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ORIGINAL REPORT

Randomized Phase II Placebo-Controlled Trial of Maintenance Therapy Using the Oral Triple Angiokinase Inhibitor BIBF 1120 After Chemotherapy for Relapsed Ovarian Cancer

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ABSTRACT

Purpose
Inhibiting angiogenesis is one of the most promising avenues for new therapies for ovarian cancer. We investigated the efficacy and safety of a novel agent, BIBF 1120, a triple angiokinase inhibitor, after chemotherapy for relapsed disease.

Patients and Methods
We conducted a randomized, double-blind, controlled phase II trial in 83 patients who had just completed chemotherapy for relapsed ovarian cancer, with evidence of response, but at high risk of further early recurrence. The patients were randomly assigned to receive maintenance therapy using BIBF 1120 250 mg or placebo, twice per day, continuously for 36 weeks. End points were progression-free survival (PFS), toxicity, and overall survival.

Results
Thirty-six–week PFS rates were 16.3% and 5.0% in the BIBF 1120 and placebo groups, respectively (hazard ratio, 0.65; 95% CI, 0.42 to 1.02; $P = .06$). Four patients continued on BIBF 1120, including two patients for another year or more. The proportion of patients with any grade 3 or 4 adverse events was similar between the groups (34.9% for BIBF 1120 *v* 27.5% for placebo; $P = .49$; mostly grade 3). However, more patients on BIBF 1120 experienced diarrhea, nausea, or vomiting (mainly grade 1 or 2 and no grade 4). There was a higher rate of grade 3 or 4 hepatotoxicity in patients on BIBF 1120 (51.2%) compared with patients on placebo (7.5%; $P < .001$), but this was rarely of clinical significance, and patients continued with the trial treatment. A single-level dose reduction to 150 mg was made in 15 patients, all on active drug.

Conclusion
BIBF 1120 is well tolerated and associated with a potential improvement in PFS. The observed treatment effect is sufficient to justify further study within a large phase III trial.

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INTRODUCTION

Advanced ovarian cancer often responds well to systemic chemotherapy, but relapse occurs in most women, and the disease is ultimately fatal. Carboplatin and paclitaxel are most commonly used as initial therapy, and many women receive several courses of treatment with these and other drugs at intervals to prolong survival. The length of the gap between treatments is variable but tends to reduce with time. This period provides an opportunity to investigate new disease-modifying drugs. Tumor growth and progression are partly dependent on angiogenesis, and there is good evidence to suggest that angiogenesis plays an important role in ovarian cancer.[1,2] Many drugs have now been developed to inhibit the angiogenic pathway. These include inhibitors of both the family of circulating vascular endothelial growth factors (VEGF) and the VEGF receptor (VEGFR) tyrosine kinases.[3]

BIBF 1120, a 6-methoxycarbonyl-substituted indolinone, is a potent inhibitor of VEGFR, as well as platelet-derived growth factor receptor and fibroblast growth factor receptor, two important additional signaling pathways involved in angiogenesis.[4] Preclinical studies have shown that BIBF 1120 inhibits vessel integrity and tumor growth.[5] Phase I studies have defined a safe dose with optimal pharmacokinetics using a twice-daily oral dosing schedule. Reversible disturbance of liver enzymes is the dose-limiting

toxicity. Other adverse effects are relatively mild, and hypertension is rare.[5] Dynamic contrast-enhanced magnetic resonance imaging has demonstrated reductions in vascular perfusion after single, twice-daily, and continuous dosing, and tumor responses were seen in renal and colorectal cancers.[6]

These data provide a clear basis for further investigation in other tumor types, but taking investigation of this drug forward rapidly and efficiently is challenging. Should antiangiogenic drugs, such as BIBF 1120, be given concurrently with chemotherapy, after chemotherapy, or both? Should they be used as part of first-line therapy or to maintain patients with stable disease later in the course of their disease? Designing trials to answer all of these questions is complex. A rapid screening approach is needed to identify whether a molecular-targeted drug, such as BIBF 1120, is likely to have an effect in ovarian cancer before launching large, expensive, and time-consuming studies to answer all of these questions.

