A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer

M. Reck¹, R. Kaiser², C. Eschbach³, M. Stefanic², J. Love², U. Gatzemeier¹, P. Stopfer² & J. von Pawel³

¹Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Hamburg; ²Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach; ³Department of Pneumology, Asklepios Hospitals Harburg, Hamburg, Germany

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Background: To assess the efficacy, safety, tolerability and pharmacokinetics of BIBF 1120 in patients with stage IIIb/IV non-small-cell lung cancer (NSCLC).

Methods: Patients with locally advanced or metastatic relapsed NSCLC in whom first- or second-line platinum-based chemotherapy failed were randomly allocated to daily 250 mg BIBF 1120 b.i.d. or 150 mg BIBF 1120 b.i.d. Primary end points were progression-free survival (PFS) and objective tumour response (RECIST). Incidence and severity of adverse events (AEs) were reported.

Results: Seventy-three patients received BIBF 1120. Median PFS was 6.9 weeks, with no significant difference between treatment arms. Median overall survival (OS) was 21.9 weeks. Eastern Cooperative Oncology Group (ECOG) 0–1 patients (n = 56) had a median PFS of 11.6 weeks and a median OS of 37.7 weeks. Tumour stabilisation was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg b.i.d.). Most commonly reported drug-related AEs were nausea (57.5%), diarrhoea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (13.7%) and aspartate aminotransferase elevations (9.6%). BIBF 1120 displayed dose-linear pharmacokinetic characteristics.

Conclusion: Continuous treatment with BIBF 1120 was well tolerated, with no difference in efficacy between treatment arms. PFS and objective response with single-agent treatment in advanced disease warrants further exploration.

Key words: angiokinase inhibitor, BIBF 1120, non-small cell lung cancer, pharmacokinetics, phase II

Introduction

Most patients with non-small-cell lung cancer (NSCLC) present with advanced or metastatic disease. Due to the high relapse rate, prognosis is poor even for patients presenting with earlier stages of disease.

Multiple signalling pathways, such as the vascular endothelial growth factor (VEGF) pathway, are dysregulated during NSCLC progression. The vascular endothelial growth factor receptor (VEGFR) is a major regulator of angiogenesis, a process that is essential for tumour growth and metastasis [1]. In NSCLC, increased microvessel count, often used as a measure of angiogenesis, has been correlated with poor prognosis [2] and associated with advanced disease and inferior outcomes [2–5]. VEGF also promotes endothelial cell proliferation and survival and increases vascular permeability [6]. Moreover, increased tumour expression of VEGFR correlates with inferior prognosis in NSCLC [5, 7–10].

Platelet-derived growth factor receptor (PDGFR) also has a role in promoting angiogenesis, tumour growth and metastasis [11]. Along with the fibroblast growth factor receptor (FGFR), PDGFR regulates the migration and adherence of pericytes and smooth muscle cells to endothelial cells, providing support and stability to vessel walls.

BIBF 1120 is a potent tyrosine kinase inhibitor that simultaneously inhibits VEGFR 1–3, FGFR 1–3 and PDGFR α, β [12]. Phase I clinical data show that BIBF 1120 has a favourable safety profile and is well tolerated up to a maximum tolerated dose (MTD) of 250 mg twice daily (b.i.d.) [13].
The primary objective of this double-blind phase II study was to investigate the activity of continuous BIBF 1120 monotherapy in second- and third-line patients with advanced NSCLC and to confirm the safety of 250 mg BIBF 1120 b.i.d. In previous phase I monotherapy studies, BIBF 1120 demonstrated encouraging antitumour activity in patients with advanced solid tumours [13], and patients with NSCLC, in combination with pemetrexed [14]. Primary end points were progression-free survival (PFS) and objective tumour response according to RECIST. Secondary end points were overall survival (OS), clinical benefit, incidence and intensity of adverse events (AEs) and pharmacokinetics.

methods

study population
Eligible patients were of either gender, aged ≥18 years with histologically or cytologically confirmed stage IIIIB (including pleural effusion) or IV advanced NSCLC. Participants had recurrent disease after chemotherapy (including one platinum-based chemotherapy) and an Eastern Cooperative Oncology Group (ECOG) criteria score of 0–2 [15]. Other inclusion criteria were ≥1 measurable tumour lesion according to RECIST [16], adequate haematopoietic bone marrow, renal and hepatic function and normal coagulation parameters.

