



## Protocol Abstract Page

# A Phase II Study of TKI258 (Dovitinib Lactate) as Salvage Therapy in Patients with Stage IV HER2-negative IBC and Local or Distant Relapse 2010-0296

### Core Protocol Information

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<b>Full Title:</b>	A Phase II Study of TKI258 (Dovitinib Lactate) as Salvage Therapy in Patients with Stage IV HER2-negative IBC and Local or Distant Relapse
<b>Protocol Phase:</b>	Phase II
<b>Version Status:</b>	Terminated 06/08/2018
<b>Version:</b>	19
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### Abstract

#### Objectives:

##### Primary

To determine an overall response (complete response [CR], partial response [PR] or stable disease [SD]) of dovitinib in patients with HER2-normal, local or distant relapse of metastatic inflammatory breast cancer

##### Secondary

- To evaluate safety analysis measures in terms of type, frequency and severity of adverse event reactions reported according to CTCAE v4.0

##### Exploratory Biomarkers:

- To explore the predictive values of baseline FGFR-R1, and VEGF-R1, signaling in tumor tissue (primary tumor or metastasis) before and during treatment with dovitinib.
- To determine the effect of dovitinib on the presence of CTC and CTCs with epithelial and/or EMT gene expression in PB.
- To collect and archive biopsy tumor tissue, serum and plasma for later hypothesis generating

associations

**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. Additional pathologic characteristics of IBC include high grade, negative hormone receptor status and overexpression of HER2 and E-cadherin; all of which are poor prognostic factors. Molecular features of IBC include mutation of the p53 suppressor gene, and an increased expression of proangiogenic factors (basic fibroblast growth factor [bFGF], vascular endothelial growth factor [VEGF], interleukin [IL]-6 and IL-8).

Receptor tyrosine kinases (RTKs) such as VEGF receptors, FGF receptors, and PDGF receptors have been shown to play an important role in tumor angiogenesis. VEGF is produced by both the host and the cancer cells and has a direct effect on endothelial cells, causing their proliferation, migration, invasion, and growth. FGFs are potent stimulators of angiogenesis in both normal and pathological tissues, having a direct effect on both vessel assembly and sprouting. A recent publication has demonstrated that a blockade of the FGF pathway can overcome resistance to VEGFR inhibitors, emphasizing the importance of FGFR and specifically the need for multi-targeted inhibitors. PDGF receptors are expressed on pericytes - smooth muscle cells that surround the vasculature and provide maintenance and support to the tumor neovasculature. Inhibition of these three growth factor receptor kinases should provide a powerful and broad inhibition of the angiogenesis process and provide potent antitumor effects. FGF family receptors play a critical role in tumorigenesis, morphogenesis, and inducers of angiogenesis. A study using tissue microarray comprised a cohort of 880 unselected breast tumors, FGF1 amplification was observed in 8.7% using chromogenic in situ hybridization (CISH), and this amplification was an independent predictor of overall survival. A model of spontaneous, highly aggressive rat model with presentation and phenotype resembling IBC has been described. This model has peculiar characteristics and angiogenesis dependent on the expression of FGF3 and FGF-4.

IBC possesses an increase of VEGF, PDGF and other proangiogenic factors as compared with non-inflammatory breast cancer. VEGF and FGF inhibitors have low IC50s in in-vitro models. We expect that anti-VEGF drug, such as Dovitinib, may have a potential role in HER2 negative IBC setting.

Dovitinib (dovitinib lactate) is an investigational new drug. Dovitinib inhibits receptor tyrosine kinases (RTKs) involved in solid and hematologic cancers, as well as tumor angiogenesis. Based upon its potency as an inhibitor of Class III/IV/V RTK signaling both in vitro and in vivo, and pharmaceutical properties including high oral bioavailability in three species, dovitinib is being studied in clinical trials as a cancer therapeutic.

The dose limiting toxicity (DLT) of dovitinib as single agent in patients with advanced cancer is being evaluated in 7 Phase I dose escalation studies. As of the 18 November 2009 cutoff date, 20 DLTs were observed in cycle 1 of dovitinib treatment. The DLTs included grade 3 anorexia/nausea/vomiting/diarrhea, grade 4 fatigue, grade 4 neutropenia, grade 3 hypokalemia, grade 2

sinus bradycardia, and delayed recovery from AST/ALT elevation, increased GGT, hypertensive.

