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# Phase I Open-Label Study of Continuous Treatment with BIBF 1120, a Triple Angiokinase Inhibitor, and Pemetrexed in Pretreated Non–Small Cell Lung Cancer Patients

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## Abstract

**Introduction:** BIBF 1120 (planned brand name Vargatef) is a novel, oral, triple angiokinase inhibitor targeting three receptor classes involved in blood vessel formation. The objectives of this phase I, open-label dose-escalation study were to determine the safety, tolerability, and maximum tolerated dose (MTD) of BIBF 1120 with pemetrexed in patients with recurrent advanced-stage non–small cell lung carcinoma.

**Patients and Methods:** Patients harboring a tumor of any non–small cell lung carcinoma histology, previously treated with one first-line platinum-based chemotherapy regimen, received a BIBF 1120 starting dose of 100 mg bid (days 2-21) with pemetrexed 500 mg/m$^2$ (day 1) over a 21-day cycle. Previous pemetrexed treatment was not permitted. BIBF 1120 dose was escalated until the MTD was determined.

**Results:** Twenty-six patients were treated. During treatment cycle (TC) 1, dose-limiting toxicities were experienced by one patient receiving 100 mg bid, one patient receiving 150 mg bid, one patient receiving 200 mg bid, and two patients receiving 250 mg bid BIBF 1120. Two additional dose-limiting toxicities were observed in TC 1 in an expanded patient cohort receiving 200 mg bid. Gastrointestinal disorders (84.6%), general disorders, and administration site conditions (76.9%) were the most frequent drug-related adverse events. One patient had a complete response 44 days after initiating trial medication; 50% had stable disease as the best overall response. No clinically relevant pharmacokinetic interactions between BIBF 1120 and pemetrexed were observed.

**Conclusion:** The MTD of BIBF 1120 in combination with standard-dose pemetrexed was 200 mg bid. Continuous daily treatment with BIBF 1120 in this combination was tolerable, with promising signs of efficacy. *Clin Cancer Res; 16(10); 2881–9. ©2010 AACR.*

Non–small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for approximately 85% of all cases, and is the leading cause of cancer mortality (1). Combination cytotoxic chemotherapy remains the standard first-line therapy for patients who suffer from recurrent or advanced disease. Although options exist for second- and third-line therapy, treatment offers modest benefits and efficacy seems to have reached a plateau (2–4). There is therefore a clinical need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic NSCLC.

Angiogenesis, the formation of new blood vessels from preexisting vasculature, is a fundamental process for tumor growth and metastasis (5). Tumors are able to stimulate the development of their own blood supply by disrupting the delicate balance of proangiogenic and antiangiogenic factors, which regulate and control the angiogenic process (5). Known proangiogenic regulators of angiogenesis include vascular endothelial growth factor (VEGF), platelet-derived growth factor, and fibroblast growth factor (6, 7).

The central role of the VEGF/VEGF receptor (VEGFR) pathway in angiogenesis and in tumor development makes disruption of this signaling pathway an attractive target for the therapy of NSCLC, a tumor whose growth and spread is driven by such angiogenic-dependent mechanisms.

Combining conventional cytotoxic chemotherapy with an angiogenesis inhibitor has been shown to improve first-line treatment options in NSCLC. The addition of the VEGF inhibitor bevacizumab to first-line chemotherapy showed significantly improved progression-free survival (PFS) and overall survival compared with chemotherapy alone (8, 9). Similar observations have also been seen in the second-line setting, where PFS and overall survival data favored the combination of bevacizumab and chemotherapy over chemotherapy alone (10). Further studies investigating the addition of the anti-VEGFR agent vandetanib to second-line chemotherapy have also reported improvements in PFS (11–13).

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## Translational Relevance

The majority of patients with non–small lung cancer present with advanced or unresectable disease or develop recurrent disease following initial treatment with platinum-based chemotherapy. However, although options exist for second- and third-line therapy, treatment offers modest benefits and efficacy seems to have reached a plateau. BIBF 1120 (planned brand name Vargatef) is a novel, oral, potent angiokinase inhibitor targeting three receptor classes involved in the formation of blood vessels. Due to its unique targeting profile, BIBF 1120 has the potential to effectively prevent both tumor growth and dissemination while also avoiding problems such as redundancy or resistance. In this phase I, open-label dose-escalation study, we assessed the maximum tolerated dose, safety, and tolerability of BIBF 1120 in combination with pemetrexed in patients with recurrent, advanced-stage non–small cell lung carcinoma who had received one prior platinum-based chemotherapy regimen. Results show that BIBF 1120 in combination with pemetrexed is a viable therapeutic regimen warranting further investigation.