Exclusion criteria included the following: a haemorrhagic or thrombotic event in the past 12 months, clinically significant haemoptysis within the last 3 months, concurrent anticoagulation or antiplatelet therapy, radiographic evidence of cavitary or necrotic tumours, symptomatic brain metastases or brain metastases requiring therapy and significant comorbidities or cardiovascular diseases.

study design
The study was carried out in compliance with the Declaration of Helsinki (1996), the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and applicable regulatory requirements. Patients provided written informed consent. The protocol was approved by the respective local ethics committees and the competent authority.

Patients were randomly allocated without stratification to receive 250 mg BIBF 1120 b.i.d. or 150 mg BIBF 1120 b.i.d.; in the event of side-effects requiring treatment interruption or discontinuation, a dose reduction was permitted to 150 mg b.i.d. or 100 mg b.i.d., respectively. Such events were pre-specified as drug-related vomiting and nausea Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2, for five or more consecutive days; drug-related diarrhoea CTCAE Grade ≥2 for ≥8 consecutive days and/or drug-related hypertension CTCAE Grade ≥3; drug-related alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation CTCAE Grade ≥3 or ALT and/or AST elevation CTCAE Grade ≥2 in conjunction with bilirubin CTCAE Grade >1; all other drug-related nonhaematological and haematological toxic effects of CTCAE Grade ≥3, except isolated gamma glutamyl transpeptidase (GGT) increases and all other drug-related nonhaematological and haematological toxic effects of CTCAE Grade 2 leading to treatment interruption for ≥14 consecutive days.

outcome measurements
PFS was defined as the time from first BIBF 1120 administration to tumour progression, the appearance of new tumour lesions, patient death or last radiological assessment. For patients without PFS events, this was the date when the patient was censored. Response was measured by tumour assessments at baseline and every 6 weeks until disease progression according to RECIST.

Secondary end points included evaluation of stable disease (SD), partial response (PR) or complete response; OS; changes in quality of life according to the European Organization for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ)-C30 and the lung cancer module EORTC QLQ-LC13 [17]. Questionnaires were distributed before clinical assessment and before patients were provided with any new information about their disease. Both questionnaires were completed at screening, Visit 2 and at 6 weekly intervals. Disease-related symptoms were assessed at screening, Visit 2 and every 2 weeks.

AEs, vital signs and laboratory measures were evaluated by the CTCAE, version 3.0 [18]. Blood samples for laboratory safety assessments were collected at screening, weekly within the first 4 weeks of treatment, every two weeks until week 13 and thereafter every 3 weeks; in cases of drug-related toxicity CTCAE Grade >1, sampling was carried out weekly. When toxicity declined to CTCAE Grade ≤1 in two consecutive visits, the standard schedule of safety laboratory measurements could be carried out.

pharmacokinetic analysis
Pharmacokinetic sampling was carried out on days 1 and 43. Venous blood was collected before and 1, 2 and 3 h after BIBF 1120 administration. Trough levels of BIBF 1120 were assessed following sampling before the first daily dose on key mandatory visits. BIBF 1120 plasma concentrations were analysed by high-performance liquid chromatography–tandem mass spectrometry. The lower limit of quantification was 0.5 ng/ml; the calibration curves were linear in a concentration range of 0.5–500 ng/ml plasma using a plasma volume of 200 µl. Pharmacokinetic parameters were summarised by descriptive statistics.

statistical methods
The objective of this explorative phase II trial was to investigate the differences in efficacy and safety between the two doses of BIBF 1120 in an exploratory manner. In keeping with this objective, all efficacy and safety end points were analysed and presented. This exploratory study used the ranking and selection approach described by Simon et al. [19] to determine the sample size. Using this method, 35 patients in each of the two treatment groups were expected to provide a 90% chance of showing 250 mg b.i.d. to be numerically superior to 150 mg b.i.d., if the true underlying difference was at least 15%. Monotherapy with chemotherapy, such as docetaxel or pemetrexed, showed a response rate of ~7%–9% in second- and third-line NSCLC patients [20, 21]. However, due to the general mode of action of anti-angiogenic compounds, tumour stabilisation rather than responses was expected with a median PFS of 2.9 months [20].