In this study, we aimed to identify whether an activity signal for BIBF 1120 is seen that would justify larger phase III studies. We selected a population of women with recurrent ovarian cancer who had responded to chemotherapy but were at high risk of further early recurrence based on the interval before their previous chemotherapy ($<$ 12 months). Standard practice is to observe these women after treatment and consider re-treatment at next progression.

PATIENTS AND METHODS

Design

We conducted a multicenter, randomized, placebo-controlled phase II trial to examine the efficacy and safety of BIBF 1120. A novel design was used based on evaluating the maintenance of response in patients who had just completed and responded to treatment for recurrent disease. Multicenter ethics approvals and written informed consent from all patients were obtained. The trial was conducted across the National Cancer Research Network, managed jointly by the Cancer Research United Kingdom and University College London Cancer Trials Centre and Boehringer Ingelheim, the legal sponsor.

Patients

Between April 2006 and March 2008, 84 patients age $\geq$ 18 years were recruited from 11 centers in the United Kingdom. Patients were included if they had histologically confirmed advanced ovarian or fallopian tube carcinoma or primary peritoneal cancer of serous type with recurrent disease; a recent response to a second or further line of chemotherapy (response was defined as either a confirmed decline in CA-125 of at least 50% from the pretreatment value or a partial/complete response according to Response Evaluation Criteria in Solid Tumors [RECIST]); treatment-free interval of $\leq$ 12 months immediately preceding the chemotherapy to which the patient had just responded; full recovery from all therapy-related toxicities (except alopecia and peripheral neuropathy); life expectancy of $\geq$ 3 months; Eastern Cooperative Oncology Group performance status of less than 2; and adequate hepatic, renal, and hematologic function. The first administration of BIBF 1120 was planned to be between 4 and 8 weeks after the completion of the prior therapy that had led to a response.

Patients were excluded if they had serious illness or surgery within the previous 4 weeks with incomplete wound healing, uncontrolled hypertension, unstable angina, history of myocardial infarction within past 9 months, congestive heart failure ($>$ New York Heart Association class II), hemorrhagic or thrombotic event in the past 12 months, full-dose anticoagulation, GI disorders that would inhibit absorption of the study drug, or CNS disease.

Patients were randomly assigned to receive BIBF 1120 or matching placebo, using a telephone interactive voice response system based at Boehringer Ingelheim. Trial staff and patients were unaware of the allocation. Minimization was used with the following stratification factors: complete or partial response to the most recent chemotherapy; length of treatment-free interval before entering the trial ($<$ *v* $\geq$ 6 months); and number of lines of previous chemotherapy (two *v* three or four lines).

Trial Treatments

All patients were scheduled to receive 250 mg twice daily of either BIBF 1120 or placebo. The dose could be reduced to 150 mg twice daily and subsequently to 100 mg twice daily in the event of unacceptable drug-related toxicity (including nausea, vomiting, diarrhea, hypertension, and ALT/AST elevation). Study drug was taken continuously (28-day cycles) for nine cycles (36 weeks) or until disease progression or patient withdrawal (eg, because of toxicity). Patients who were alive and progression free after nine cycles were allowed to continue BIBF 1120 after discussion with their clinician (treatment allocation unblinded).

Assessments

Baseline assessments with tumor imaging (magnetic resonance imaging or computed tomography scan) were performed not greater than 4 weeks before starting treatment, and serum CA-125 measurement was performed within 7 days of starting drug. All patients had a physical examination, blood and urine tests, and evaluation of clinical adverse events (AEs) at the following time points: the first day of trial treatment, every 28 days, at the end of the study (when patients finished treatment or withdrew from the trial), and 1 month after the end-of-study visit. The same assessments were also performed after 15 days of a cycle if patients suffered a trial treatment–related AE in the previous cycle. Tumor assessments were performed using serum CA-125 every 4 weeks and imaging at least once every 12 weeks, or as clinically indicated. Progression based on CA-125 was determined according to revised criteria in Vergote et al.[7]

