THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

A phase II study of BIBF1120 (Nintedanib) for patients with metastatic HER2-negative inflammatory breast cancer (IBC)
2014-0464

Core Protocol Information

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Full Title:	A phase II study of BIBF1120 (Nintedanib) for patients with metastatic HER2-negative inflammatory breast cancer (IBC)
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Abstract

Objectives:

1. Primary Objectives: To determine the clinical benefit rate (complete response [CR], partial response [PR] or stable disease [SD] rate) of BIBF 1120 (Nintedanib) in patients with HER2-negative, metastatic inflammatory breast cancer.
2. Secondary Objectives: To analyse the safety measures of BIBF1120 in terms of type, frequency and severity of adverse event according to CTCAE v4.0 in patients with metastatic IBC.
3. Exploratory Biomarkers:
   3.1 Pharmacodynamic analysis of BIBF-1120: to evaluate the changes in the levels of pVEGF-R2, pPDGF-Rß, and pFGF-R1 in tumor tissues at pretreatment and 8 weeks post treatment, and to determine the correlates with clinical outcomes.
   3.2 Determine the effects of BIBF 1120 on the presence of CTC and CTCs with epithelial and/or EMT gene expression in peripheral blood.
   3.3. Explore the utilization of the ViSion Reporting System to accurately measure tumor response to BIBF1120.

Rationale: (Be as concise as possible)

Inflammatory breast carcinoma (IBC) is one of the most aggressive forms of primary breast carcinoma that accounts for 1-6% of all invasive breast tumors in the United States and Western Europe. IBC is distinguished from other types of breast cancer by clinical, pathologic and molecular features and is classified by the American Joint Committee on Cancer (AJCC) as a separate clinic pathological entity (T4d). Unfortunately, there is no current standard treatment for those patients with HER2-negative disease that recur after the multidisciplinary management. Vascular lymphatic processes include

angiogenesis, lymphangiogenesis, and vasculogenesis have more prominent roles in IBC than in non-IBC. Treatment strategies that target angiogenic pathways have shown effective results in IBC. Several clinical studies have demonstrated the role of antiangiogenesis treatment in patients with IBC.

The rationale for measuring CTCs is due to the number of CTC in metastatic BC has been shown to be a prognostic indicator for treatment response, progression free survival, and overall survival. The presence of circulating tumor cells (CTCs), detected using CellSearch, in women with metastatic breast cancer (MBC) is predictive of early recurrence and poor survival. However, there is discrepancy in a study with this technique. Thus, in a prospective study conducted in our institution we isolated epithelial and non-epithelial cells from patients with MBC and characterized their epithelial differentiation, transcript levels of transcription factors known to induce EMT (EMT-TF), and stem cell features to better understand circulating tumor cell seeding.

BIBF 1120 is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells, which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signalling by FGF-receptors has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted. Preclinical models show that BIBF 1120 may have a direct anti-tumour effect on those malignant cells which overexpress PDGFR and/or FGFR.

Clinical trials revealed BIBF 1120 is generally well tolerated with mild to moderate adverse effects, and has anti-tumor efficacy; the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. The maximum tolerated dose for combination therapy of BIBF 1120 and other anti-cancer drugs (such as docetaxel, paclitaxel, pemetrexed, carboplatin, 5-FU, oxaliplatin) was determined to be 200 mg twice daily. BIBF 1120 is non-mutagenic, even at high doses.

The purpose of the study is to collect data and define the efficacy and safety of BIBF1120 in patients with HER-2 negative metastatic IBC. Antiangiogenic treatment with the orally available triple angiokinase inhibitor BIBF 1120 with inhibition of VEGFR, PDGFR and FGFR offers the chance to control both locally recurrent and distant metastatic disease on an outpatient basis.

Eligibility: (List All Criteria)

Inclusion:

1) Patients are 18 years of age or older

2) Patients are female or male.