BIBF 1120 (planned brand name Vargatef) is a novel, oral, potent triple angiokinase inhibitor targeting three receptor classes involved in the formation of blood vessels: VEGFR, platelet-derived growth factor receptor, and fibroblast growth factor receptor (14). Due to its unique targeting profile, BIBF 1120 has the potential to effectively prevent both tumor growth and dissemination while also avoiding problems such as redundancy or resistance. BIBF 1120 shows tumor growth inhibition in all preclinical animal models investigated to date across a range of tumor types (14). *In vivo* experiments in xenograph models have shown that combination therapy with BIBF 1120 and pemetrexed resulted in enhanced antitumor activity compared with the activity of either drug alone (15).

With regard to clinical experience, promising results have been obtained from phase I monotherapy studies showing that BIBF 1120 is well tolerated in patients with advanced malignancy (16, 17). Furthermore, the clinical adverse event profile of BIBF 1120 is largely nonoverlapping with that of pemetrexed. In addition, the two compounds are excreted differently, pemetrexed predominantly via the kidney and BIBF 1120 via the liver, suggesting that combination therapy could be feasible and tolerable.

In this phase I, open-label dose-escalation study, we assessed the maximum tolerated dose (MTD), safety, and tolerability of BIBF 1120 in combination with pemetrexed in patients with recurrent, advanced-stage NSCLC who had previously been treated with one prior platinum-based chemotherapy regimen.

## Objectives

The primary objective of this trial was to assess the MTD, safety, and tolerability of BIBF 1120 in combination with pemetrexed in patients with recurrent NSCLC. Secondary objectives were to characterize the pharmacokinetic (PK) profiles of BIBF 1120 and pemetrexed when used in combination and to identify any preliminary antitumor activity.

## Patients and Methods

### Study design

This was a phase I, open-label, multicenter study performed at two sites in the United States and Canada between September 2005 and May 2007. Patients received a standard dose of i.v. pemetrexed (500 mg/m$^2$) on day 1 followed by oral BIBF 1120 twice daily on day 2 through day 21. BIBF 1120 was not administered until day 2 to avoid any possible additive adverse events that could interfere with or influence the administration of pemetrexed. This is due to a partial overlap between pemetrexed and BIBF 1120 with regard to adverse events such nausea, vomiting, diarrhea, and fatigue.

Standard phase I methods were used. The starting dose of BIBF 1120 was 100 mg bid. Three patients were initially treated at each BIBF 1120 dose level. If no dose-limiting toxicity (DLT) was observed, the BIBF 1120 dose for the next cohort was escalated by a 50 mg bid increment. If one patient experienced a DLT at a particular dose, three additional patients were enrolled into that dose level to treat a minimum of six evaluable patients. If no other subjects experienced a DLT, the dose was escalated to the next level. If two or more subjects within a dose level experienced a DLT, enrollment into that cohort was stopped. The dose of BIBF 1120 was de-escalated to treat a total of six subjects at the previous dose level. The MTD was defined as the dose of BIBF 1120 that was one dose cohort below the dose at which two or more of six patients experienced a DLT during the first treatment cycle (TC). Once the MTD was identified, this cohort was then expanded to a total of 12 patients to fully evaluate this dose level, and patient enrollment into higher dose cohorts was suspended.

Patients who experienced a DLT discontinued study medication to enable recovery, but could resume treatment if all clinically relevant drug-related adverse events recovered to baseline within 2 weeks. Patients who required a BIBF 1120 dose reduction were not subsequently eligible for reescalation to a higher dose.

Patients who did not experience clinical disease progression or a DLT during the first TC were eligible for subsequent combination therapy without interruption. Patients were scheduled to receive a minimum of four and a maximum of six TCs of combination therapy. On completing a minimum of four cycles of combination therapy, patients who had experienced clinical benefit were eligible to continue on BIBF 1120 monotherapy. Patients were allocated

to escalating dose cohorts by order of their admission into the study.

**Study population**

Adult patients with a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group performance score of 0 to 2 were included in the study. Patients were required to have pathologically confirmed metastatic, unresectable, or locally advanced NSCLC of any histology and had to have relapsed during or following one prior platinum-based chemotherapy regimen. At the time of study conduct, there was no label restriction for pemetrexed treatment in patients with nonsquamous cell histology. All patients were required to have bidimensionally measurable disease by one or more techniques (computerized tomography, magnetic resonance imaging, or X-ray). Patients with gastrointestinal abnormalities that would interfere with the intake or absorption of study drug or patients with symptomatic brain metastases or brain metastases requiring therapy were excluded from the trial. Patients were also required to have adequate renal and hepatic functions. Prior treatment with an EGFR tyrosine kinase inhibitor or anti-EGFR monoclonal antibody was permitted; however, prior treatment with pemetrexed or another agent targeting the VEGF pathway was not permitted. Patients with centrally located tumors with radiologic evidence (computerized tomography or magnetic resonance imaging) of local invasion of major blood vessels were excluded. Patients with a history of hemorrhagic or thrombotic events in the past 12 months, clinically significant hemoptysis in the past 3 months, or significant cardiovascular diseases were also excluded.

