# An Open-label Dose-escalation Study of BIBF 1120 in Patients with Relapsed or Refractory Multiple Myeloma

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**Abstract.** *Background: To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of BIBF 1120, a triple angiokinase inhibitor administered once-daily in patients with advanced multiple myeloma. Patients and Methods: This Phase I study included 17 patients. Planned dose escalations of BIBF 1120 were 100, 200, 250 and 300 mg. Safety and pharmacokinetic (PK) assessments were performed. Results: Two DLTs (200 and 250 mg) occurred due to increased gamma-glutamyltransferase levels (CTC grade 3). The 250 mg dose was well tolerated; no dose escalation beyond 250 mg was made. The most common adverse events included diarrhoea, nausea and vomiting. No detectable deviation from dose linear PKs was observed. Regarding tumour control, two patients had stable disease for ≥4 months. Conclusion: BIBF 1120 was safe and well tolerated up to 250 mg/day. The MTD was not reached.*

Although new treatment modalities for multiple myeloma (MM), such as bortezomib, thalidomide and its derivative lenalidomide can induce antitumour responses in MM, there is a requirement for the development of novel therapeutic approaches. Vascular endothelial growth factor (VEGF) is involved in tumour-related neovasculature and has a key role in angiogenesis (1). Increased microvessel density in the bone marrow of patients with MM has been correlated with disease progression and poor prognosis (2-4). In addition to its angiogenic activities, VEGF may also have a direct role in the pathophysiology of MM and has been shown to stimulate both MM and plasma cell leuakemia cell proliferation and the malignant cell migration pathway (5-9).

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BIBF 1120 (Vargatef™ ; trade name not FDA approved) is a triple angiokinase inhibitor that simultaneously acts on three receptors that are involved in the formation of blood vessels (10). This agent is an indolinone derivative and a potent inhibitor of VEGF receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR). The triple inhibitory action of BIBF 1120 is thought to account for its high antitumour potential (11). BIBF 1120 has been shown to be efficacious in established tumour xenografts in mice (12), and has shown significant tumour growth inhibition in all preclinical models (10). At the time when this study was planned, preclinical data indicated that the target exposure required for biological activity may be achieved by once-daily oral dosing in humans with a maximum tolerated dose (MTD) of 250 mg/day (13). The preclinical safety profile is considered favourable with respect to the intended oncological indication, with the clinical side-effects in patients primarily pertaining to the gastrointestinal tract and reversible increases in liver enzymes. The principle objective of this study was to determine the MTD of BIBF 1120 in terms of drug-related adverse events (AEs) in patients with relapsed or refractory MM. The safety, efficacy and pharmacokinetics (PKs) of BIBF 1120 were also evaluated.

## Patients and Methods

*Study design and population.* This open-label, non-comparative Phase I dose-escalation study was designed to determine the MTD of BIBF 1120. The study was conducted in compliance with the Declaration of Helsinki (October 1996 amendment), in accordance with the International Conference on Harmonization Good Clinical Practice, and had been approved by the relevant Independent Ethics Committees. Freely given, written informed consent was obtained from all patients. Patients (>18 years) with a confirmed diagnosis of MM, who did not respond to or relapsed after either anthracyclines and pulsed glucocorticoids or high-dose therapy and who were not eligible for transplant modalities were included. Bortezomib, thalidomide and lenalidomide were not available at the time of study design. Additional inclusion criteria included a life expectancy >6 months and an Eastern Cooperative Oncology Group (ECOG) performance score of <2. Patients with a history of relevant surgical procedures during the 4

weeks prior to treatment with the trial drug, or with active ulcers, fractures or injuries with incomplete healing were excluded, as were patients with an absolute neutrophil count <1000/MM$^3$, a platelet count <30,000/MM$^3$, conjugated bilirubin >2 mg/dl (>34 μmol/l, SI unit equivalent) and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 times the upper limit of normal.

*Removal of patients from therapy/discontinuation of study medication*. Patients were taken off the study if they withdrew consent, were no longer able to participate due to AEs, surgery or concomitant diagnoses, had violated their eligibility criteria, had missed ≥7 doses of treatment due to non-compliance, or had any dose-limiting/other drug-related toxicity that had not been resolved after 14 days of treatment interruption. Treatment with BIBF 1120 was discontinued if a patient developed a DLT, autoimmune phenomena of Common Terminology Criteria (CTC) grade ≥2 or other intolerable symptoms.