3) Have histological confirmation of breast carcinoma with a clinical diagnosis of IBC based on presence of inflammatory changes in the involved breast, including diffuse erythema and edema (peau d'orange), with or without an underlying palpable mass involving the majority of the skin of the breast. Pathological evidence of dermal lymphatic invasion should be noted but is not required at diagnosis.

4) Have confirmed distant metastasis with or without local recurrence.

5) Have negative HER2 expression by IHC (defined as 0 or1+), or FISH. If HER2 is 2+, negative HER2 expression must be confirmed by FISH.

6) Patients may undergo an optional biopsy of the metastatic disease at baseline and after 2 cycles of BIBF-1120.

7) Estimated life expectancy of at least 3 months

8) Have ECOG performance status score 0-2

9) Have received at least one any prior treatment for local recurrence or metastatic disease and have relapsed.

10) Signed and dated written informed consent prior to admission to the study

11) If Patients have been treated with anti-VEGF agents, such as Bevacizumab, last dose must be >/= 4 weeks.

12) Have tissues from a biopsy, or have up to 20 unstained slides available from archived metastatic tissue block for biomarker evaluation

13) Patients are able to swallow and retain oral medication

Exclusion:

1) Patients have an active infection and require IV or oral antibiotics.

2) Patients have impaired cardiac function or clinically significant cardiac diseases, including any of the following: a) History or presence of serious uncontrolled ventricular arrhythmias or presence of atrial fibrillation; b) Clinically significant resting bradycardia (< 50 beats per minute); c) LVEF assessed by 2-D echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) < 45%; d). pericardial effusion

3) Any of the following within 6 months prior to study entry: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF) > NYHA II, Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE),

4) Uncontrolled hypertension defined by an SBP>150 and/or a DBP>100 mm Hg with or without anti-hypertensive medication

5) History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug as determined by the investigator.

6) Patients have a concurrent disease or condition that would make them inappropriate for study participation, or any serious medical disorder that would interfere with patients' safety as determined by the investigator.

7) Patients with only locally or regionally confined disease without evidence of metastatic disease

8) Prior treatment with BIBF 1120 or any other VEGFR inhibitor within 4 weeks

9) Known hypersensitivity to the trial drugs , to their excipients or to contrast media

10) Chemotherapy, hormonal therapy, radiotherapy (except for brain and extremities) or immunotherapy or therapy with monoclonal antibodies or small tyrosine kinase inhibitors within the past 4 weeks prior to treatment with the trial drug

11) Persistence of toxicity from previous chemo and/or radiotherapy > grade 2.

12) Active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy will be allowed if administered as stable dose for at least one month before randomisation).

13) Radiographic evidence of cavitary or necrotic tumors

14) Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels

15) Treatment with other investigational drugs or treatment in another clinical trial within the past 4 weeks before start of therapy or concomitantly with the trial

16) Therapeutic anticoagulation(except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325mg per day

17) Major injuries within the past 10 days prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period

18) History of clinically significant haemorrhagic or thromboembolic event in the past 6 months

19) Known inherited predisposition to bleeding or thrombosis

20) Proteinuria CTCAE grade 2 or greater

21) Creatinine >/= 1.5 x ULN or GFR < 45 ml/min

22) Hepatic function: total bilirubin outside of normal limits; ALT or AST >1.5 x ULN in pts without liver metastasis. For Pts with liver metastasis: total bilirubin outside of normal limits, ALT or AST >2.5 x ULN

23) Coagulation parameters: International normalised ratio (INR) > 2, prothrombin time (PT) and partial thromboplastin time (PTT) > 50% of deviation of institutional ULN

24) Absolute neutrophil count (ANC) < 1500/ml, platelets < 100000/ml, Haemoglobin < 9.0 g/dl

25) Other malignancies within the past 5 years other than basal cell skin cancer or carcinoma in situ of the cervix

26) Known history of active or chronic hepatitis C and/or B infection

27) Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study.