This trial was carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki (1996 Version), and in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and applicable regulatory requirements. Written informed consent was obtained from each patient before their participation in the study.

**Concomitant medications**

All patients received oral dexamethasone on the day before, the day of, and the day after pemetrexed administration. Patients were supplemented with daily folic acid 1 to 2 weeks before the first pemetrexed dose and daily through the 21-day TC. Patients also received vitamin B12 1 week before therapy, which was repeated every three cycles while on therapy. Additional chemotherapy, immunotherapy, biotherapy, hormone therapy, or radiotherapy was not permitted during the study.

**Efficacy assessments**

Efficacy was a secondary end point in this study and was assessed in terms of objective tumor response according to Response Evaluation Criteria in Solid Tumors (18). Computerized tomography and magnetic resonance imaging assessments carried out at screening identified 1 to 10 target lesions, which were followed during the course of the study and assessed every 6 weeks after initiating BIBF 1120 treatment. Tumor measurements at earlier time points after the initiation of study treatment were permitted if clinically indicated as assessed by the investigator. Duration of response and time to tumor progression were also reported for each dose cohort.

**Safety and tolerability assessments**

Incidence and intensity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, laboratory safety evaluations, physical examination, vital signs, and electrocardiogram were used to assess safety. Vital signs were recorded at screening and at every subsequent visit. Electrocardiograms were done at screening and every 6 weeks thereafter.

DLTs were defined as a drug-related CTCAE grade ≥3 nonhematologic toxicity (except for glutamyl-transpeptidase increases), drug-related gastrointestinal toxicity or hypertension of CTCAE grade 3 despite optimal supportive care/intervention, drug-related uncomplicated CTCAE grade 4 neutropenia (not associated with fever) for 7 days, neutropenia of any duration associated with fever, platelet levels of <25,000/μL or CTCAE grade 3 thrombocytopaenia associated with bleeding that required transfusion, and the inability to resume BIBF 1120 dosing within 14 days of stopping due to treatment-related toxicity.

**PK sampling and data analysis**

For quantification of drug plasma concentrations of BIBF 1120, blood samples were obtained on day 2 before the first administration of BIBF 1120 and on days 8 and 15 of TC 1. During TC 2, PK samples for BIBF 1120 were obtained on day 2 (before BIBF 1120 administration and 1, 2, 3, 4, and 6 hours after administration) and on day 3 (24 hours after administration), followed by trough sampling on days 8 and 15. Due to PK reasons, BIBF 1120 was only administered as a once-daily morning dose on day 2 of TC 2. For patients receiving additional treatment courses (≥3), blood samples to determine BIBF 1120 trough levels were collected before drug administration on day 1. For quantification of pemetrexed plasma concentrations, blood samples were taken on day 1 of TC 2 (immediately after pemetrexed infusion and 1, 2, 4, 6, 24, and 48 hours after infusion).

Plasma concentrations of BIBF 1120 and pemetrexed were analyzed by a fully validated high-performance liquid chromatography-tandem mass spectrometry method. Noncompartmental analysis was conducted using WinNolin (version 4.1, Pharsight). Standard noncompartmental methods were used to calculate PK parameters.

**Statistical analyses**

The analyses in this trial were descriptive and exploratory. All patients who received BIBF 1120 were included in the safety analysis. With the dose-escalation scheme used in this trial, there was a probability of 80% that at least two patients would experience a DLT for a given dose, if

the underlying possibility of a DLT was between 45% and 50% for each patient.

## Results

### Patient population

Thirty-one patients were enrolled in this study, 26 of whom received treatment. Patient demographics and clinical characteristics are summarized in Table 1.

### Treatment received

Of the 26 patients treated, 21 completed the initial 21-day TC and were eligible to continue in the second TC and beyond. Nine patients completed four cycles of combination therapy and seven patients went on to receive BIBF 1120 monotherapy. One patient with a complete response completed the study and has remained on 100 mg bid BIBF 1120 monotherapy for more than 3 years. The most common reasons for study discontinuation were disease progression (57.7%) and DLTs (19.2%).

### Safety and tolerability

All 26 treated patients were included in the safety analysis. The MTD of BIBF 1120 when administered for 21 days in combination with standard-dose pemetrexed was determined to be 200 mg bid.