*Dosing of study medication and concomitant medication*. During all courses (28-day period), BIBF 1120 was administered in a once-daily oral dose. The planned dose levels were 100, 200, 250 and 300 mg/day. Initially, three patients were entered at each level. Patients were only entered at a higher dose level after ensuring that all three patients treated with BIBF 1120 at an ongoing dose level had completed the initial course of continuous BIBF 1120 dosing. When one patient had experienced a DLT at an ongoing dose level, this cohort was increased to a total of six patients. If no other patient experienced a DLT, the dose was escalated to the next level. If ≥2 patients experienced a DLT, three additional patients were treated at the lower-tier dose unless six patients had already been treated at that level. The MTD was defined as the highest dose at which no more than one patient out of six experienced a DLT. Once the MTD had been determined, patient enrolment at higher levels was to be suspended. Repeated-course patients were to receive BIBF 1120 at the MTD and further patients were to be included in this cohort until 12 patients had been treated at the MTD.

If no DLTs had been observed during treatment, a subsequent course was commenced after a ≥7-day washout period. If a DLT had not recovered to baseline within 14 days, the patient was excluded from further treatment courses. Patients who exhibited any drug-related AEs and fully recovered after a break from medication of ≥1 week were eligible for further treatment. The selection of each patient's subsequent dose schedule/level was determined as follows: patients who had objective responses (minimal response [MR], partial response [PR] or complete response [CR]) received a repeated course of the same dose of BIBF 1120; patients without objective response (no change [NC] or progressive disease [PD]) after the first course received additional dexamethasone treatment. If dexamethasone inclusion induced an objective response, patients were eligible for a further course of BIBF 1120 plus dexamethasone. In the case of no change after the second cycle, dose-escalation of BIBF 1120 was stipulated by the protocol in the subsequent cycle. Patients with no change after BIBF 1120 and an additional course of BIBF 1120 plus dexamethasone were escalated to the next dose tier.

Patients on BIBF 1120 and dexamethasone and/or patients who had CD4 counts <200/μl received standard *Pneumocystis carinii* prophylaxis. Additionally, symptomatic treatment of side-effects or tumour-associated symptoms, including radiation, were allowed, as was treatment with bisphosphonates.

*Outcome measurements*. The primary endpoint was to determine the MTD of BIBF 1120 in terms of drug-related AEs. Only DLTs that occurred during the initial treatment period of 28 days and during the 1-week washout were used to determine the MTD. DLTs were defined as non-haematological drug-related toxicities of CTC grade 3 or greater (except for alopecia and untreated vomiting) and/or haematological toxicity CTC grade 4. Neutropenia <500/μl had to persist for ≥4 days to be deemed a DLT.

Safety and tolerability of BIBF 1120 were assessed in terms of changes in laboratory parameters (including haematological status and immunophenotyping parameters), vital signs, electrocardiogram (ECG), patient performance, and the incidence and severity of AEs and toxicities according to CTC. Patients were monitored for AEs during and after treatment courses. Weight and ECOG scores were assessed at baseline, weeks 2 and 4, and at treatment end. Vital signs were recorded at screening and at every subsequent visit.

Efficacy of the drug was evaluated through tumour assessment after each course. Tumours were assessed according to the European Group for Blood and Marrow Transplantation (EBMT) (14) criteria for evaluating disease response and progression in patients, and by the number of patients with CR, PR, MR, NC and PD. The number of patients with objective responses (CR, PR and MR) was stratified by dosage cohort and separated according to those receiving and those who did not receive dexamethasone.

*Pharmacokinetic sampling*. Blood samples (5 ml) were collected prior to first dosage of BIBF 1120, as well as 2 and 24 hours after initial dosing on day 1 and immediately before drug administration on days 7, 14 and 21. A PK profile was undertaken on day 28, and at 0.5, 1, 2, 3, 4, 8 and 24 hours after the last drug administration. A change to the original protocol was introduced during this study as a result of the time to reach maximum plasma concentration during the dosing interval τ (24 h) at steady state ($t_{max,ss}$) appearing later than anticipated. This amendment resulted in the 100 mg/day and 200 mg/day cohorts having blood samples taken at 0.5 hours post-drug administration, whilst in the 250 mg/day cohort, samples were taken every 3 hours. Plasma concentrations of BIBF 1120 were analyzed by a fully validated high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method (Boehringer Ingelheim, method on file).