Statistical Considerations

The primary end point was progression-free survival (PFS) at 36 weeks, which was measured from the date of random assignment until disease progression determined by RECIST criteria, CA-125 (defined based on progressive serial elevations), or other clinical evidence of progression. Imaging assessments took precedence. Secondary end points were overall survival (OS), treatment compliance, and AEs classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The maximum grade for each AE was obtained for each patient. Data on progression and survival were collected up to June 2010, when the database was closed for analysis. Sample size was determined by a Fleming's single-stage design, assuming a 36-week PFS rate of $\geq$ 70% with BIBF 1120 and that the true rate should not be less than 50%, based on published data.[8,9] Thirty-six weeks was chosen to allow enough time for a treatment effect to emerge and to observe a sufficient number of PFS events. The target sample size was at least 40 patients in the BIBF 1120 group (80% power and 5% one-sided test of significance), with an equal number in the placebo group.

RESULTS

Figure 1 (CONSORT diagram) shows the number of patients in the trial and the reasons for stopping study treatment early. All of the analyses presented here are based on 83 patients (BIBF 1120, n = 43; placebo, n = 40), after excluding one patient who had been inadvertently given BIBF 1120 instead of placebo. One of the key eligibility criteria was having a treatment-free interval of $\leq$ 12 months between the start of the most recent chemotherapy and the end of the treatment before that. However, it was later realized that this interval exceeded 13 months in 11 patients, six in the BIBF 1120 group (range, 13 to 47 months) and five in the placebo group (range, 13 to 60 months). Baseline characteristics were well balanced (Table 1).

Compliance

All 83 patients started BIBF 1120 or placebo, and the median time on treatment was 2.8 months in each group (Fig 2). However, after

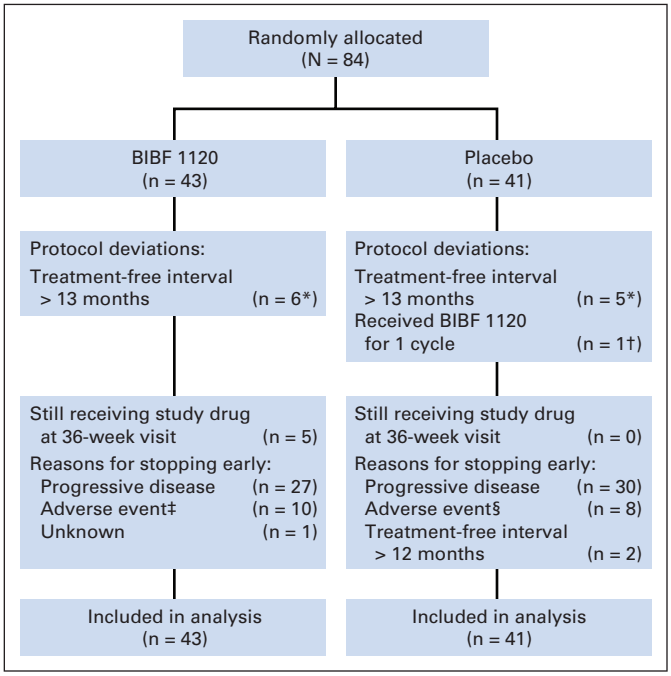

Fig 1. CONSORT diagram. (*) The eligibility criterion was not more than 12 months, but we allowed up to 13 months here. (†) Excluded from the analysis. (‡) Of the 10 patients with adverse events in the BIBF 1120 group, five patients had GI events (eg, any patients with diarrhea, vomiting, or abdominal pain, including four with diarrhea, two with vomiting, two with abdominal pain, and one with hepatotoxicity), one patient had rectal bleeding, two patients had ascites; one patient had behavioral disorders, and one patient had hepatotoxicity. (§) Median time on drug was 1.5 months (range, 0.03 to 3.0 months). Of the eight patients with adverse events in the placebo group, three patients had GI events, one patient had night sweats, one patient had ascites, one patient had hepatotoxicity, one patient had vaginal bleeding, and one patient had lung/neuroendocrine tumor. Median time on drug was 2.6 months (range, 0.03 to 3.8 months).