During the first TC, seven patients on study medication (26.9%) experienced a DLT: one patient receiving 100 mg bid BIBF 1120, one patient receiving 150 mg bid BIBF 1120, three patients receiving 200 mg bid BIBF 1120 (one patient in the original dose-escalation cohort and two patients in the extension phase), and two patients

**Table 1.** Patient demographics and clinical characteristics

| | 100 mg bid BIBF 1120 plus 500 mg/m$^2$ pemetrexed | 150 mg bid BIBF 1120 plus 500 mg/m$^2$ pemetrexed | 200 mg bid BIBF 1120 plus 500 mg/m$^2$ pemetrexed | 250 mg bid BIBF 1120 plus 500 mg/m$^2$ pemetrexed | Total |
|---|---|---|---|---|---|
| Patients treated | 6 (100.0) | 6 (100.0) | 12 (100.0) | 2 (100.0) | 26 (100.0) |
| Gender | | | | | |
| Male | 2 (33.3) | 4 (66.7) | 7 (58.3) | 0 | 13 (50.0) |
| Female | 4 (66.7) | 2 (33.3) | 5 (41.7) | 2 (100.0) | 13 (50.0) |
| Race | | | | | |
| White | 6 (100.0) | 6 (100.0) | 12 (100.0) | 2 (100.0) | 26 (100.0) |
| Age (y) | | | | | |
| Mean | 60.5 | 65.0 | 60.1 | 75.0 | 62.5 |
| Weight (kg) | | | | | |
| Mean | 69.7 | 81.8 | 81.0 | 72.4 | 77.9 |
| Smoking history | | | | | |
| Never smoker | 3 (50.0) | 0 | 0 | 1 (50.0) | 4 (15.4) |
| Ex-smoker | 2 (33.3) | 4 (66.7) | 6 (50.0) | 1 (50.0) | 13 (50.0) |
| Current smoker | 1 (16.7) | 2 (33.3) | 6 (50.0) | 0 | 9 (34.6) |
| Baseline ECOG | | | | | |
| 0 | 4 (66.7) | 3 (50.0) | 2 (16.7) | 1 (50.0) | 10 (38.5) |
| 1 | 2 (33.3) | 3 (50.0) | 10 (83.3) | 1 (50.0) | 16 (61.5) |
| Tumor histology | | | | | |
| Adenocarcinoma | 3 (50.0) | 1 (16.7) | 2 (16.7) | 1 (50.0) | 7 (26.9) |
| Large cell | 0 | 0 | 1 (8.3) | 0 | 1 (3.8) |
| Squamous cell | 0 | 1 (16.7) | 2 (16.7) | 0 | 3 (11.5) |
| Adenosquamous | 0 | 0 | 0 | 1 (50.0) | 1 (3.8) |
| NSCLC (not specified) | 3 (50.0) | 4 (66.7) | 7 (58.3) | 0 | 14 (53.8) |
| Clinical stage at screening | | | | | |
| IIIB | 1 (16.7) | 2 (33.3) | 1 (8.3) | 1 (50.0) | 5 (19.2) |
| IV | 5 (83.3) | 4 (66.7) | 11 (91.7) | 1 (50.0) | 21 (80.8) |
| Prior chemotherapy regimens | | | | | |
| 1 | 4 (66.7) | 5 (83.3) | 11 (91.7) | 2 (100.0) | 22 (84.6) |
| 2 | 1 (16.7) | 1 (16.7) | 1 (8.3) | 0 | 3 (11.5) |
| ≥3 | 1 (16.7) | 0 | 0 | 0 | 1 (3.8) |

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

receiving 250 mg bid BIBF 1120. These DLT events included elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) liver enzymes (3.8%); elevated AST enzymes (3.8%); elevated ALT enzymes (7.6%); gastrointestinal events including vomiting (3.8%), esophageal pain (3.8%), and nausea (3.8%); fatigue (19.2%); confusion (3.8%); and anorexia (3.8%). All DLTs were of CTCAE grade 3. A second patient in the 150 mg bid BIBF 1120 dose cohort also developed a DLT of CTCAE grade 3 fatigue in TC 1; however, this was during the follow-up period and not while receiving study drug. Most DLTs occurred during the first week of the TC.

Two additional patients experienced DLTs in TC 2 and TC 3: one patient receiving 200 mg bid BIBF 1120 experienced CTCAE grade 3 fatigue followed by elevated ALT levels during the follow-up period, whereas one patient in the 200 mg bid BIBF 1120 dose cohort developed CTCAE grade 3 diarrhea.

All patients experienced an adverse event throughout the course of the study. Gastrointestinal disorders (84.6%; consisting of mainly nausea, vomiting, abdominal pain, and diarrhea), general disorders, and administration site conditions (76.9%; predominantly rash) were the most frequently reported drug-related adverse events. As shown in Table 2, the most frequent individual drug-related adverse events reported across all dose groups were fatigue (65.4%), nausea (61.5%), anorexia (53.8%), rash (38.5%), diarrhea (34.6%), and vomiting (34.6%).

In general, adverse events were of low severity, with the majority being CTCAE grades 1 and 2; rash did not exceed a severity of CTCAE grade 2. Adverse events of CTCAE grade 3, the highest grade that occurred in the study, were reported in 12 patients (46.2%). These included gastrointestinal disorders: diarrhea, vomiting, constipation, nausea, abdominal pain, and esophageal pain. CTCAE grade 3 fatigue was reported in seven patients (26.9%).