*Statistical methods*. All safety, efficacy and PK measurements were summarized descriptively. Safety and tolerability results were reported for each dose level separately and in terms of overall means, if appropriate. Time to progression was defined as time elapsed since first administration of the trial drug. Survival time was defined as time from first administration of BIBF 1120 to death. Non-compartmental analysis of PK parameters was conducted using WinNonlin® (Version 4.1, Pharsight, Mountainview, CA, USA).

## Results

*Patient demographics and disposition*. A total of 17 patients (9 male, 8 female) with relapsed or refractory MM were enrolled in this study. Patient accrual was terminated after 17 patients were treated due to lack of objective antimyeloma responses to BIBF 1120 at doses that were efficacious in solid tumours (13). All patients were Caucasian and the median age was 61 years. Previous therapies included chemotherapy (n=17), radiotherapy (n=12) and immunotherapy (n=7). Three patients had prior tumour-related surgery. At diagnosis, one patient had stage I and 16 patients had stage III MM according to the Durie/Salmon

classification. All patients had osteolytic sites, had received prior treatment with anthracyclines and pulsed glucocorticoids or high-dose therapy and were dexamethasone resistant. Three patients received 100 mg/day and seven received 200 mg/day and 250 mg/day BIBF 1120.

*Dose escalation*. At a dose of 250 mg/day, the MTD was not reached and the study was discontinued due to the lack of encouraging signs of BIBF 1120-induced antimyeloma activity. In the initial course, three patients were enrolled in the 100 mg/day tier and seven patients each were in the 200 and 250 mg/day dosage tiers, respectively. Nine (52.9%) patients had a second course, with three, five and one patient receiving 100, 200 and 250 mg/day, respectively; seven participants completed Course 2. Eight patients entered a third course, with all participants completing treatment. One patient was treated in ≥3 courses. Only two DLTs occurred, which were due to increased gamma-glutamyltransferase (GGT) levels of CTC grade 3, one each in the 200 and 250 mg dosage tiers.

*Safety*. Six patients discontinued their treatment prematurely due to AEs. Reasons for discontinuation included progressive disease (one each in 100, 200 and 250 mg/day cohorts), elevations of ALT CTC grade 2, of AST CTC grade 1 and GGT CTC grade 3 (250 mg/day n=1), CTC grade 3 GGT (250 mg/day n=1) and diarrhea and vomiting (250 mg/day n=1). During all courses, all 17 patients experienced ≥1 AE. The most frequently reported were diarrhea (82.4%), disease progression (70.6%), nausea (58.8%), fatigue (58.8%), vomiting (47.1%) and upper abdominal pain (41.2%). The majority of these AEs were CTC grade 1 or 2. Drug-related AEs were seen in two, seven and seven patients in the 100, 200 and 250 mg/day treatment groups, respectively. The most common were gastrointestinal disorders (diarrhea [70.6%] and nausea [58.8%]), predominantly in the 200 and 250 mg/day tiers (two patients had CTC grade 3). Increases of ALT, AST and GGT of CTC grade ≤2 were observed in three patients (all in the 250 mg/day cohort).

Serious AEs were reported by 12 patients (70.6%). Progression of MM occurred in all 12 patients, and there was one report each of hyperviscosity, pyrexia and infection (all in the 200 mg/day tier). Three deaths were reported, two as a result of disease progression and one due to pneumonia; none were considered to be related to treatment with BIBF 1120. Overall, 15 out of 17 patients experienced progressive disease at some point during the study.

Abnormal laboratory values corresponding to CTC grade 3 were mostly concerned with the lymphocyte and $CD4^+$ T-cell count. During all courses, three incidences of $CD4^+$ T-cell count CTC grade 4 were observed; however, these events were not considered to be DLTs in patients with advanced myeloma. No significant changes to vital signs, such as blood pressure and pulse rate, or to weight, were observed during any course of the study.

*Efficacy*. During the initial course, no objective response was observed and two patients had stable disease, whereas 14 patients developed progressive disease and one patient was not evaluable. Of the nine patients who entered repeated treatment courses, seven also received dexamethasone. Objective responses were observed in five patients, all of whom were receiving dexamethasone. No change was observed in three patients (with one of these taking dexamethasone) and one patient receiving dexamethasone developed tumour progression.