For PFS and OS, treatment groups were compared using an unstratified log-rank test among all treated patients. Efficacy analyses were carried out for all patients and separately among patients with ECOG 0–1. Evidence of tumour shrinkage was assessed by comparing doses in terms of the best RECIST evaluation and maximum decrease from baseline in the sum of tumour diameters. The distribution of BIBF 1120 and BIBF 1202 plasma concentrations was graphically assessed and summarised by time point using descriptive statistics. The one-sided Fisher’s exact test was used to compare treatment arms for key safety parameters.

results

patient demographics
Seventy-three patients were enrolled—37 were randomly assigned to receive 150 mg b.i.d. and 36 to receive 250 mg b.i.d. (Table 1; Figure 1). For patients treated with 150 mg BIBF 1120 b.i.d., the median duration of exposure was 49 days (range 7–420 days). For those treated with 250 mg BIBF 1120 b.i.d., the median duration of exposure was 43 days (range 5–470 days).
efficacy
There was no superiority of the higher dose 250 mg BIBF 1120 b.i.d. group versus the lower dose 150 mg BIBF 1120 b.i.d. group with respect to the median PFS (53 versus 48 days). Median PFS for all patients (both doses; ECOG 0–2) was 6.9 weeks. Median OS for all patients was 21.9 weeks. There was a trend towards prolonged survival in patients receiving the higher dose of BIBF 1120 (150 versus 250 mg b.i.d., 20.6 versus 29.7 weeks; hazard ratio (HR) = 0.693; P = 0.21), although this was not observed when the analysis was adjusted for baseline tumour size. In patients with ECOG 0–1, PFS was similar between treatment arms (150 mg b.i.d. versus 250 mg b.i.d., 81 versus 85 days). However, as expected, PFS was longer in patients with baseline ECOG 0–1 than in those with ECOG 2 (Figure 2; 11.6 versus 6 weeks; HR = 3.194, P = 0.0002).

Patients with ECOG 0–1 had a median OS of 37.7 weeks (Figure 3). The risk of death was significantly associated with baseline tumour size, baseline ECOG and the presence of liver metastases (P < 0.01). Subgroup analyses showed no difference in PFS between squamous cell carcinoma patients and those with nonsquamous cell carcinoma.

Best tumour response data as assessed by the investigator for all treated patients are shown in Table 2. Tumour stabilisation (defined as such if a patient’s first overall disease assessment at 6 weeks was SD, complete response or PR) was achieved in 46% of all patients and 59% in patients with ECOG 0–1. One confirmed PR was observed in the high-dose cohort. Three patients maintained clinical benefit (a patient was considered to have clinical benefit until the date of occurrence of progressive disease) for >1 year, with one (in the 250 mg b.i.d. group) sustaining a 74% reduction (PR) in tumour size for up to 9 months. Four patients achieved a maximum decrease of at least 25% in tumour size. Among patients with ECOG 0–1, both doses of BIBF 1120 had comparable efficacy, with 16 patients (59.3%) in the 150 mg b.i.d. arm and 17 patients (58.6%) in the 250 mg b.i.d. arm experiencing clinical benefit. Of the 17 patients with a baseline ECOG of 2, one patient (receiving 150 mg BIBF 1120 b.i.d.) achieved clinical benefit (SD).

With respect to physical functioning and global health status, 67.8% and 82.1% of all patients remained stable or showed an improvement within the first 42 days as measured by the EORTC QLQ-C30. More than 50% of patients reported stable or improved cough, dyspnoea and pain on day 42 (87.5%, 58.9% and 57.1% for each symptom, respectively) as measured by the EORTC QLQ-LC13. Twenty-two per cent of patients discontinued before day 42 (19% and 26% for the 150 mg BIBF 1120 b.i.d. and 250 mg BIBF 1120 b.i.d. dose cohorts, respectively).

safety
Independent of relatedness, all 73 patients experienced at least one AE during the study period; most were CTCAE Grade 1 or 2. The most frequently reported drug-related AEs are listed in Table 3. The most commonly reported drug-related AEs were nausea (57.5%), diarrhoea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and elevations of ALT (13.7%) and AST (9.6%) across all dose groups.

As shown in Table 3, patients treated with the higher dose had more CTCAE Grade ≥3 AEs compared to patients treated with 150 mg BIBF 1120 b.i.d. (41.7% versus 8.1%). Patients in the 250 mg BIBF 1120 b.i.d. dose cohort experienced more nausea, vomiting and diarrhoea than patients in the 150 mg BIBF 1120 b.i.d. dose cohort. In addition, increases in AST and ALT were only observed in the 250 mg BIBF 1120 b.i.d. dose group.