For all treatment courses, the most common adverse event observed at the MTD was CTCAE grade 3 fatigue (4 of 12 patients), with seven patients reporting fatigue of CTCAE grade 1 to 3. Gastrointestinal adverse events were observed in 9 of 12 patients, but only two cases were of CTCAE grade 3. Fully reversible elevated liver enzymes (ALT and/or AST) were reported in three patients. Two of these events were of mild severity (CTCAE grade 1) and one patient had an ALT elevation of CTCAE grade 3. This resolved to baseline levels within 4 weeks of discontinuing study medication.

Five patients (19.2%) experienced one or more serious adverse events during the trial, all requiring hospitalization. The most frequent serious adverse event was pneumonia (two patients; 7.7%). One patient died during the posttreatment period as a result of respiratory failure attributed to progressive disease.

Hemoglobin levels decreased in four patients, the most severe case being of CTCAE grade 3. CTCAE grade 3 to 4 neutropenia was determined in two patients in each of the 100 mg bid, 150 mg bid, and 200 mg bid cohorts. As shown in Table 3, no drug-related bleeding events were observed at the MTD and above. All bleeding events were reversible and of mild to moderate intensity (CTCAE grade 1 and 2). None of these events occurred in patients with squamous cell histology. The majority of patients did not have a significant change in liver enzymes during the trial. Overall, eight patients had AST or ALT elevations, with three patients experiencing CTCAE grade 3 readings. All patients recovered from these events. One patient experienced CTCAE grade 1 hypertension.

**Table 2.** Frequency of patients with drug-related adverse events (≥10%) across all dose groups

| | All CTCAE grades, *n* (%) | CTCAE grade 3,* *n* (%) |
|---|---|---|
| Fatigue | 17 (65.4) | 6 (23.1) |
| Nausea | 16 (61.5) | 1 (3.8) |
| Anorexia | 14 (53.8) | 2 (7.7) |
| Rash | 10 (38.5) | 0 |
| Diarrhea | 9 (34.6) | 1 (3.8) |
| Vomiting | 9 (34.6) | 1 (3.8) |
| ALT increases | 7 (26.9) | 3 (11.5) |
| Abdominal pain | 6 (23.1) | 2 (7.7) |
| Dysgeusia | 6 (23.1) | 0 |
| Pruritus | 6 (23.1) | 0 |
| Insomnia | 5 (19.2) | 1 (3.8) |
| AST increases | 5 (19.2) | 0 |
| Dyspepsia | 4 (15.4) | 0 |
| Headache | 4 (15.4) | 0 |
| Constipation | 3 (11.5) | 0 |
| Stomatitis | 3 (11.5) | 0 |
| Chills | 3 (11.5) | 0 |
| Dermatitis acneiform | 3 (11.5) | 0 |

NOTE: Data presented are the highest ever reached CTCAE grade. One patient may have experienced more than one event.
*No grade 4 adverse events were observed.

## Efficacy

All 26 treated patients had measurable lesions according to Response Evaluation Criteria in Solid Tumors. Of these, one patient, who was treated with 100 mg bid BIBF 1120, showed a complete response 44 days after initiating treatment. At the time of manuscript preparation, this patient was still continuing on BIBF 1120 mg bid monotherapy (>3.5 years) and was still in complete response. Of the 26 treated patients, 13 patients (50%) had stable disease as the best overall response. Eight patients showed progressive disease as best response, three patients had missing follow-up radiology data due to early treatment termination, and one patient was classified as being nonevaluable. Median PFS for all 26 treated patients was approximately 5.4 months.

**Table 3.** Frequency of patients with bleeding events

| | Below MTD (*n* = 12) | At MTD (*n* = 12) | Above MTD (*n* = 2) | Total (*n* = 26) |
|---|---|---|---|---|
| Patients with any bleeding events* [*n* (%)] | 7 (58.3) | 3 (25.0) | 1 (50.0) | 11 (42.3) |
| CTCAE grade of most intense bleeding event [*n* (%)] | | | | |
| CTCAE grade 1 | 6 (50.0) | 2 (16.7) | 1 (50.0) | 9 (34.6) |
| CTCAE grade 2 | 1 (8.3) | 1 (8.3) | 0 (0.0) | 2 (7.7) |
| Patients with drug-related bleeding event [*n* (%)] | 4 (33.3) | 0 (0.0) | 0 (0.0) | 4 (15.4) |
| Patients with any bleeding event determined to be DLT [*n* (%)] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

*Bleeding events include the MedDRA PT of "epistaxis," "hematuria," "hemoptysis," and "rectal hemorrhage."