Considering time to tumour progression, 15 out of 17 patients developed tumour progression within 35 days and received additional dexamethasone treatment. The remaining two patients did not receive further dexamethasone. One patient had no tumour progression until day 119, having concluded five cycles of treatment, whereas the other patient had a time to tumour progression of 315 days, after seven treatment cycles. After the initial treatment phase, four patients had an ECOG score of 0; at the end of courses 2 and 3, similar numbers of patients had scores of 0, 1 and 2. At no point did any patient have an ECOG score >2.

*Pharmacokinetics*. The geometric mean (gMean) plasma concentration versus time curves of BIBF 1120 over each of the three doses at day 28 are displayed in Figure 1. Quantifiable plasma concentrations of BIBF 1120 were seen at the lowest dose of 100 mg/day. A comparison of the gMean predose plasma BIBF 1120 concentrations from the initial treatment course demonstrated that there was a positive correlation between the gMean value and the dose. Steady state was reached by 6 days after once-daily dosing but may have been reached earlier. On day 28, gMean plasma concentrations increased with dose, although the curves of the 200 mg/day and 250 mg/day groups overlapped.

Geometric mean PK parameters at day 28 (–1) (steady state) obtained after multiple daily administration of the respective doses of BIBF 1120 are displayed in Table I. For each dose cohort, maximum plasma concentrations ($C_{max,ss}$) were observed 2–2.33 hours post-dose. There was no obvious deviation from dose proportional behaviour when dose-normalized $C_{max,ss}$ and area under curve $(AUC)_{\tau,ss}$ values were compared. Moderate-to-high variability was observed for all PK parameters.

## Discussion

This study demonstrated that BIBF 1120 was safe and well-tolerated at doses up to 250 mg once-daily in patients with advanced MM. The MTD in this study was not defined, since patient accrual was terminated prematurely due to lack of antimyeloma activity at daily doses that were considered to be efficacious in patients with solid tumours at that time (13). BIBF 1120 at comparable doses had been shown to be pharmacodynamically and clinically active in solid tumours,

