THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Phase II Study of erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in the treatment of recurrent or metastatic squamous cell carcinoma of the skin
2009-0888

Core Protocol Information

Short Title:	Phase II Study of Erlotinib in the Treatment of Recurrent or Metastatic CSCC of the Skin
Study Chairman:	Bonnie S. Glisson
Department:	Thoracic and Head and Neck Med
Phone:	713-792-6363
Unit:	432
Full Title:	Phase II Study of erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in the treatment of recurrent or metastatic squamous cell carcinoma of the skin
Protocol Phase:	Phase II
Version Status:	Terminated 05/03/2019
Version:	14
Document Status:	Final

Abstract

Objectives:

The primary objective is to:

Determine the overall response rate with erlotinib in patients with locoregionally recurrent or metastatic squamous cell carcinoma of the skin (CSCC) that is not amenable to curative treatment.

The secondary objectives are to determine:

- Duration of response and duration of stable disease
- Progression-free and overall survival
- Safety and tolerability of erlotinib

Exploratory objectives are:

- To correlate baseline expression of EGFR, expression of markers of EGFR activation (such as pEGFR and pAKT) and related cell-signaling pathways, and EGFR mutation status with response to erlotinib therapy
- To determine the effects of erlotinib on relevant biomarkers of the EGFR pathway in tumor tissue and in normal skin, and to correlate with response to therapy.
- To determine if there is a correlation between the development of erlotinib-induced skin rash and response to therapy

Rationale: (Be as concise as possible)

There is no defined standard treatment for locoregionally recurrent cutanneous squamous cell carcinoma (CSCC) that is not amenable to definitive local therapy or for distant metastatic disease, and cytotoxic chemotherapeutic agents have limited activity in this disease. Therapy directed toward inhibiting the epidermal growth factor receptor (EGFR) (small molecules such as erlotinib (Tarceva®) and gefitinib (Iressa®) as well as monoclonal antibodies cetuximab (Erbitux®)) has been shown to improve survival in multiple cancers, including lung, colon, pancreatic, and head and neck cancers. Since EGFR activation has been linked with the pathogenesis of CSCC, it is possible that EGFR-directed agents will have biologic activity against CSCC.

We have conducted two studies of gefitinib for CSCC at M. D. Anderson Cancer Center with very encouraging results. In a phase II clinical trial among patients with recurrent or metastatic CSCC of the skin, we administered gefitinib at a dose of 250mg orally daily for 4 weeks. Forty patients were enrolled and 37 were evaluable for response. Partial responses were observed in 4 patients, and 15 patients had stable disease. We also conducted a CTEP-sponsored induction trial of gefitinib for patients with aggressive primary CSCC at M. D. Anderson Cancer Center. Eligibility criteria included patients with CSCC greater than or equal to 2 cm in diameter, perineural invasion, deep invasion into cartilage, muscle or bone and lymph node metastasis. Patients were administered daily with gefitinib for sixty days prior to definitive surgery or radiation therapy or both. The daily dose of drug was 250 mg with dose escalation to 500 mg daily for patients with stable disease at two weeks after initiation of therapy. Results have been provocative. Twenty-three patients (22 evaluable) with CSCC have been enrolled, and 10 patients experienced significant responses; complete clinical responses in 4 patients, partial responses in 6 patients, and stable disease in 5 patients. Six patients had dose escalation of gefitinib to 500 mg, one of who had a complete response and three had stable disease.

Our rationale for testing erlotinib includes the desire to study other EGFR targeted therapies in CSCC, the possible increased plasma concentrations of erlotinib as opposed to gefitinib that could translate into increased efficacy, and anecdotal reports of the effectiveness of erlotinib.