Subsequently, dovitinib is being studied as a single agent in eight Phase I and one Phase II clinical trials designated to characterize safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity.

Additionally, in one study, 3 DLTs were reported by the investigators beyond cycle 1 treatment, including a grade 3 hypertension (occurred on cycle 2 day 8 in 1 patient at 100 mg/day), a grade 3 anorexia (occurred on cycle 2 day 9 in 1 patient at 175 mg/day), and a grade 3 alkaline phosphatase increase (occurred on cycle 2 day 29 in 1 patient at 175 mg/day).

There are four studies that were terminated prior to reaching the maximum tolerated dose (MTD). The MTD for continuous daily dosing regimen was defined at 400 mg; the MTD for 5 days on/2 days off dosing regimen was defined at 500 mg. Based on previous phase I safety data, and ongoing study for metastatic breast cancer, we propose a 500 mg daily 5 days on/2 days off schedule for this study.

#### **Eligibility: (List All Criteria)**

##### **Inclusion:**

- 1) Patients 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 for diagnosis.
- 2) Patients have stage IV disease with local or distant relapse
- 3) Patients have negative HER2 expression by IHC (defined as 0 or 1+), or FISH. If HER2 is 2+, negative HER2 expression must be confirmed by FISH.
- 4) Patients are able to swallow and retain oral medication.
- 5) Patients have ECOG performance status 0-2.
- 6) Patients have received two or more standard chemotherapies for metastatic disease and have relapsed.
- 7) Patients have ability and willingness to sign written informed consent.
- 8) Patients are 18 years of age or older.
- 9) Female patients of childbearing potential (A female not free from menses > 2 years or not surgically sterilized) must be willing to use highly effective contraception to prevent pregnancy or agree to abstain from heterosexual activity throughout the study. Highly effective contraception, defined as male condom with spermicide, diaphragm with spermicide, intra-uterine device. Highly effective contraception must be used by both sexes during the study and must be continued for 8 weeks after the end of study treatment. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study.
- 10) Female patients of childbearing potential must have negative serum pregnancy test  $\leq$  14 days prior to starting study treatment.

- 11) If Patients have been treated with anti-VEGF agents, such as Bevacizumab, last dose must be > 4 weeks.
- 12) Patients have biopsy tissue of the metastatic disease (including chest wall or regional nodes) available (paraffin blocks or up to 20 unstained slides), if no biopsy tissue available, a biopsy (or thoracentesis if patient has pleural effusion only) of the metastatic disease will be performed to confirm the diagnoses.
- 13) Serum total bilirubin must be within Upper Limited Normal (T. Bilirubin ULN=1.0 mg/dl)
- 14) AST and ALT must be < 2.5 x ULN(with or without liver metastases).

**Exclusion:**

- 1) Patients are receiving concurrent anti-cancer therapy (chemotherapy, immunotherapy, radiation therapy and biological therapy) while taking study medication.
- 2) Cirrhosis of liver, or known hepatitis B or C infection have hepatic impairment Child-Pugh Score of B or worse.
- 3) ANC < 1.5
- 4) Patients have an active infection and require IV or oral antibiotics.
- 5) 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) < 50% or lower limit of normal (which ever is higher) or multiple gated acquisition scan (MUGA) < 45% or lower limit of normal (which ever is higher). d) 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), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE); e) Uncontrolled hypertension defined by an SBP>150 and/or a DBP>100 mm Hg with or without anti-hypertensive medication.
- 6) History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.
- 7) 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.
- 8) Patients with only locally or regionally confined disease without evidence of metastatic disease.

**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.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:**

TKI258

**Proposed Treatment/Study Plan:**

Is treatment assignment randomized?  Yes  No

Is this a blinded or double-blinded study?  Yes  No

A complete treatment cycle is defined as 28 days or 4 weeks (+/- 2 days). Patients will receive a single daily oral dose of 500 mg of dovitinib for 5 consecutive days, followed by a 2-day rest period (5 days on/2 days off schedule).

For patients who are unable to tolerate the protocol-specified dosing schedule of dovitinib, two steps of dose reduction are permitted. Dose reduction should be based on the worst toxicity demonstrated at the last dovitinib administration. A patient who requires a delay of treatment of >21 days must discontinue the study treatment. All dose modifications should be based on the worst preceding toxicity. Patients are only allowed two dose reductions to 400 mg and 300 mg.