## Pharmacokinetics

***PK characteristics of BIBF 1120.*** The gMean drug plasma concentration-time profiles of BIBF 1120 on day 2 of TC 2 (only a single dose of BIBF 1120 was administered on that day) are shown in Fig. 1. Generally, gMean plasma concentrations of BIBF 1120 increased with the BIBF 1120 dose. For the MTD group, BIBF 1120 peak plasma concentrations were achieved mainly within 1 to 3 hours. Steady state seemed to be reached at 7 days after BIBF 1120 administration. Although a high inter- and intra-patient variability of predose plasma concentrations was observed, there was no sign of a systematic increase or decrease of BIBF 1120 plasma concentrations during continuous treatment with BIBF 1120 in combination with pemetrexed.

As shown in Table 4A, BIBF 1120 was moderately fast absorbed and maximum plasma concentrations ($C_{max}$) were reached 2 hours postdose on day 2 of TC 2 in the MTD cohort (200 mg bid). The BIBF 1120 gMean $C_{max}$ value was 50.4 ng/mL (gCV% 81.2), the gMean area under the curve $(AUC)_{0\text{-}24}$ was 308 ng h/mL, and the gMean terminal half-life ($t_{1/2}$) was approximately 12 hours. A relatively high apparent total body clearance (CL/*F*) for BIBF 1120 was determined with a gMean value of 8,180 mL/min. BIBF 1120 exhibited a high apparent volume of distribution of 8,580 liters during the terminal phase, which might indicate a high tissue distribution. However, these values for total body clearance and volume of distribution should be interpreted carefully as the absolute bioavailability (*F*) of BIBF 1120 in humans is unknown. There was no obvious deviation of dose proportionality of BIBF 1120 PK characteristics detectable in all tested dose groups in combination with pemetrexed therapy (data not shown).

One patient suffering from Gilbert's syndrome did not show deviating BIBF 1120 PK characteristics compared with the rest of the 200 mg bid BIBF 1120 dose cohort.

***PK characteristics of pemetrexed.*** As shown in Fig. 2, pemetrexed exhibited at least triexponential kinetics with a first disposition phase within 1 hour after i.v. infusion, a second disposition phase over the next 1 to 4 hours, and a third disposition phase during the 4 to 6 hours after the end of infusion. The gMean pemetrexed concentration 24 hours after administration was 0.26 μg/mL.

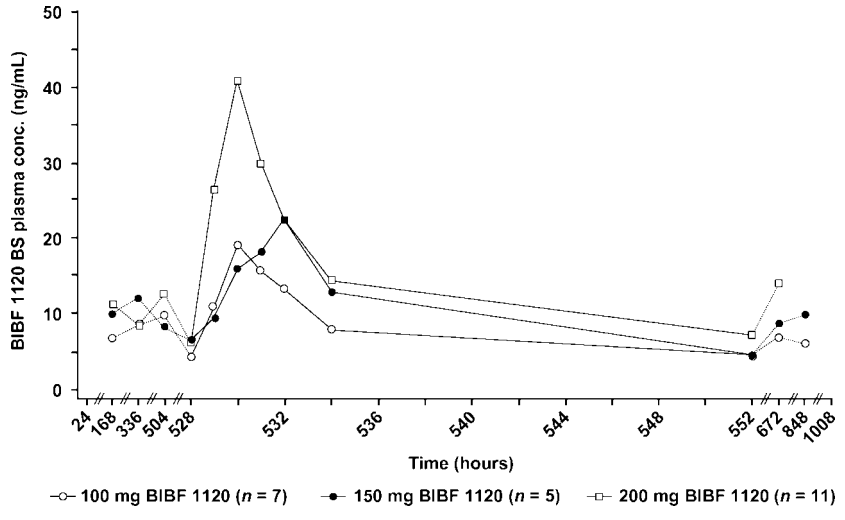


**Fig. 1.** gMean drug plasma concentration-time profiles of BIBF 1120 after multiple oral administrations of 100 mg, 150 mg, and 200 mg bid BIBF 1120 for TCs 1 to 3, with only a single dose of BIBF 1120 administered on day 2 of TC 2.

As shown in Table 4B, at the MTD, the gMean $C_{max}$ was 98.0 μg/mL (gCV% 21.8). The gMean exposure ($AUC_{0-24}$) was 200 μg h/mL on day 1 of TC 2. The median $t_{max}$ values for pemetrexed were approximately 0.3 hour (range, 0.02-0.5 hour). The gMean terminal half-life ($t_{1/2}$) was 3.7 hours. The gMean total CL was 4.8 L/h, the volume of distribution during the terminal phase ($V_z$) was 25.6 liters, and the volume of distribution at steady state ($V_{ss}$) was 15.4 liters.