about 12 weeks, more patients on placebo had stopped treatment, which was largely a result of progressive disease. Dose reductions to 150 mg twice daily were made in 15 patients on BIBF 1120 and no patients on placebo; 11 reductions were a result of hepatotoxicity (one after 21 days of starting drug, nine after 35 to 63 days, and one after 175 days), two reductions were a result of diarrhea, and two reductions were a result of both diarrhea and nausea. There were no further reductions to 100 mg. The reasons for stopping treatment are shown in Figure 1. At the end of 36 weeks, five patients remained on study drug and were allow to continue treatment if they had not experienced progression and were tolerating treatment; all five patients were in the BIBF 1120 group. One patient did not wish to continue treatment, and the other four patients continued for another 12, 19, 74, and 139 weeks.

Efficacy

The number of PFS events was 41 in the BIBF 1120 group and 40 in the placebo group (58% of patients who experienced progression did so based on CA-125, 31% based on RECIST, and 11% based on both). At the time of the PFS and OS analysis, only two women had not experienced progression. The Kaplan-Meier curves for PFS are shown in Figure 3. The PFS rate at 36 weeks was 16.3% (95% CI, 5.2% to 27.3%) in the BIBF group and 5.0% (95% CI, 0% to 11.8%) in the placebo group; both rates were markedly lower than those assumed for the sample size calculation (70% and 50%, respectively; see

Table 1. Baseline Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	BIBF 1120 (n = 43) No. of Patients	%	Placebo (n = 40) No. of Patients	%
Age, years				
Median	60		63	
Range	27-76		40-75	
Body weight, kg				
Median	70		69	
Range	36-112		46-94	
Diastolic blood pressure, mmHg				
Median	74		77	
Range	50-102		57-106	
Systolic blood pressure, mmHg				
Median	122		129	
Range	82-174		100-160	
CA-125, U/mL				
Median	36		23	
Range	5-1,510		7-518	
Time between start of chemotherapy before trial and random assignment, weeks				
Median	21.2		23.8	
Range	12.8-32.0		15.1-91.7	
ECOG score				
0	27	63	30	75
1	15	35	9	22
Missing data	1	2	1	3
Response to most recent chemotherapy				
Complete	5	12	4	10
Partial	38	88	36	90
Treatment line				
Second line	21	49	21	52
Third line or greater	22	51	19	48
Length of treatment-free interval, months				
< 6	17	40	17	42
≥ 6	26	60	23	58
Cancer type				
Epithelial ovarian cancer	40	93	38	95
Primary peritoneal cancer	3	7	2	5
Histology				
Serous	34	79	35	88
Mucinous	1	2	0	0
Endometrioid	0	0	1	2
Clear cell	0	0	2	5
Other	8	19	1	2
Missing data	0	0	1	2
FIGO stage at diagnosis				
I	2	5	2	5
II	1	2	4	10
III	32	74	25	63
III/IV	1	2	0	0
IV	7	16	9	22
Missing data	1	2	0	0
Differentiation grade				
Well	4	9	1	3
Moderate	9	21	8	20
Poorly	22	51	23	57
Unspecified	8	19	8	20