Dose reduction*			
	Starting dose level - 0	Dose level - 1	Dose level - 2
Dovitinib	500 mg	400 mg	300 mg**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
**Dose reduction below 300 mg is not allowed.			

Evaluation and Treatment	Screening (D -21 to -1)	Day 1 Pre dose	C2	C3	C4	C5	C6	Every 2 cycles from cycle 6	Discontinuation of study drug <sup>6</sup>	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	X	x <sup>1</sup>	x	X	X <sup>10</sup>	X	X <sup>10</sup>	X	X		
ECOG Performance Status	X	x <sup>1</sup>	x	X	X <sup>10</sup>	X	X <sup>10</sup>	X	X		
Hematologic and Biochemical Profiles <sup>8</sup>	X	x <sup>1</sup>	x	X	X <sup>10</sup>	X	X <sup>10</sup>	X	X		
Dovitinib concentration			X <sup>9</sup>								
Serum 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.) <sup>7</sup>	X			X		X		X	X		
PET CT (as clinically indicated for standard of care)	X			X		X		X	X		
Chest wall breast photos, as clinically indicated for standard of care	X			X		X		X	X		
EKG, ECHO/MUGA, will be repeated as clinically indicated for standard of care	X										
Biopsy Tissue <sup>2</sup>	X			X							
Blood Collection <sup>3</sup>	X			X							
Adverse Events	X	x <sup>1</sup>	x	X	X <sup>10</sup>	X	X <sup>10</sup>	X	X	X <sup>5</sup>	
Dovitinib 500mg dispense <sup>4</sup> (PO 5 days on, 2 days off)		x	X	X	X	X	X	X			
Study Drug Accountability <sup>11</sup>			X	X	X	X	X	X	X		
Survival Follow-up <sup>5</sup>											X <sup>5</sup>

1. will not be repeated if done within 8 (+/- 3 days) days before the start of treatment
2. Chest wall punch or core biopsy, u/s guided lymph nodes biopsy or FNA, thoracentesis or biopsy of a metastatic site 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. One time DOVITINIB concentration will be performed on day 5 of week 2, 4 or 6. (see appendix J for instructions). If patients are unable to come on day 5 of week 2, 4 or 6, dovitinib concentration samples can be collected at the end of week 4 before cycle 2 when patients are in the clinic for evaluation. Samples will be labeled to reflect the time points.
4. Dovitinib 4-week 500mg supplies will be dispensed for months 1 to 6, and 8-week 500mg supplies will be dispensed thereafter. Patient will take 500mg dovitinib PO daily for 5 days and rest for 2 days.
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 according to the time points
8. CBC at baseline and before each cycle. Chemistry including total bilirubin, Creatinine, ALT, AST, urea/BUN, serum creatinine, calcium, sodium, magnesium, potassium, phosphorus, fasting glucose, albumin, alkaline phosphates, GGT, LDH, amylase and lipase) on Day 1 ± 3 of every cycle, C1D8 (± 3 days) and Day22(± 3 days), C2D8 (± 3 days), and at the end of treatment will be performed.
9. One time dovitinib trough concentration before cycle 2.
10. Can be done at local oncologist's office.
11. 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.

**Study Enrollment:**

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

Only at MDACC

**Estimated Accrual:**

Total Accrual at MDACC: 33  
Estimated monthly accrual at MDACC: 0-1

**Accrual Comments:**

An average monthly accrual is about 0-1.

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

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

**Statistical Considerations:**

This is a phase II study, single arm evaluating the efficacy and safety of dovitinib. The treatment plan consists in continuous treatment of dovitinib 500 mg PO daily 5 days on and 2 days off.

The primary endpoint is the six-month overall response rate (ORR) defined as the percentage of patients experiencing stable disease, complete or partial response (SD, CR or PR) as defined by RECIST. A response is anyone who experiences SD, CR or PR in the first 6 months. In other words, any patient that has not achieved either SD, CR or PR in the first 6 months will be considered a treatment non-responder. The trial will be conducted by the Simon's two-stage design using the mini-max criterion and the response rate will be estimated accordingly.