28) Patients who are sexually active and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females) during the trial and for at least three months after end of active therapy (Contraception in patients with preserved reproductive capacity, patients will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years.)

29) Patients with child bearing potential must have a negative pregnancy test (urine or serum) prior to study treatment

30) Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule

31) Active alcohol or drug abuse

32) Significant weight loss (> 10% of BW) within past 6 months prior to inclusion into the trial

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Phase I or Phase II study targeting cancer that is very unusual in pediatrics (e.g., prostate, lung, breast, chronic lymphocytic leukemia, etc.)

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Breast

Treatment Agents/Devices/Interventions:

BIBF 1120 nintedanib

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

Initial dose is BIBF 1120 200 mg twice daily orally. The capsules of the defined dose should be swallowed unchewed with 8 ounces of water (240ml). If taken twice daily the dose interval should be of around 12 hours at the same times every day, usually in the morning and the evening within 30 minutes after food intake. Each cycle/course will be 28 days.

Study Calender

Evaluation and Treatment	Screening (D -21 to -1)	Day 1 Pre dose	C2	C3	C4	C5	C6 and every 2 cycles there-after	C7 and every 2 cycles thereafter	Discontinuation of study drug [6]	30 Ds Post (+/- 10)	Q 3 Mos up to 1 Year
Eligibility Screening, Consent, Registration	X										
Medical History (prior therapies and procedures for breast cancer)	X										
Physical Examinations, Vital Signs as standard of care[11]	X	X [1]	X	X	X	X	X[9]	X	X		
ECOG Performance Status[11]	X	X [1]	X	X	X	X	X[9]	X	X		
Hematologic, Biochemical and UA Profiles [8]	X	X[1]	X	X	X	X	X[9]	X	X		
Serum/Urine pregnancy test, if applicable (D-14 to -1)	X										
Radiological Evaluation (CT-chest, abdomen, US, bone scan and x-ray, as clinically indicated for standard of care.) [7]	X			X		X		X	X		
PET CT (as clinically indicated for standard of care) [11]	X			X		X		X	X		
Chest wall breast photos, as clinically indicated for standard of care[11]	X			X		X		X	X		
EKG, ECHO or MUGA, will be repeated as clinically indicated for standard of care	X										
Biopsy Tissue[2]	X			X							
Blood Collection[3]	X			X							
Adverse Events[11]	X	X [1]	X	X	X	X	X[9]	X	X	X[5]	
BIBF 1120 dispense[4]		X	X	X	X	X	X	X			
Study Drug Accountability[10]			X	X	X	X	X	X	X		
Survival Follow-up[5]											X[5]

1. will not be repeated if done within 8 (+/- 3 days) days before the start of treatment

2. Tissue from chest wall, lymph nodes, or metastatic site will be collected for biomarkers at baseline and before cycle 3 (optional). If patient has paraffin blocks from untreated metastatic disease, the material can be used for baseline biomarker tissue validation. Up to 20 unstained slides from each block will be collected for biomarker evaluation. Biopsy before cycle 3 is an optional.

3. Blood samples will be collected for biomarkers at baseline and before cycle 3- Dr. Reuben's lab and IBC core lab archival.

4. BIBF1120 4-week supplies will be dispensed for months 1 to 6, and 8-week supplies will be dispensed for cycle 7 and every other cycle thereafter. Patient will take BIBF1120 PO twice daily according to appropriate dose level

5. Follow-up by clinical visit (at MD Anderson or a local physician), telephone and/or email correspondence

6. The day when the subject is determined to no longer be eligible for protocol treatment. Exams and tests will not be repeated if done within 14 (+/- 1 day) days before discontinuation of study drug, or patients are unable to come to MD Anderson for follow up.

7. The same method of evaluation , specific to the subject's condition, will be performed ± 5 days according to the time points of next treatment

8. CBC at baseline and before each cycle. Chemistry including total bilirubin, Creatinine, ALT, AST, urea/BUN, serum creatinine, calcium, sodium, magnesium, potassium, phosphorous, fasting glucose, albumin, alkaline phosphates, LDH on Day 1 ± 5 days of every cycle, and at the end of treatment will be performed. PT/PTT/INR and urine will be tested only at baseline.

