

Phase II evaluation of ZD1839 in metastatic breast cancer patients refractory to treatment.

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A. Introduction, Study Purpose, and intended Laboratory Correlates

a. Background on tumor

In the United States there are approximately 180,000 new cases of breast cancer diagnosed each year. Unfortunately, this disease accounts for approximately 46,000 deaths per year. Currently there is no cure for stage IV breast cancer, and the average life expectancy is approximately 2 years. While initial chemotherapy can produce a complete or partial response in 50-65% of patients, major prolongation of survival is not seen. Combination chemotherapy for refractory advanced breast cancer yields response rates of 10-30%, with a median duration of response typically measured in months.

b. Background and rationale for new treatment

Prognostic and predictive factors have been increasingly important in the treatment for breast cancer patients. ER, PR, and HER2-Neu have been strongly validated as predictors of outcome(1). Recent research has underscored the importance of growth factor receptor kinases such as EGFR in the progression and prognosis of mammary tumors(2,3). In contrast to oncogenes, EGFR is normally expressed on mammary cell surfaces that translates signals derived from the extracellular environment toward the regulation of intracellular functions including cell proliferation and cell survival. EGFR expression correlates inversely with ER expression, making it indicative of poor prognosis(4,5). The importance of this pathway was further elucidated in the transduction of cells following radiation treatment. Furthermore, it appears that primary chemotherapy may induce significant variations in the phenotype of breast cancer cells: most importantly an overexpression of EGFR(6).

ZD1839 is a small organic molecule (MW 446.91) that is a potent and selective inhibitor of epidermal growth factor receptor tyrosine kinase. It works by competing with adenosine triphosphate for its binding site on the intracellular domain of the receptor and by noncompetitively inhibiting EGF primarily by inhibiting its intrinsic tyrosine kinase activity. Following oral dosing, significant growth delay was seen in a range of human tumor xenografts and tumor regressions were observed in some tumor models(9). This inhibition persisted 24 hours post withdrawal of the drug *in vivo*. On an oral dosing schedule, significant growth delay was seen in a range of human tumor xenografts and tumor regressions were observed in some tumor models with minimal toxicity. Preliminary results from Phase I studies suggest that antitumor activity has been observed, with reports of stable or improved disease. In addition, the toxicity profile seems to be well tolerated. Two trials are assessing escalating doses of ZD1839 administered on a continuous daily schedule. Dose limiting toxicity has not been reached at doses levels of 600 and 800 mg/day.

In an ongoing phase I study in which 60 patients were reported on, escalating doses were given for 14 days followed by cessation for 14 days. If there was no progression or toxicity, the drug was reinitiated at the same dose. 94 14-day treatment cycles are reported in Table 1 in Section 6.0. In a phase I/II trial on continuous once-daily treatment there were no grade 3 or 4 adverse events noted in 58 patients (Abstract 29). Noted toxicity are reported in Table 2 in Section 6.0.

In summary the most frequent adverse events were grade 1-2 skin rash (58%), diarrhea (44%), nausea (25%) and vomiting (22%). Grade 3 adverse events included diarrhea, skin rash, increased transaminases, nausea and vomiting(7,8). In pharmacodynamic studies were performed in rats and dogs the bioavailability is approximately 50% with peak plasma concentrations observed between 2 and 6 hours after dosing. The elimination half-life was between 3 and 5 hours. The agent was extensively distributed and eliminated mainly via the biliary route with only 2-6% of the dose renally eliminated. Binding is approximately 90% to plasma proteins.

c. Laboratory Correlates

To examine the effect of ZD1839 on EGFR expression and activity, we will use monoclonal and polyclonal antibodies directed against EGFR to examine its expression level on de-paraffinated tissue or frozen tissue sections. In addition, tissue section will be incubated with antibodies that detect the presence of phosphorylated tyrosine residues indicative of increased tyrosine kinase in a sample. EGFR tyrosine kinase activity will be studied by in vitro kinase assays using specific substrate peptide or polypeptide protein substrates using incorporation of ³²P-gammaATP as an endpoint. Proliferation of tissue cells will be determined by immunohistochemical staining, cell apoptosis in situ will be determined using TUNEL stain of frozen and fixed section, the activity and expression of apoptotic marker will be examined using tissue lysates. If post study biopsy sample can be obtained, repeat measures will be performed, and the effect of ZD1839 will be analyzed.