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

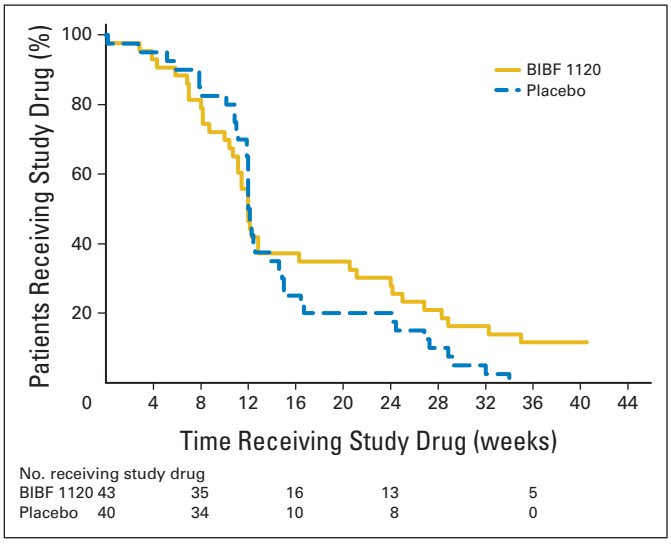

Fig 2. Compliance: time on study drug.

Patients and Methods). The PFS hazard ratio (HR) was 0.65 (95% CI, 0.41 to 1.02; $P = .06$). In an exploratory analysis, we also analyzed the data after excluding 11 patients who had a prior treatment-free interval of more than 13 months (PFS HR, 0.56; 95% CI, 0.34 to 0.92; $P = .02$).

There were 30 and 32 deaths in the BIBF 1120 and placebo groups, respectively; almost all of the deaths were a result of ovarian cancer. Figure 3 shows the Kaplan-Meier curves. The HR for OS was 0.84 (95% CI, 0.51 to 1.39; $P = .51$). After excluding 11 patients with a treatment-free interval of more than 13 months, the HR was 0.75 (95% CI, 0.44 to 1.27; $P = .28$).

AEs

The proportion of patients with any grade 3 or 4 AEs was similar between the two trial arms (34.9% for BIBF1120 *v* 27.5% for placebo; $P = .49$; Table 2). There was a higher proportion of patients with diarrhea, vomiting, or nausea in the BIBF 1120 group, but these events were largely grade 1 or 2 (Table 3); there were no grade 4 events. No GI perforations occurred. The only differences in grade 3 or 4 toxicities between the groups concerned the liver function tests (raised AST, ALT, and γ-glutamyltransferase) in 51.2% of patients on BIBF 1120 *v* 7.5% of patients on placebo. Only two patients, one in each group, stopped treatment as a result of these events. Ten and eight patients in the BIBF 1120 and placebo groups, respectively, stopped BIBF 1120 or placebo early because of AEs (Fig 1). A serious AE was reported in 32.6% of patients on BIBF 1120 and 25.0% of patients on placebo. There were no fatal AEs, but one life-threatening serious AE occurred in the placebo group. Four patients had a reported suspected unexpected serious adverse reaction, all in the BIBF 1120 arm. The reasons were high temperature and elevated liver enzymes (n = 2), although the latter outcome is expected for BIBF 1120; deep vein thrombosis (n = 1); and confusion and altered behavior (including paranoia) in a patient who also had a chest infection and diarrhea (n = 1). Despite being reported as suspected unexpected serious adverse reactions, they were unlikely to be causally related to BIBF 1120 (except hepatotoxicity).