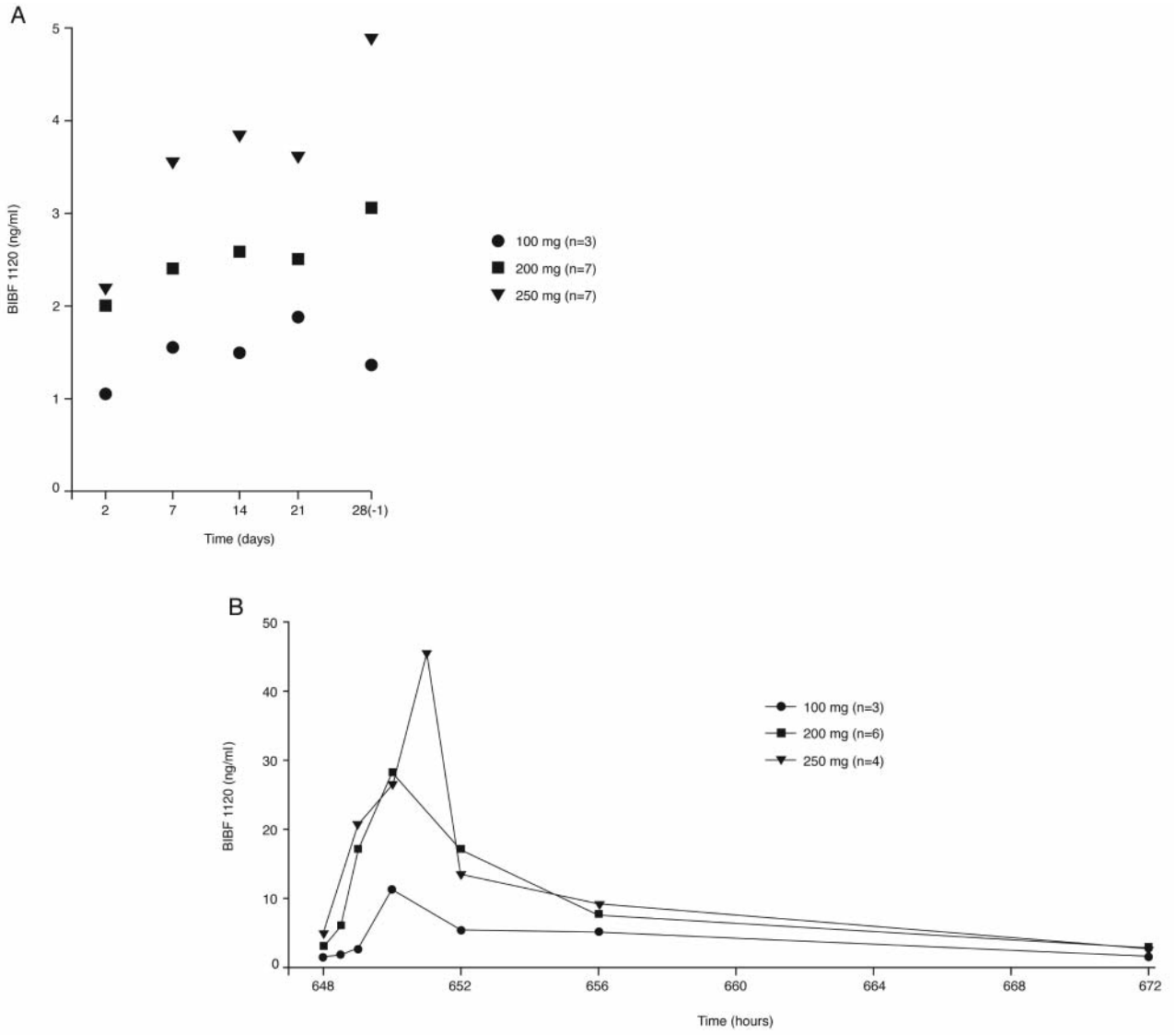


Figure 1. *A, Geometric mean BIBF 1120 predose concentrations on days 2 (24 h), 7 (144 h), 14 (312 h), 21 (480 h) and 28 (648 h) after multiple rising oral administration of 100 mg, 200 mg and 250 mg BIBF 1120 once-daily over course 1 (linear scale). B. Geometric mean BIBF 1120 plasma concentration–time profiles on day 28 after multiple rising oral administration of 100 mg, 200 mg and 250 mg BIBF 1120 once-daily over course 1 (linear scale)*

with dynamic contrast-enhanced magnetic resonance imaging data indicating that BIBF 1120 does have significant antivascular/antiangiogenic effect (13, 15). In this study, short-lived partial remissions were observed in five out of seven MM patients, who received additional dexamethasone treatment in repeated courses after progression with BIBF 1120 monotherapy in the first course.

However, in the meantime, 400 mg/day was defined as the MTD in patients with advanced solid malignancy. Following promising efficacy and good tolerability in patients with advanced, relapsed non-small cell lung cancer, a Phase III study in this malignancy is ongoing with twice-daily dosing.

The majority of AEs in this study were of CTC grade 1 and 2, with the most frequent being gastrointestinal disorders (nausea, vomiting, diarrhoea), a typical class effect of small-molecule VEGFR2 inhibitors (16-18). The two DLTs that occurred may suggest that adverse liver symptoms occur at higher doses of BIBF 1120, although both incidences proved to be reversible.

BIBF 1120 was seen to be bioavailable after once-daily dosing and was moderately quickly absorbed (median $t_{max,ss}$ values of about 2 hours). BIBF 1120 showed dose proportionality behaviour and had a high volume of distribution and total body clearance. The observed high volume of distribution may suggest a high tissue distribution of BIBF 1120,

Table I. *Geometric mean (and gCV%) pharmacokinetic parameters of BIBF 1120 BS at day 28 (–1) after multiple oral administration of 100 mg/day, 200 mg/day and 250 mg/day BIBF 1120 once-daily in course 1.*

| | | Dose *qd* | | |
|---|---|---|---|---|
| | | 100 mg/day | 200 mg/day | 250 mg/day |
| Variable | N | 3 | 6 | 4 |
| $t_{max,\ ss}$* | h | 2.33 (2.20–8.0) | 2.17 (1.17–4.08) | 2.08 (1.05–4.08) |
| $C_{max,ss}$ | ng/ml | 11.4 (55.4%) | 32.7 (86.87%) | 28.3 (231%) |
| $C_{max,ss,norm}$** | (ng/ml)/mg | 0.11 (55.4%) | 0.16 (86.7%) | 0.11 (231%) |
| $AUC_{\tau,ss}$ | ng. h/ml | 99.8 (16.1%) | 212 (63.7%) | 231 (175%) |
| $AUC_{\tau,ss,\ norm}$** | (ng. h/ml)/mg | 0.10 (16.1%) | 1.06 (63.7%) | 0.093 (175%) |
| $C_{pre,ss}$ | ng/ml | 1.38 (28.7%) | 3.09 (51.1%) | 4.61 (42.6%) |
| $t_{½,ss}$ | h | 8.89 (21.4%) | 11.2 (27.6%) | 7.93 (17.1%) |
| $CL/F_{,ss}$ | ml/min | 16700 (16.1%) | 15800 (63.7%) | 18000 (175%) |
| $V_z/F_{,ss}$ | l | 12800 (35.0%) | 15300 (94.9%) | 12400 (146%) |