Eligibility: (List All Criteria)

Inclusion:

1) Have histologically or cytologically confirmed cutaneous squamous cell carcinoma (CSCC) that is not amenable to curative therapy. If the biopsy was collected outside of MDACC, the MDACC Pathology Department must assess and confirm the SCC diagnosis.
2) Have measurable disease.
3) Be at least 18 years of age.
4) Have ECOG performance status 0-2.
5) Must have ability to understand and the willingness to sign a written Informed Consent Document (ICD). In the event that non-English speaking participants are eligible for this study, a short form (if applicable) or an ICD in their language will be utilized and completed in accordance with the MDACC "Policy For Consenting Non-English Speaking Participants."
6) Must have adequate organ and marrow function as follows:(a) leukocytes >/= 3,000/mm^3 (b) absolute neutrophil count >/= 1,500/mm^3 (c) platelets >/= 75,000/mm^3 (d) hemoglobin >/= 8g/dL (e) total bilirubin </= 2 x institutional upper limit of normal (ULN) (f) AST(SGOT)/ALT(SGPT) </= 2.5 x ULN if alkaline phosphatase is normal, or alkaline phosphatase </= 4 x ULN if transaminases are normal (g) Creatinine </= 2.0 x ULN or creatinine clearance >/= 60 mL/min/1.73 m^2
7) Prior radiotherapy is allowed if: (a) there is measurable disease outside the radiation field OR (b) radiotherapy was completed more than 4 weeks ago and there is clearly recurrent and growing disease within the radiation field.
8) Must be able to take intact tablets by mouth, or be able to take tablets dissolved in water by mouth or by a percutaneous gastrostomy tube.
9) Patients – both males and females – with reproductive potential (includes women who are menopausal for less than 1 year and not surgically sterilized) must practice effective contraceptive measures such as barrier methods, condom or diaphragm with spermicide, or abstinence throughout the study. Birth control should continue for 4 weeks after discontinuation of erlotinib therapy. Women of childbearing potential must provide a negative pregnancy test (serum betaHCG) within 72 hours prior to first receiving protocol therapy.
10) Organ transplant patients are eligible as long as they do not have active signs of rejection and have adequate bone marrow function.

Exclusion:

1) Women who are pregnant, breastfeeding, and women and men not practicing effective birth control. Erlotinib is a signal transduction inhibitor agent with the potential for teratogenic or abortifacient effects. There is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with erlotinib. Breastfeeding should be discontinued if the mother is treated with erlotinib.
2) Prior EGFR inhibitor therapy is not allowed (including, but not limited to, erlotinib, gefitinib, cetuximab, panitumumab, vandetanib).
3) Patients who are receiving any other anticancer or investigational agents at time of study enrollment. Patients may have received one other systemic therapy or investigational agent in the past, but a washout time period of at least 4 weeks and recovery of any treatment-related toxicities to < CTCAEv4 grade 2 is required.
4) History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib.
5) Patients with a history of an invasive malignancy (other than the one treated in this study) or lymphoproliferative disorder within the past 3 years. Patients with a history of adequately treated non-melanoma skin cancer, ductal carcinoma in situ of the breast, or carcinoma in situ of the cervix are allowed.
6) Patients with incomplete healing from previous surgery.
7) Patients with pulmonary fibrosis (other than in a radiated field) or active interstitial lung disease.
8) Patients with active gastrointestinal disease or a disorder that alters gastrointestinal motility or absorption, including lack of integrity of the gastrointestinal tract (for example, a significant surgical resection of the stomach or small bowel, inflammatory bowel disease or uncontrolled chronic diarrhea.
9) Patients with skin rash ≥ CTCAEv4 grade 2
10) In the opinion of the investigator, patients with any condition that is unstable or could jeopardize the safety of the patient or could limit compliance with the study's requirements. These include, but are not limited to, ongoing or active infection requiring parenteral antibiotics at time of study registration, psychiatric illness that would limit compliance with study requirements or symptomatic congestive heart failure (NYHA class II or greater), unstable angina pectoris or cardiac arrhythmia requiring maintenance medication.
11) Patient is unwilling or unable to discontinue prohibited concomitant therapies, (i.e St. John's wort, grapefruit juice, H2 blockers/proton pump inhibitors, strong CYP3A4 inhibitors and inducers).

Is there an age limit? Yes

Why? Provide scientific justification:
These tumors are extremely rare in children under the age of 18.