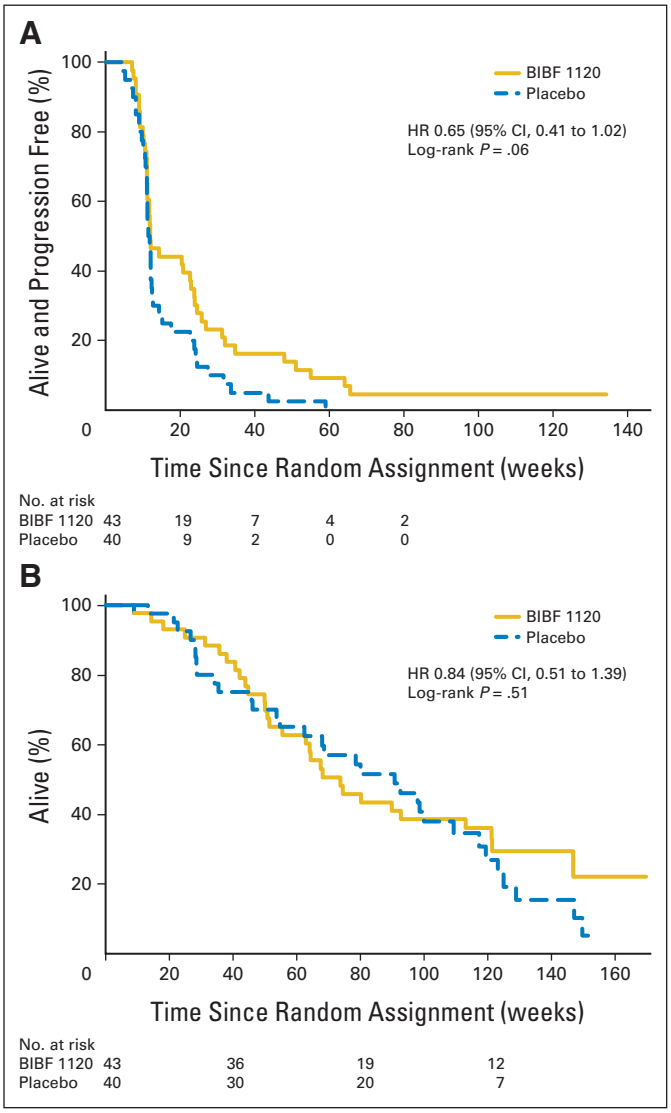

Fig 3. (A) Progression-free survival and (B) overall survival. HR, hazard ratio.

DISCUSSION

Our randomized study was designed with two aims. First, we wanted to determine whether BIBF 1120 has sufficient activity in ovarian cancer to justify conducting a larger randomized trial. Second, we wanted to develop a system in which new molecular-targeted drugs for ovarian cancer could undergo a rapid initial screening evaluation, before being taken forward into larger, longer, and more costly randomized trials. The time to progression after relapse treatment is variable and depends on factors such as the magnitude of response, the number of lines of chemotherapy, and the prior treatment-free interval. The trial had a novel design for new agents in ovarian cancer: BIBF 1120 was not given to treat recurrent disease but to prolong the progression-free interval (ie, maintenance of the response). It was evaluated after the completion of chemotherapy for relapsed ovarian cancer. Our hypothesis was that the efficacy of BIBF 1120 as maintenance treatment would be detectable in a small

Table 2. Grade 3 or 4 Adverse Events (CTCAE version 3.0)

Adverse Event	BIBF 1120 (n = 43) No. of Patients	%	Placebo (n = 40) No. of Patients	%	*P* (Fisher's exact test)
Physical adverse events					
Abdominal pain	4	9.3	3	7.5	
Diarrhea	4	9.3	1	2.5	
Nausea	1	2.3	0	0	
Vomiting	2	4.6	1	2.5	
Fatigue	2	4.6	0	0	
Anorexia	1	2.3	0	0	
Constipation	3	7.0	4	10.0	
Hypertension (or exacerbation of)	2	4.6	0	0	
Ascites	3	7.0	4	10.0	
Other	5*	11.6	5†	12.5	
Any of the above (each patient counted once)	15	34.9	11	27.5	.49
Blood measurements‡					
Anemia (low hemoglobin)	0	0	0	0	
Neutropenia (low neutrophil count)§	1	2.3	0	0	
Thrombocytopenia (low platelet count)§	1	2.3	1	2.5	
Leucopenia (low WBC count)	0	0	0	0	
Raised creatinine	0	0	0	0	
Low glucose	0	0	0	0	
Raised potassium	0	0	0	0	
Low potassium	0	0	1	2.5	
Raised sodium	0	0	0	0	
Low sodium	3	7.0	2	5.0	
Raised uric acid	0	0	1	2.5	
Raised bilirubin	0	0	0	0	
Raised AST	6	14.0	1	2.5	
Raised ALT	16	37.2	0	0	
Raised ALP	0	0	1	2.5	
Raised GGT	19	44.2	1	2.5	
Any of the liver function tests (each patient counted once)	22‖	51.2	3	7.5	< .001

NOTE. All events were grade 3, except where indicated.