Recently, a novel breast and prostate cancer-associated tumor marker (BPAM) which is a cytosolic non-secreted protein found only in breast and prostate adenocarcinoma but not in normal tissues, has been identified at the Herbert Irving Comprehensive Cancer Center (manuscript in preparation). This marker is released to the surrounding media only as a result of cancer cell destruction and therefore can be used as an indicator of tumor regression. In vitro studies show that the treatment of different breast cancer cell lines by selected chemotherapeutic drugs causes the emergence of BPAM in culture media. This is the result of cellular apoptosis. The results have been confirmed in a time and dose dependent mode. The testing of BPAM levels in patients sera prior to treatment and during the course of treatment will allow for both evaluation of the applicability of this marker to monitor chemotherapy and evaluation of the effectiveness of treatment itself.

Positron Emission Tomography Scanning (PET) has been used to determine metabolic activity in a number of tumors, including breast cancer. It is currently approved for use in the diagnosis and staging of lung cancer and lymphoma. Radioactively labeled glucose is injected, and picked up by lesions that are metabolically active. ZD1839's role in disrupting the tumors cellular metabolism may be demonstrated using PET. Activity on PET will be compared to CT Scan response.

B. Objectives

To determine the response rate, duration of response, duration of survival, quality of life effects of ZD1839, and correlation with tumor markers and PET scanning in patients with metastatic breast cancer.

C. Eligibility Criteria

a. Patients must fulfill the following criteria

- Histologically confirmed breast cancer, metastatic who have demonstrated progression.
- Measurable disease: Any mass reproducibly measurable in two perpendicular diameters by x-ray, physical examination, or CT scan; or evaluable disease
- Ineligible for other high priority national or institutional study.
- Prior therapy allowed
 - Any number or prior chemotherapy or hormonal therapy regimens
 - >1 week since surgery
 - >4 weeks since RT
- Non pregnant, non lactating
- Clinical Parameters
 - Life expectancy >2 months
 - Age 18-80 years
 - Brain CT or MRI no visible metastases.*

- Performance Status KPS >60

*Since persons with cerebral metastases have very short life expectancy, they will not be eligible unless they have a single lesion amenable to resection by surgery or if they have stable lesions.

- Required initial laboratory data

White cell count	>3000/ul
Platelet count	>100,000/ul
BUN	<1.5 x normal
Creatinine	<1.5 x normal
Bilirubin	<ULN
SGOT or SGPT	<1.5 x normal
- Informed Consent: Each patient must be completely aware of the nature of her disease process and must willingly give consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.
- No prior malignancy (other than curatively treated carcinoma in-situ of the cervix or skin cancer). If in the opinion of the treating physician, sufficient time has elapsed such that extremely likely that the patient has been cured of a prior malignancy, the patient may be eligible for the protocol.
- No serious medical or psychiatric illness preventing informed consent or intensive treatment (e.g., serious infection). HIV status or other severe illnesses will be assessed using medical records.

D. Patient Entry

- Referrals: Referral from the consultation service may take place only with the agreement of the responsible physician
- Staging: Evaluate all areas of original disease via Chest X-Ray, CT Scan Chest, Abdomen/Pelvis, and Head. Bone Scan.
- Registration: To register the patient, fax or deliver the completed Eligibility Criteria Form and signed Informed Consent to the Columbia Cancer Center Protocol Office (6 Garden North Knuckle- room 435) (212) 305-8615, fax 3035. Send hard copy for faxed registration by intrahospital mail
- Required Forms
 - Eligibility Criteria Form
 - Informed Consent
 - On Study Form
 - Summary & Evaluation Form
 - Summary Update Form
- Expected rate of accrual 3-4 patients/month

E. Treatment Plan

- Patients will receive ZD1839 600 mg/day as outpatients..
- Patient will continue to receive the drug daily until progression of disease is noted

F. Potential Toxicity and Management

a. Definitions

- i. Serious adverse event: any experience that is fatal or life-threatening, is permanently disabling or is overdose.
- ii. Associated with the use of the drug: there is a reasonable possibility that the experience may have been caused by the drug.
- iii. Unexpected adverse event: any adverse event that is not identified in nature, severity, or frequency in the **current investigators brochure or package insert**.

b. Reporting

Adverse events will be reported as required by section 312.32 of the Code of Federal Regulations

c. Report to the IRB within 24 hours:

- i. All life-threatening (Grade 4) and (Grade 5) unexpected reactions. Written report to follow writing 10 working days.
- ii. Report in writing within 10 working days:
 - 1. Grade 2 and 3 unexpected reactions.
 - 2. Life-threatening and lethal (grade 4 and 5) unexpected reactions.

d. Reported Toxicities

Table 1(7)

Adverse Event	Grade or Incidence
Infection	10%
Nausea/vomiting	Grade 1-2 in 20%
Skin Changes*	18%

Grade 3-4 adverse events were rare, non-mechanism based, or related to disease progression, except for transient transaminase elevation in 1 and a skin rash in 1.