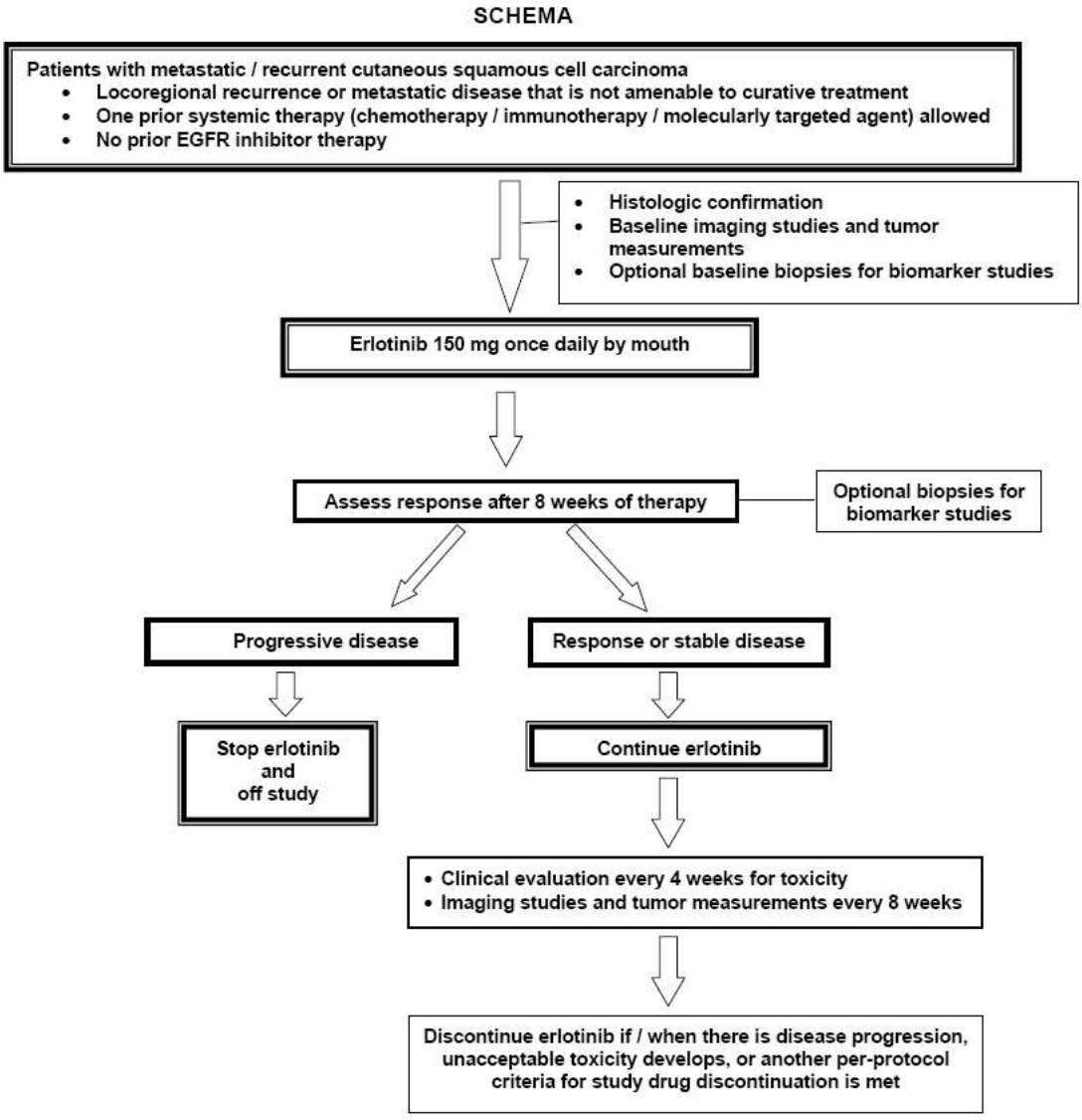
Disease Group:

Skin

Treatment Agents/Devices/Interventions:

Erlotinib

Proposed Treatment/Study Plan:



Study Calendar

	Screening	Baseline	During treatment		Off-treatment[h]	Follow-up[i]
Action / assessment	Day -28 to 0	Day – 14 to 0 +/- 5 days	Day 1	Every 4 weeks +/- 5 days	30 days (+/- 7 days) after last dose of study drug	Every 3 months for up to two years
Daily erlotinib[a]			X	X		Collect information on survival status and any subsequent anti-cancer therapy
Informed consent	X					
Demographics		X	X[k]	X		
Medical history		X	X[k]	X		
Smoking history		X	X[k]	X		
Concurrent medications		X	X[k]	X		
Physical exam[c]		X	X[k]	X	X	
Vitals signs		X	X[k]	X	X	
Height		X				
Weight		X	X[k]	X	X	
Performance status		X	X[k]	X	X	
CBC w/diff and plts		X	X[g]	X		
Serum chemistry[d] and PT/INR		X	X[g,l]	X		
β-HCG[e]		X (day -3 to 0)				
EKG (as indicated)[f]	X					
CXR	X					
Imaging studies and tumor measurements[g]	X			Every 8 weeks (+/- 5 days)		
Toxicity / Adverse event evaluation[h]				X	X[h]	
Optional tumor biopsy[j]	X			At the end of week 8 (+/- 5 days)		

a. Patients who are receiving erlotinib are seen and assessed every 4 weeks
b. Patients self-administer erlotinib once every day. Erlotinib is dispensed to patients at each 4-week visit.
c. Physical examination must be documented carefully and tumor measurements done if applicable. Photographs may be taken for documentation.
d. Serum chemistry includes: ALT, AST, GGT, LDH, bilirubin, albumin, total protein, alkaline phosphatase, electrolytes, BUN, creatinine. Hematology, serum chemistry and PT/INR are assessed within 14 days before starting trial. If results meet the eligibility criteria and there has been no change in a patient's clinical condition, the test need not be repeated on Day 1 of treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 24 hours prior to initiation of therapy
e. All women of childbearing potential must be tested for pregnancy using serum beta HCG within 72 hours prior to first receiving protocol therapy.
f. EKGs can be obtained up to 28 days before enrollment. A repeat EKG will subsequently be done as clinically indicated.
g. Includes chest radiograph, computer tomography (CT) scan or magnetic resonance imaging (MRI), and color photography of skin lesions (with ruler in photo). Responses will be on the basis of a comparison to the pre-treatment tumor evaluation. All patients who have received at least 1 dose of erlotinib will be considered evaluable for response. Tumor assessment will be done within 28 days before trial therapy. Tumor assessment on therapy will done every 8 weeks (+/- 5 days) thereafter. Assessment should be performed before the scheduled time if progression is suspected or to confirm tumor response. Lesions must be assessed using the same methods on each occasion. (see Section 9).
h. Any ongoing trial treatment-related toxicity or SAE at withdrawal must be monitored until resolution.
i. Patients will have clinic visit or telephone interview every 3 months for up to two years post completion of protocol therapy to collect information on survival and on any further anti-cancer therapy, including chemotherapy type and other systematic therapies, radiation therapy and surgical interventions.
j. Optional tumor biopsies for correlative / biomarker studies will be performed within 28 days before trial therapy and after 8 weeks (+/- 5 days) on erlotinib.
k. Demographics, medical history, concurrent medication, physical exam, vital signs, weight and performace satatus are recorded 14 days before starting trial and do not need to be repeated on Day 1 of treatment, if there has been no change in a patient's condition or information.
l. PT/INR will be assessed on all patients at baseline and only on patients taking anticoagulants during treatment.

Statistical Considerations:

This is an open label, phase II clinical trial to evaluate the efficacy of erlotinib in patients with metastatic or recurrent cutaneous squamous cell carcinoma that is not amenable to curative treatment. The primary objective of this study is to assess the efficacy of erlotinib in treating patients with recurrent or metastatic squamous cell carcinoma of the skin. The primary endpoint is the overall response rate (ORR), which will be evaluated after 8 weeks of study therapy. A patient will be considered a non-responder if tumor does not regress to complete or partial response as specified in RECIST v1.1 at that time point. ORR will be based on the overall response of each evaluable patient, and is defined as the percentage of patients who achieve an overall response of complete response or partial response in the total number of evaluable patients. It is expected for the current trial that the erlotinib will improve the ORR to 20%, as compared with the ORR of 11% observed in the trial with gefitinib.