Abbreviations: ALP, alkaline phosphatase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, γ-glutamyltransferase.

*Of the five patients, one patient had pleuritic pain and dyspnea; one had bowel obstruction (grade 4); two had deep vein thrombosis; and one had behavioral disorders.

†Of the five patients, one had back/shoulder pain; one had tinnitus, insomnia, and grade 4 depression; one had pancytopenia and pulmonary embolism; one had neuroendocrine and lung tumors; and one had bowel obstruction.

‡Grade 4 blood measurements included low sodium (n = 1), AST (n = 1), ALT (n = 1), and GGT (n = 2) on BIBF 1120 and raised uric acid (n = 1) on placebo.

§The neutropenia and thrombocytopenia events all occurred ≥ 30 days after BIBF 1120 or placebo was stopped.

‖Four patients had grade 4 events.

Table 3. GI or Fatigue Adverse Events, All Grades, According to CTCAE Version 3.0 (based on the maximum grade for each patient in each category)

Adverse Event and CTCAE Grade, at Any Time*	BIBF 1120 (n = 43) No. of Patients	%	Placebo (n = 40) No. of Patients	%	*P* (Fisher's exact test)†
Abdominal pain					.22
1	19	44.2	11	27.5	
2	6	14.0	3	7.5	
3	2	4.6	3	7.5	
Diarrhea					< .001
1	19	44.2	12	30.0	
2	11	25.6	2	5.0	
3	4	9.3	1	2.5	
Nausea					< .001
1	25	58.1	12	30.0	
2	7	16.3	2	5.0	
3	1	2.3	0	0	
Vomiting					< .001
1	20	46.5	5	12.5	
2	5	11.6	3	7.5	
3	2	4.6	1	2.5	
Fatigue					.74
1	9	20.9	10	25.0	
2	5	11.6	5	12.5	
3	2	4.6	0	0	
Any of the above					.03
1	16	37.2	20	50.0	
2	18	41.9	9	22.5	
3	8	18.6	4	10.0	

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

*Each patient is counted once in each category.

†Including grade 0.

number of patients because of the high rate of early events expected in this patient population.

We overestimated the PFS rate at 36 weeks, by assuming it would be 50%.[8,9] It should be noted that this value includes the time during preceding chemotherapy. The PFS calculation in our trial is taken from entry after chemotherapy. In addition, 52% of patients entered onto the study after a third or greater line of therapy. Only approximately 10% of patients were in complete remission, and in approximately 40% of patients, the treatment-free interval was ≤ 6 months. At 36 weeks, the PFS was only 5.0% in the placebo group. Thus, the study was not able to reach its assumption that the 36-week PFS would be 70% with BIBF 1120. However, a direct comparison of PFS between the trial groups produced an HR of 0.65 ($P = .06$), suggesting that BIBF 1120 has activity in this group of patients that merits further investigation. At completion of the trial (36 weeks), patients still on treatment were reconsented to continue study drug if they had not experienced progression. All patients in the placebo arm had experienced progression, but five patients on BIBF 1120 were still on treatment. Four patients decided to continue treatment; two patients continued for more than a year, and one patient is still on treatment, suggesting that, in some patients, prolonged maintenance may have significant therapeutic benefit.

BIBF 1120 is a triple angiokinase inhibitor that is well tolerated.[5] Conducting a placebo-controlled randomized trial in patients with advanced ovarian cancer is important because many of the inhibitors of VEGFR tyrosine kinase have been shown to have multiple toxicities in addition to the well-known AE of hypertension. However, unlike other VEGFR inhibitors, hypertension is unusual with BIBF 1120, whether used alone or in combination with chemotherapy,[5,6,10-12] and we observed only two patients with grade 3 hypertension. Overall toxicity (all grades) was similar in the two groups (34.9% for BIBF 1120 and 27.5% for placebo), but diarrhea, nausea, vomiting, and abdominal pains were more common with BIBF 1120, although