9. Can be done at local oncologist's office.

10. Patient will record the number of study drug taken daily on the Dose Administration Record. Pill count will be performed at MD Anderson clinical visit.

11. All assessments/evaluations will be performed ± 5 days according to the time points.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: up to 44
Estimated monthly accrual at MDACC: 0-2

Accrual Comments:
An average monthly accrual is about 0-2.

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

Up to 44 patients will be enrolled in this phase II study to assess the efficacy of BIBF-1120 (Nintedanib). The primary endpoint of this study is the clinical benefit rate (CR, PR, and SD as determined by RECIST 1.1) of BIBF-1120 as single agent in metastatic IBC. Patients receiving clinical benefit is defined as patients who achieve complete response or partial response within 3 months after the initiation of treatment or patients who experience stable disease for at least three months after the initiation of treatment.

The purpose of this trial is to determine the clinical benefit rate (complete response [CR], partial response [PR] or stable disease [SD] rate) of BIBF 1120 (Nintedanib) in patients with HER2-negative, metastatic inflammatory breast cancer. Given a planned maximum number of patients, N=44, we would like to implement futility monitoring at 15, 30 and 44 patients and stop the trial when Bayesian Predictive Probability (PP) = å= Sumi=0,1,2,3,…, m {P(Y=i | x, n) ´ (P(p > 1%| x, n, Y=i)>= 95%)}<= 10%, where *x* represents current number response or stable disease in *n* treated patients, *m* represents the future number of patients. This means that given what are observed, there is a less than 10% chance that the clinical benefit rate is better than 1% if the trial continues to the end. With this rule, and assuming that the prior of response rate follows a beta distribution, beta (0.01, 0.99), we have the boundaries and the operating characteristics as listed below.

Futility Monitoring Boundaries

Cohort	Stop if # CR, PR or SD <=
15	0
30	1
44	2

Operating Characteristics

True Rate	PET	EN	Prob(Non-Negative)
1%	0.972	17.5	0.006
5%	0.633	28.2	0.272
10%	0.277	37.0	0.684
20%	0.040	42.9	0.959
30%	0.005	43.9	0.995
40%	0.000	44.0	1.000

At the end of the study, we will estimate the clinical benefit rate with 95% credible interval. Toxicity data, pharmacodynamic data, CTC and EMT gene expression in peripheral blood will be summarized using descriptive statistics. For the exploratory objective, we will correlate the number of CTC with EMT gene expression in peripheral blood using Spearman correlation, or estimate EMT gene expression in peripheral blood in patients with or without the presence of CTC, separately. Similarly we will evaluate if there are differential the pharmacodynamics biomarkers change in different groups by response status.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
The study is not randomized and not blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? Yes

Provide a summary or schedule of interim analysis.

The study design requires 25 patients in the first stage. If no patients respond to the treatment, the trial will be stopped and the regimen will be declared as ineffective. If at least one of the first 25 patients achieve clinical benefit (PR or CR) to the treatment, 19 additional patients will be enrolled onto the study to reach a total of 44 patients.

Protocol Monitoring Plan:

This study will be monitored by the MD Anderson IND office and a protocol-specofic monitoring plan will be followed.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MD Anderson
IND Number: 125610

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Boehringer Ingelheim
Support Type: Industry Funding

This Sponsor/Supporter/Granting Agency will receive data.

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	No

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

● Yes
○ No
○ Not Applicable For This Protocol

Please provide the name of the test(s), the purpose of the test, the performing laboratory identification and contact information, and confirm that the testing lab is CLIA certified (may attach a certificate or provide a certificate number).

HER-2/neu need to be negative to qulify for this study.

CLIA - Pathology.pdf

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree?	No