*Skin rash frequency occurred dose-dependently, rashes were usually grade 1-2, reversible, pustular and involved the face and/or upper torso.

Table 2 (8)

Adverse Event	Grade or Incidence
Diarrhea	10%
Nausea	7%
Anorexia	7%
Mechanism-based skin reactions	Grade 1-2 in 19% of patients*

*Skin reactions were reported as dry skin, papular/pustular rashes. Manifestations did not worsen despite continued therapy.

e. Management of Toxicity

Grade 3 and 4 Toxicity will be managed by discontinuing the drug for 2 weeks or until the symptoms resolve. At that time, the drug will be resumed. Recurrence of the toxicity will be managed again by withdrawal of the drug followed by a 25% reduction in dose following resolution of symptoms.

G. Drug Formulation, Availability And Preparation

Zd1839 is made by AstraZeneca Pharmaceuticals and is supplied by the national Cancer Institute Division of Cancer Treatment and Diagnosis, Cancer Therapy Evaluation Program (CTEP). The drug is in pill form and will be stored as recommended in the product insert.

Required Data

<i>Tests & Observations</i>	<i>On Study</i>	<i>2 weeks*</i>	<i>4 weeks</i>
Signed informed consent	X		
History and interval note	X	X	
Physical Examination	X	X	
Pulse, Blood Pressure	X	X	
Height, Surface Area	X		
Weight	X	X	
Performance Status	X	X	X
Tumor Measurements	X	X	X
Drug Toxicity	X	X	X
Staging			
Chest x-ray ^A	x		X**
CT scan of involved area	X		X**
CT head X			
PET Scanning	X		X**
Bone Scan	X		X** ^B
EKG	X		Laboratory
CEA & CA-15-3	X		X
BPAM	X		X
CBC, Platelet Count & diff	X	X	
Creatinine	X	X	
Electrolytes	X	X	
Coagulation Profile	X		
SGOT, SGPT, Bilis	X	X	

** Denotes q 2 months rather than q 4 weeks

^A Chest X-Ray will not be required if CT scanning is performed

^B Bone Scanning will be repeated only in initially positive

H. Criteria For Evaluation

- a. Complete Response: Disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor, for >4 weeks, during which no new lesions may appear.
- b. Partial Response: When compared with pretreatment measurements, a reduction of >50% in the sum of the products of the perpendicular diameter of all measurable lesions lasting >4 weeks, during which no new lesions may appear.
- c. Stable disease: A <50% reduction of <25% increase in the um of the products of two perpendicular diameters of all measured lesions, and the appearance of no new lesions for >8 weeks.
- d. Objective Progression:
 - i. An increase in the product of two perpendicular diameters of any measured lesion by >25% over the size present at entry on study or for patients who respond, the size at the time of maximum regression.
 - ii. The appearance of new areas of malignant disease except for CNS lesions
 - iii. The following in and of themselves do not constitute progression; however, they

should initiate a new evaluation for extent of disease.

Deterioration in performance status, >10% loss of pretreatment weight, or deterioration in prior symptoms.

- iv. Time to treatment failure. Time from day 1 of receiving the drug to the time of death or disease progression.

I. Removal Of Patients From Protocol Therapy

- a. Disease progression: Any patient with rapid disease progression may be removed from the study.
- b. Extraordinary medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, the patient shall be withdrawn from treatment. In this event:
- Notify the Study Chairperson.
 - Document reason(s) for withdrawal on the flow sheets.
 - Follow the patient for progression and survival
- c. Unexpected, Life-threatening or Lethal Toxicity:
Notify the Protocol Office and Study Chair within 3 business days.

J. Ancillary Therapy

- 11.1 Patients should receive full supportive care including transfusion of blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets.
- 11.2 Treatment with hormones or other chemotherapeutic agents is not permitted while the patient is on study, except for steroids administered for antiemesis, premedication, documented CNS metastases, adrenal failure, or septic shock or hormones administered for non-disease-related conditions (e.g., insulin for diabetes).

K. Cost And Compensation To Subjects

There will be no personal cost or financial compensation to subjects.

L. Statistical Aspects

The objectives of this phase II trial are to estimate the probabilities of response, survival, and toxicity in women with refractory metastatic breast cancer treated with ZD1839. We will use a two-stage Gehan design in which the first stage involves the enrollment of 11 patients. If at least one patient responds, an additional 14 patients will be enrolled. The design has a power of 90% to detect a response rate of 20% with a standard error of 10%. We will summarize survival and progression-free survival by Kaplan-Meier curves.

M. References

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