most were mild. Grade 3 diarrhea occurred in 9.3% of patients on BIBF 1120 and 2.5% of patients on placebo. Abnormal liver function tests were found in 51.2% of patients on BIBF1120 and 7.5% of patients on placebo ($P < .001$). However, these were rarely clinically significant; a pause in treatment and a dose reduction were made in 11 patients; only one patient stopped taking BIBF 1120 as a result of liver toxicity. Four other patients stopped treatment as a result of GI events. All other grade 3 or 4 toxicities occurred at a frequency of less than 5%, other than abdominal pain, which was more common with placebo than BIBF 1120 (7.5% *v* 4.6%, respectively), perhaps reflecting better disease control with BIBF 1120.

Most of the data on the action of antiangiogenic agents in ovarian cancer come from studies with bevacizumab, a monoclonal antibody that targets circulating VEGF. Tumor responses to single-agent therapy have been encouraging,[13,14] and the recent demonstration of a prolongation in PFS after first-line therapy combining bevacizumab with chemotherapy and as maintenance provides further support for a key role of antiangiogenic agents for treating ovarian cancer.[15,16] Several VEGFR tyrosine kinase inhibitors have been studied in ovarian cancer. In addition to the presence of VEGFR on blood vessel cells, VEGFR-2 has been found on ovarian cancer cells,[17] and this may increase the spectrum of activity of VEGFR tyrosine kinase inhibitors in ovarian cancer. A clinical benefit rate of 30% (response or nonprogression, or nonprogression of CA-125 for > 16 weeks) was found using cediranib, an inhibitor of VEGFR-1, -2, and -3 and c-kit, in a single-arm phase II trial.[18] Hypertension, diarrhea, and fatigue were the most common significant AEs. Cediranib is now being examined in a randomized trial in combination with platinum-based chemotherapy and as maintenance therapy in platinum-sensitive ovarian cancer in first relapse (International Collaborative Ovarian Neoplasm 6 study). Friedlander et al[19] conducted a phase II trial with pazopanib, a drug that inhibits VEGFR, platelet-derived growth factor, and c-kit. A CA-125 response (decrease of ≥ 50% from baseline) was seen in 31% of patients. In this trial, fatigue, diarrhea, vomiting, and disturbance in liver function tests were the most common AEs. Hypertension was relatively uncommon. Pazopanib is now being compared to placebo as maintenance treatment after first-line therapy with carboplatin and paclitaxel in the Arbeitsgemeinschaft Gynaekologische Onkologie studiengruppe/GlaxoSmithKline trial OVAR-16. To our knowledge, the trial with BIBF 1120 is the first randomized study of a triple angiokinase inhibitor to be reported; it provides guidance on assessing the attribution of reported AEs that are not clearly drug related (eg, hypertension) and gives an indication of the behavior of the tumor in a heterogeneous population.

Where feasible, randomized phase II trials allow a better assessment than single-arm studies.[20] Furthermore, our trial design can be used to evaluate other novel molecular-targeted agents in ovarian cancer. The randomized, placebo-controlled design in a population normally observed after completion of relapse therapy allows rapid identification of potential activity of novel compounds and allows comparisons of toxicity to be made. This design is now being used in other studies to identify active agents in ovarian cancer, such as a randomized phase II trial of the PARP inhibitor olaparib in high-grade serous cancer after relapse chemotherapy. BIBF 1120 is a well-tolerated drug that has activity in recurrent ovarian cancer, delaying time to progression. It has been shown to be safe when used in comparison with carboplatin and paclitaxel.[10] The drug is now given at a dose of 200 mg twice daily because this dose is associated with less hepatotoxicity, and it is now being evaluated in a randomized phase III trial of first-line treatment, given in combination with chemotherapy and for up 120 weeks as maintenance (Arbeitsgemeinschaft Gynaekologische Onkologie studiengruppe/Boehringer Ingelheim trial OVAR-12).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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