*Median and range; **dose-normalized parameters; BS=free base; *qd*=once-daily dosing; $t_{max,\ ss}$=time to reach maximum plasma concentration during the dosing interval τ at steady state; $C_{max,ss}$=maximum plasma concentration during the dosing interval τ at steady state; $AUC_{\tau,ss}$=area under the plasma concentration–time curve during the dosing interval τ (24 h) at steady state; $C_{pre,ss}$=plasma concentration at the time point immediately before dosing at steady state; $t_{½,ss}$=terminal half-life at steady state; $CL/F_{,ss}$=apparent plasma clearance at steady state; $V_z/F_{,ss}$=apparent volume of distribution during the terminal phase at steady state.

although these data should be interpreted with caution as the absolute bioavailability in humans is unknown. The observed terminal half-life supports a once- or twice-daily dosing regimen.

A critical role for VEGF in MM has been demonstrated in both *in vitro* and *in vivo* studies. Preclinical data obtained with the indolinone BIBF 1000, a similar compound to BIBF 1120, that simultaneously inhibits VEGF, FGF and PDGF receptors, provided the rationale for clinical evaluation of this class of targeted inhibitors in MM (9); the administration of BIBF 1000 in combination with bortezomib and/or dexamethasone has demonstrated enhanced antimyeloma activity in cytogenetically defined MM cell lines (19). BIBF 1000 was shown to induce apoptosis in t(4;14)-positive cell lines, in $CD138^+$ marrow cells from patients with t(4;14) myeloma and in cells carrying the translocation t(14;16), and had additive proapoptotic properties when given in combination with dexamethasone (9). Another VEGFR inhibitor, pazopanib, was shown to inhibit *in vitro* MM cell growth, survival and migration. In addition, in a mouse xenograft model of human MM, pazopanib induced inhibition of *in vivo* tumour growth, which was associated with increased MM cell apoptosis, decreased angiogenesis and prolonged survival (20). However, the role for VEGFR inhibitors has not yet been confirmed in clinical trials; several studies targeting angiogenesis *via* VEGFR inhibition as potential treatment for patients with MM have reported a lack of antitumour activity (17, 18).

In one phase II study (18), patients with advanced MM received a biweekly dose of the VEGFR2 inhibitor, SU5416. Despite displaying a good safety profile, with few CTC grade 3 or 4 AEs, no objective responses to SU5416 were observed. Similarly, the selective VEGFR and EGFR tyrosine kinase inhibitor, vandetanib, was well tolerated in patients with relapsed MM, but no objective response or other clinical benefits were observed despite adequate drug levels. One possible explanation in human myeloma trials may relate to the different expression levels of VEGF and VEGFRs at different stages of the disease. By preselecting patient populations who have earlier or later disease stages, a different outcome may be observed with VEGFR inhibitors.

Due to the limited antitumour activity of VEGF inhibitors as monotherapies that has been reported to date, further studies exploring the combination of BIBF 1120 with other agents is warranted. Data from this investigation provide a rationale for exploring the potential benefit of BIBF 1120 in cytogenetically defined subgroups.

In conclusion, BIBF 1120 was seen to be safe and well tolerated at once-daily doses up to 250 mg. There was no detectable deviation from dose-linear behaviour of BIBF 1120. BIBF 1120 was not seen to be efficacious as a single agent in the treatment of MM in this small unselected patient subset. However, further investigations with BIBF 1120 in combination with other drugs and in cytogenetically defined MM patients are warranted.

## Conflict of Interest Statement

Martin Kropff has nothing to disclose; Joachim Kienast received research support from Boehringer Ingelheim for the purpose of the study; Guido Bisping has obtained financial research grants from Boehringer Ingelheim for a related project; Wolfgang E. Berdel has obtained financial research grants from Boehringer Ingelheim for a

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