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Table 1. Baseline patient demographic and disease characteristics (treated set)

<table>
<thead>
<tr>
<th></th>
<th>150 mg b.i.d.</th>
<th>250 mg b.i.d.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients treated, n (%)</td>
<td>37 (100)</td>
<td>36 (100)</td>
<td>73 (100)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (standard deviation)</td>
<td>62.4 (9.2)</td>
<td>62.9 (8.3)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male</td>
<td>18 (48.6)</td>
<td>26 (72.2)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>37.7 weeks; hazard ratio (HR) = 0.693; P = 0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ECOG performance, n (%)</td>
<td>0</td>
<td>8 (21.6)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Histological classification, n (%)</td>
<td>Adenocarcinoma</td>
<td>22 (59.5)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>Location of metastatic sites, n (%)</td>
<td>Lung</td>
<td>24 (64.9)</td>
<td>18 (50.0)</td>
</tr>
<tr>
<td>Stage, n (%)</td>
<td>IIB</td>
<td>1 (2.7)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Number of prior chemotherapy regimens, n (%)</td>
<td>1</td>
<td>21 (56.8)</td>
<td>23 (63.9)</td>
</tr>
<tr>
<td>Best response to previous platinum chemotherapy, n (%)</td>
<td>Complete response</td>
<td>2 (5.4)</td>
<td>0</td>
</tr>
<tr>
<td>Days since last chemotherapy</td>
<td>≤90</td>
<td>21 (56.8)</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td>≥90</td>
<td>16 (43.2)</td>
<td>19 (52.8)</td>
<td>35 (48.0)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
The overall safety pattern was similar between patients with squamous and nonsquamous cell cancer histology and predominantly related to gastrointestinal AEs, such as nausea, vomiting or diarrhoea (data not shown). There was no significant difference in the frequency of CTCAE Grade 1 or 2 AEs of squamous versus nonsquamous cell cancer patients. However, there was a higher overall frequency of CTCAE Grade 3 or 4 AEs for squamous versus nonsquamous cell cancer patients (35.3% versus 21.4%). This difference was mainly related to dyspnoea (29.4% versus 14.3%), vomiting (5.9 versus 3.6%) and nausea (11.8% versus 7.1%). Three squamous cell cancer patients (17.6%) had haemoptysis of CTCAE Grade 1 compared with two patients (3.6%) with nonsquamous cell cancer histology. One squamous and one nonsquamous cell cancer patient died due to significant pulmonary bleeding, with both events being considered unrelated to BIBF 1120.

No CTCAE Grade >2 hypertension, haematological toxic effects or significant skin alterations were observed. Grade 3 AEs largely comprised nausea, diarrhoea and increased ALT levels and were of higher frequency in the 250 mg b.i.d. dose group (10 patients, 27.8%). Grade 3 increased ALT levels were only reported in patients receiving 250 mg b.i.d. BIBF 1120 (19.4%). Three patients (8.3%) in the 250 mg b.i.d. dose group experienced Grade 3 GGT elevations and one patient (2.8%) experienced a Grade 3 AST elevation. Of the seven patients with a Grade 3 ALT increase, two required dose reductions and two permanently discontinued from the study. All seven patients recovered.
Twenty patients of 37 (150 mg b.i.d., \(n=18\); 250 mg b.i.d., \(n=19\)) discontinued BIBF 1120 treatment due to AEs that were solely attributed to disease progression. The remaining patients discontinued treatment due to other events, such as nausea, vomiting and elevated hepatic enzymes. All patients recovered from these events after BIBF 1120 discontinuation.

In 14 patients, drug-related AEs required treatment interruption or permanent discontinuation, with significantly more occurring in the 250 mg b.i.d. treatment group (150 versus 250 mg b.i.d., 5.3 versus 33.3%; \(P=0.0025\)). Seven patients experienced Grade 3 ALT elevations, which were associated with increased AST in three patients and marginally increased bilirubin (up to a maximum of 1.3 mg/dl) in three patients. Other AEs included nausea and vomiting (\(n=4\) and \(n=3\), respectively). All patients recovered from these events.

In 14 patients, drug-related AEs required treatment interruption or permanent discontinuation, with significantly more occurring in the 250 mg b.i.d. treatment group (150 versus 250 mg b.i.d., 5.3 versus 33.3%; \(P=0.0025\)). Seven patients experienced Grade 3 ALT elevations, which were associated with increased AST in three patients and marginally increased bilirubin (up to a maximum of 1.3 mg/dl) in three patients. Other AEs included nausea and vomiting (\(n=4\) and \(n=3\), respectively). All patients recovered from these events.