## Discussion

This phase I, open-label dose-escalation trial was done to determine the MTD of BIBF 1120 in combination with standard-dose pemetrexed in patients with recurrent, advanced-stage NSCLC who had previously been treated with one prior platinum-based chemotherapy regimen. Results show that 200 mg bid BIBF 1120 in combination with standard-dose pemetrexed is the recommended dose for continuous daily treatment for patients with advanced or metastatic NSCLC. With regard to DLTs, CTCAE grade 3 fatigue was the most frequently observed in this study. At the MTD, 4 of the 12 patients treated experienced CTCAE grade 3 fatigue across all courses of treatment, with a total of seven patients reporting fatigue of CTCAE grade 1 to 3. Three patients had DLTs related to fatigue, whereas four patients discontinued due to fatigue. The toxicity profile of standard-dose pemetrexed when used as a single agent includes neutropenia, thrombocytopenia, nausea, fatigue, diarrhea, rash, and anorexia (19). Thus far, gastrointestinal adverse events and reversible liver enzyme elevations are the predominant adverse events associated with BIBF 1120 treatment, as reported in the phase I monotherapy data (16, 17). This current phase I trial investigating the combination of BIBF 1120 with pemetrexed revealed that the overall observed adverse event profile was consistent with the safety profiles observed with BIBF 1120 and pemetrexed monotherapy (16, 17). Specifically, there was no increase in hematologic toxicity observed when BIBF 1120 and pemetrexed were combined.

BIBF 1120 also revealed a similar adverse event profile with respect to fatigue, nausea, and diarrhea as compared with other VEGFR tyrosine kinase inhibitors (20). In contrast to other agents of its class, no hand-foot syndrome and only a low frequency of hypertension were observed across all dose groups in this trial (20). Due to the small sample size of 26 patients treated with BIBF 1120, it is difficult to conclude whether this low frequency is a result by chance. However, this observation is in line with the safety data from other phase I and phase II trials of BIBF 1120 (16, 17, 21, 22).

In this study, patients with squamous cell cancer histology were enrolled. At the time of study conduct, there was no label restriction with regard to patients with squamous cell histology receiving pemetrexed treatment. Previous studies investigating other VEGF or VEGFR inhibitors such as bevacizumab or sorafenib in combination with paclitaxel and carboplatin in first-line patients with NSCLC have shown a higher risk of bleeding events and a higher mortality for this group of patients (8, 23, 24). None of the patients with squamous cell histology enrolled into this study showed any bleeding event irrespective of relatedness. However, three patients with squamous and one patient with mixed squamous cell histology are too few a number of patients to conclude whether the combination of BIBF 1120 with pemetrexed has a low risk of inducing bleeding complications in this subgroup of patients.

With regard to efficacy, a stable disease rate of 50% was observed, and the median PFS for all patients was 5.4 months. This compares favorably to a PFS of approximately 3 months observed in a phase III trial investigating the efficacy and toxicity of pemetrexed versus docetaxel in patients with NSCLC previously treated with chemotherapy (19).

Observed PK parameters for pemetrexed in this study are comparable with those in the current literature and were not affected by continuous treatment (except on the day of pemetrexed infusion) with BIBF 1120 (25–27). This indicates that there was no clinically relevant influence of

**Table 4.** BIBF 1120 and pemetrexed PK parameters

**A**

| BIBF 1120 day 2, TC 2 | 200 mg bid ($n$ = 8) | |
|---|---|---|
| | gMean | gCV (%) |
| $AUC_{0-24}$ (ng h/mL) | 308* | 43.9* |
| $C_{max}$ (ng/mL) | 50.4 | 81.2 |
| $t_{max}$† (h) | 2.00 | 1.00-23.8 |
| $t_{1/2}$ (h) | 12.1* | 43.4* |
| CL/$F$ (mL/min) | 8,180* | 33.5* |
| $V_z$/$F$ (L) | 8,580* | 56.0* |

**B**

| Pemetrexed day 1, TC 2 (MTD) | TC 2 ($n$ = 8) | |
|---|---|---|
| | gMean | gCV (%) |
| $AUC_{0-24}$ (μg h/mL) | 200‡ | 17.1‡ |
| $C_{max}$ (μg/mL) | 98.0 | 21.8 |
| $t_{max}$† (h) | 0.275 | 0.0160-0.500 |
| $t_{1/2}$ (h) | 3.71‡ | 31.6‡ |
| CL (L/h) | 4.78‡ | 24.2‡ |
| $V_z$ (liter) | 25.6‡ | 31.1‡ |
| $V_{ss}$ (liter) | 15.4‡ | 18.9‡ |

NOTE: A, comparison of BIBF 1120 PK parameters for the 200 mg bid BIBF 1120 dose group (MTD). B, PK parameters (gMean and gCV%) of pemetrexed after administration of 500 mg/m$^2$ pemetrexed over 8 to 15 min on day 1 (TC 2) after continuous treatment of 200 mg bid BIBF 1120 (days 2-21 of TC 1).

