.]

Day 1

Day 29

**Time (h)**

- 0
- 4
- 8
- 12
- 16
- 20
- 24

- 0
- 672
- 720
- 768
- 800
- 832
- 864
- 896
- 928

**BIBF1120 plasma conc. (ng/mL)**

- 0
- 25
- 50
- 100
- 150

**Legend:**

- ○ 150 mg (N=3)
- △ 200 mg (N=12)
- ■ 250 mg (N=6)
Figure 3

A

B

% Reduction of sVEGFR2 (day 20/Pre)

Trough drug level (ng/ml)
Figure 4
Molecular Cancer Therapeutics

Phase I Safety, Pharmacokinetic, and Biomarker Study of BIBF 1120, an Oral Triple Tyrosine Kinase Inhibitor in Patients with Advanced Solid Tumors

Isamu Okamoto, Hiroyasu Kaneda, Taroh Satoh, et al.

Mol Cancer Ther Published OnlineFirst August 5, 2010.

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