There were 34 deaths during the study period (17 patients in each dose group). None were considered related to BIBF 1120 by the investigators but were considered related to underlying NSCLC. Thirty-one deaths were due to disease progression and three cases were attributed to general deterioration in physical health in the context of disease progression (one patient in the 150 mg b.i.d. group), haemorrhage (one patient in the 250 mg b.i.d. cohort) and haemoptysis (one patient in the 250 mg b.i.d. cohort).

### pharmacokinetics

Steady state was reached by day 15 for both groups. As no pharmacokinetic sampling was carried out between days 1 and 15, steady state may have been reached earlier. gMean BIBF 1120 pre-dose plasma concentrations (\(C_{\text{pre,ss}}\)) on days 15, 29 and 43 were stable during this period for both doses (Table 4), with no deviation from dose proportionality. Moderate-to-high interpatient variability of BIBF 1120 pre-dose plasma concentrations was observed. Within the 150 mg BIBF 1120 b.i.d. dose group, BIBF 1120 plasma concentrations increased (within the first 3 h after the first drug administration), with gMean BIBF 1120 values of 12.3 ng/ml (0.533–66.1 ng/ml) at 1 h, 13.2 ng/ml (0.754–46.6 ng/ml) at 2 h and 18.2 ng/ml (0.662–77.0 ng/ml) at 3 h after drug administration. Within the 250 mg BIBF 1120 b.i.d. dose group, BIBF 1120 plasma concentrations increased (within the first 3 h after the first drug administration), with gMean BIBF 1120 values of 12.3 ng/ml (0.533–66.1 ng/ml) at 1 h, 13.2 ng/ml (0.754–46.6 ng/ml) at 2 h and 18.2 ng/ml (0.662–77.0 ng/ml) at 3 h after drug administration. There was only slight accumulation of BIBF 1120 plasma concentrations from day 1 to day 43 for both dose groups.

### discussion

This study revealed that continuous daily treatment with BIBF 1120 is well tolerated and showed signs of clinical activity, particularly in ECOG 0–1 patients with advanced NSCLC. Patients with an ECOG score of 2 progressed rapidly within the first 6 weeks of treatment. There was no difference in efficacy between both doses tested, whereas the higher dose presented a higher frequency regarding some AEs.

PFS and median OS were comparable between both groups, and patients with ECOG 0–1 experienced a longer OS when compared with patients with ECOG 2.

Results demonstrate that BIBF 1120 displays efficacy in patients with ECOG 0–1 being comparable, regarding OS data, to historical phase II data of other VEGFR inhibitors in
a similar patient population [22–25]. Sorafenib 400 mg b.i.d. has been associated with a median PFS of 83 days and a median OS of 205 days [24] compared with 264 days for BIBF 1120. Also, the percentage of patients with SD was comparable with sorafenib. Data from other phase II studies with VEGF inhibitors—sunitinib, vandetanib and vatalanib—in similar patient populations are comparable with the efficacy observations in this study (PFS; sunitinib [22]: 84 days, vandetanib [26]: 77 days and vatalanib (b.i.d. cohort): 104 days [23]).

Continuous daily treatment with BIBF 1120 was generally well tolerated. The majority of AEs were mild to moderate and fully reversible gastrointestinal side effects, a typical class effect of small-molecule VEGFR-2 inhibitors [27–30]. The overall frequency and intensity of these AEs were in the range observed in a previous phase I monotherapy study [13]. In phase I, the predominant dose-limiting toxic effects were reversible liver enzyme elevations, mostly in patients receiving BIBF 1120 doses above the MTD, suggesting a dose threshold for this particular AE. As in phase I, the most frequent AEs requiring dose adjustment or discontinuation were elevated liver enzymes. These elevations were fully reversible and responded rapidly within 2 weeks of treatment discontinuation or dose reduction.

Of the patients who experienced nausea, eight patients discontinued treatment. Of the remainder, 27 were treated with metoclopramide, two received dimenhydrinate and nine required treatment with a 5HT3 receptor antagonist; no dose reductions were necessary. There were no differences in the frequency of nausea and vomiting between males and females nor was there a difference in the frequency of gastrointestinal AEs between dose groups. There were no treatment discontinuations as a result of diarrhea, although three patients required a dose reduction and 17 patients required loperamide treatment.