*$n$ = 6.

†Median and range.

‡$n$ = 7.

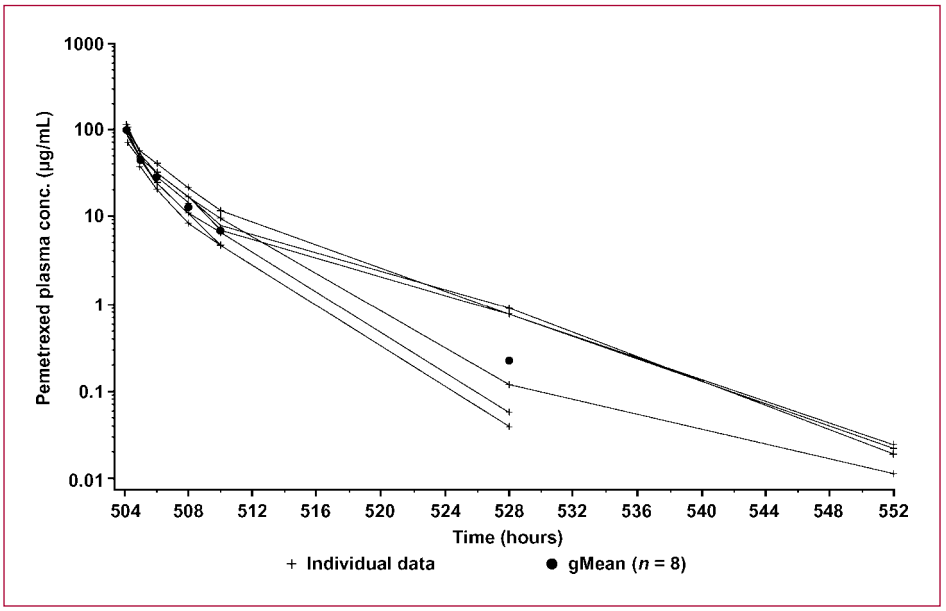


**Fig. 2.** Individual and gMean drug plasma concentration-time profiles of pemetrexed after a single dose of 500 mg/m$^2$ i.v. to MTD patients on day 1 of TC 2 (semi-log scale).

BIBF 1120 treatment on the PK parameters of pemetrexed in this study, showing that this combination is viable for future trials. Furthermore, the PK profile observed for BIBF 1120 when combined with pemetrexed was similar to those observed for BIBF 1120 in the phase I monotherapy studies (16, 17, 28). Based on these PK data, it is possible to consider administering BIBF 1120 on the same day as pemetrexed infusion. *In vitro* studies with human liver microsomes have shown that drug-drug interaction between pemetrexed and BIBF 1120 due to CYP450 enzyme involvement is unlikely to occur.[6] Moreover, pemetrexed is solely excreted unchanged via the kidney as compared with BIBF 1120, which is solely excreted via the liver. Based on a terminal half-life of 7 to 19 hours for BIBF 1120, dosing was not initiated until day 2 to reduce or avoid any potential additive adverse events. This is due to a partial overlap between pemetrexed and BIBF 1120 with regard to adverse events such nausea, vomiting, diarrhea, and fatigue.

Results from phase I combination therapy trials are consistent with those of phase I monotherapy trials and indicate that dose reduction of BIBF 1120 is not required when used in combination with other cancer medications. Specifically, a phase I study investigating the combination of BIBF 1120 together with carboplatin and paclitaxel in patients with NSCLC showed that this combination was well tolerated and associated with promising efficacy (29). In this study, the MTD of BIBF 1120 was 200 mg BID in combination with standard carboplatin and paclitaxel. Importantly, the adverse event profile observed in patients receiving these regimens is consistent with that seen with those for BIBF 1120 monotherapy and the respective chemotherapy agent. Phase I combination studies therefore show that BIBF 1120 can be administered together with other anticancer agents for the treatment of various solid malignancies (29–31).

## Conclusions

In conclusion, 200 mg bid is the MTD of BIBF 1120 when used in combination with standard-dose pemetrexed (500 mg/m$^2$) and is considered to be the recommended dose for continuous daily treatment for patients with advanced or metastatic NSCLC. Continuous daily treatment with BIBF 1120 in combination with pemetrexed was tolerable. Promising signs of efficacy were observed in this trial and there were no clinically relevant PK interactions between BIBF 1120 and pemetrexed. Therefore, BIBF 1120 in combination with pemetrexed is a viable therapeutic regimen warranting future investigation.

### Disclosure of Potential Conflicts of Interest

P.M. Ellis: advisory boards for Boehringer Ingelheim, Eli Lilly Canada, Hoffman La Roche Canada, Pfizer Canada; honoraria for talks, Eli Lilly and Hoffman La Roche; N. Hanna, commercial research support from Eli Lilly. The other authors declare no conflicts.

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[6] Unpublished data.

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