It is assumed that dovitinib will have a target ORR of 30%. An ORR of 10% or lower is considered a failure based on the typical ORR with a second line regimen for IBC and the new regimen will be rejected under this circumstance. When the probability of accepting a "bad" regimen (i.e. response rate 10%) is 0.05 and the probability of rejecting a "good" regimen (i.e. response rate 30%) is also 0.10, Simon's design to minimize the maximum sample size requires 22 patients in the first stage. If two or less patients respond to the treatment, the trial will be stopped and the regimen will be declared as ineffective. If at least three of the first 22 patients respond to the treatment, 11 additional patients will be entered in the study to reach a total of 33 patients. By the end of the study, the new regimen will be rejected if response rate is less than or equal to 6 out of 33 patients and will be accepted otherwise. Patient accrual will be suspended in the case when there are not at least 3 responders in the first 22 patients and not all 22 patients have been evaluated for 6 months. The operating characteristics of the trial are given as follows. When the true response rate is 0.10, the probability of stopping the trial early is 62.0%. On the other hand, if the true response rate is 0.30, the probability to stop the trial early is 2.1%. The expected sample sizes are 26.18 and 32.77 when the true response rates are 0.10 and 0.30, respectively. At the end of the study, the overall response rate and the

95% confidence interval will be reported and the toxicity profile of the regimen will be summarized.

As a secondary analysis we will evaluate safety by grading each adverse event (e.g., neutropenia, neurotoxicity, and CINV) according to CTCAE v4.0 and reporting the type, frequency and severity. In order to understand the relationship of FGF R1, FGF9, FGF, and VEGF-R1 signaling in serum and those in the tumor tissue (primary tumor or metastasis) with tumor growth, a correlation analysis of the expression levels of the biomarkers and tumor size will be conducted. For each biomarker, baseline expression level (EB) and post-treatment expression level (EP) will be determined by Immunohistochemistry (IHC). Pearson product-moment correlation coefficient measuring the linear relationship between the percent change in expression level,  $[EB-EP]/EB$ , and the percent change in tumor size as measured by CT scan will be reported along with the associated 95% confidence interval and the p-value for testing that the true linear correlation coefficient is non-zero. A linear model will be used to assess the joint impact of down regulation of FGFR-R1 and VEGF-R1 on tumor growth. The change in the number of circulating tumor cells (CTC) at baseline as compared to the number post-dovitinib will be investigated using a paired t-test. If the change in CTC is not normally distributed based on Shapiro-Wilk test, we will consider a robust non-parametric procedure such as the Wilcoxon Rank-Sum test.

#### **Data Safety Monitoring Board / DSMB at MDACC:**

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

Please explain:

This is not a randomized and not blinded study.

#### **Protocol Monitoring:**

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

Provide a summary or schedule of interim analysis.

We will conduct an interim analysis after the first 22 patients following Simon's 2 stage min-max design.

#### **Protocol Monitoring Plan:**

Adverse events will be assessed according to the CTCAE version 4.0. All study patients who have received any dose of dovitinib will be evaluable for safety. Unexpected adverse events including laboratory adverse events deemed clinically significant by the investigator will be graded and recorded.

The ongoing review of safety data will include review of clinical AEs and SAEs. The NCI-CTC version 4.0 will be used to grade all AEs. An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (diabetes, congestive



heart failure, rheumatoid arthritis) that occurs after initiation of investigational product whether or not considered to be investigational product related. A worsening of an existing medical condition is one that was present at baseline (e.g., cancer, diabetes, migraine headaches, gout) and became more severe, more frequent, or increased in duration during investigational product treatment.

Reporting Procedures for AEs ( $\geq 2$  non-hematological and  $\geq 3$  hematological AEs) occurring after informed consent signing observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be documented to the medical record then entered into the case report form. Abnormal laboratory values should not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE. The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

All patients will be followed for safety 30 days (+/- 10 days) after the last dose of dovitinib, and every 3 months for duration of up to one year or until death, whichever occurs first for response, PFS and OS. Patients will be followed a minimum of every 3 months by clinic visit (at MD Anderson or a local physician), telephone or e-mail correspondence.

**Intellectual Property:**

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

**Investigational New Drugs (IND):**

Does this protocol require an IND?            Yes

Who is the IND Holder/Regulatory Sponsor?

MDA

IND Number:    Pending

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: Novartis  
Support Type: Industry Funding

This Sponsor/Supporter/Granting Agency will receive data.

**Radioactive Material:**

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Does this study involve the administration of radioisotopes or a radioisotope labeled agent? No

[Click here for help](#)

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**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).

[HER2 status is the only one for determination of eligibility. IHC and FISH are both MDACC CLIA certified.](#)

[Other biomarkers](#) FGFR-R1, VEGF-R1, Cytokines and Micro RNA, CTC, and EMT  
CTC are for research only.

**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