Severe hypertension [24] and hand–foot syndrome are common side effects of other VEGFR/targeted inhibitors [24, 27, 31–33]. In this study, no patients suffered from hand–foot syndrome and no cases of severe hypertension were reported. Thromboembolic events were infrequent and were of maximum CTCAE Grade 2.

There was no deviation from dose proportionality detectable for the pharmacokinetic characteristics. The observed high interpatient variability may reflect the range of sampling times post-drug administration (8–14 h).

Both BIBF 1120 doses demonstrated comparable efficacy; however, CTCAE Grade 3 AEs were observed at a higher frequency in the 250 mg b.i.d. dose group. This may indicate that the lower dose of BIBF 1120 (150 mg b.i.d.) may result in a more favourable safety profile when administered to patients with NSCLC and an ECOG score of 0–1. However, the patient with the PFS of 205 days was treated with the PR received 250 mg BIBF 1120 b.i.d. Thus, the recommended monotherapy dose for continuous treatment with BIBF 1120 in further studies lies in the range of 150–250 mg b.i.d. In phase I studies investigating the combination of BIBF 1120 with various chemotherapies, 200 mg BIBF 1120 b.i.d. was the MTD [14, 34, 35].

### Table 3.

<table>
<thead>
<tr>
<th>AE</th>
<th>Grades 1 and 2</th>
<th>Grades 3 and 4</th>
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<tbody>
<tr>
<td>All grades</td>
<td>Total, n (%)</td>
<td>150 mg b.i.d., n (%)</td>
</tr>
<tr>
<td>Total with AE</td>
<td>59 (80.8)</td>
<td>29 (78.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (57.5)</td>
<td>23 (62.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>35 (47.9)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31 (42.5)</td>
<td>19 (51.4)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21 (28.8)</td>
<td>11 (29.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (13.7)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>10 (13.7)</td>
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</tr>
<tr>
<td>AST increase</td>
<td>7 (9.6)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (9.6)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>6 (8.2)</td>
<td>3 (8.1)</td>
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<tr>
<td>Weight decrease</td>
<td>6 (8.2)</td>
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<tr>
<td>GGT increase</td>
<td>5 (6.8)</td>
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</tr>
<tr>
<td>Constipation</td>
<td>4 (5.5)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4 (5.5)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>4 (5.5)</td>
<td>3 (8.1)</td>
</tr>
</tbody>
</table>

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

### Table 4.

<table>
<thead>
<tr>
<th>BIBF 1120 BS</th>
<th>150 mg b.i.d.</th>
<th>250 mg b.i.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gMean</td>
<td>gCV (%)</td>
</tr>
<tr>
<td>Cpre, ss, 29 (ng/ml)</td>
<td>35</td>
<td>8.77</td>
</tr>
<tr>
<td>Cpre, ss, 29, norm (ng/ml/mg)</td>
<td>35</td>
<td>0.0558</td>
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<tr>
<td>Cpre, ss, 57 (ng/ml)</td>
<td>31</td>
<td>8.68</td>
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<tr>
<td>Cpre, ss, 57, norm (ng/ml/mg)</td>
<td>31</td>
<td>0.0579</td>
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<tr>
<td>Cpre, ss, 85 (ng/ml)</td>
<td>33</td>
<td>9.68</td>
</tr>
<tr>
<td>Cpre, ss, 85, norm (ng/ml/mg)</td>
<td>33</td>
<td>0.0645</td>
</tr>
</tbody>
</table>

Cpre, pre-dose concentration of the analyte in plasma immediately before administration of the Nth dose after N – 1 doses were administered. BS, Base; gCV, geometric coefficients of variation.
In conclusion, BIBF 1120 showed comparable efficacy data to other angiogenesis inhibitors in similar patient populations. As ECOG 2 patients progressed rapidly, the adequate selection of patients based on clinical factors such as ECOG score should be considered when identifying appropriate patient populations. With regards to safety, the incidence of hypertension, bleeding and thromboembolic events and fatigue was low and no patients suffered from hand–foot syndrome. In line with phase I data, controlled trials of BIBF 1120, as a monotherapy or in combination with chemotherapeutic agents, should be considered. Using BIBF 1120 as part of a multimodality strategy with other targeted agents may also warrant investigation.

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disclosure
Martin Reck is a member of advisory boards of Hoffmann-La Roche, AstraZeneca, Merck and Lilly and he received honoraria for lectures from Hoffmann-La Roche, AstraZeneca, Merck and Lilly.

references