A Bayesian design based on predictive probability will be implemented. This design allows for early stopping when data indicates that the treatment is ineffective. The stopping boundary is chosen by computing the predictive probability from observed data. Specifically, we will stop the trial if the current data indicates that, by the end of the trial, it is highly unlikely that the response rate in erlotinib treated patients will be higher than 0.05.

The maximum number of patients is N=33. The treatment outcomes will be monitored for patients in cumulative cohort sizes of 17, 29, 32, and 33. The following table lists the cumulative number of patients (n) and the rejection region in the number of responses in n patients. The trial will be stopped and the treatment will be considered ineffective when the number of responses first falls into the rejection region.

n	Rejection Region in Number of Responses
17	0
29	1
32	2
33	3

The operating characteristics of the trial are: If the response rate is 0.05 (i.e. the trial is ineffective), the probability of accepting the treatment is 0.08 (corresponding to the type I error rate). On the other hand, if the true response rate is 0.20 (i.e. the treatment is effective),

the probability of accepting the treatment is 0.91 (corresponding to the power of the study). The probabilities of terminating the trial early are 0.80 and 0.05 if the true response rates are 0.05 and 0.20 and the resulting expected sample sizes are 25.3 and 32.6, respectively.

Where Will Participants Be Enrolled:

Only at MDACC

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

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

Estimated Accrual:

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

Accrual Comments:
This is an open label, phase II clinical trial to evaluate the efficacy of erlotinib in patients with metastatic or recurrent cutaneous squamous cell carcinoma that is not amenable to curative treatment. The maximum number of patients that will be recruited is 33.

Do you expect your target population to include non-english speaking participants? No

Location of Treatment:

This protocol is performed on an Outpatient basis.

Length of Stay: What is the length & frequency of hospitalization?

This protocol is performed on an Outpatient basis.

Return Visits: How often must participants come to MDACC?

Once every 4 weeks while receiving erlotinib and every 3 months for up to 2 years following treatment.

Home Care: Specify what, if any, treatment may be given at home.

None

Name of Person at MDACC Responsible for Data Management: Cynthia Trainer

Prior protocol at M. D. Anderson:
Has the Principal Investigator ever had a clinical or behavioral protocol at MDACC that accrued patients?
Yes

Data Monitoring Committee:

Is treatment assignment randomized? No

Is this a blinded or double-blinded study? No

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

Please describe:
The Bayesian design allows the trial to be stopped early when data suggest that the treatment is unlikely to be effective.

Radiation Safety:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent?	No
Is the radioactive compound (or drug) FDA approved and/or commercially available?	No

Investigational New Drugs:

Does this protocol require an IND? Yes
Please list the IND holder and provide the IND number:

IND Holder: MDACC
IND Number: TBD

Investigational Device:

Is the Investigational Device approved by the FDA?	N/A
Is the Investigational Device being used in the manner approved by the FDA?	N/A
Has the Investigational Device been modified in a manner not approved by the FDA?	N/A

Name of Device:

Manufacturer:

What is the FDA Status of the Investigational Device?

Is the study being conducted under an Investigational Device Exemption (IDE)? No

IDE Holder:

IDE Number:

Risk Assessment:
Please answer the following questions regarding the Investigational Device.

Intended as an implant?	No
Purported or represented to be for use supporting or sustaining human life?	No
For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health?	No

You may attach sponsor documentation of the risk assessment:

Will participant be charged for the Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor or Supporter? Yes

Sponsor or Supporter: OSI Pharmaceuticals
Type(s) of Support: Funds
Agent
Monitored by Sponsor or Sponsor Represenative (CRO)? No

Is this Protocol listed on any Federal Grant or Foundation Funding Application? 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 stem cells? No

Technology Commercialization:

Does this study include any agents or devices manufactured or produced at MD Anderson Cancer Center? No

Laboratory Tests:

Where will laboratory tests be performed on patient materials? (Please select all that apply)
Division of Pathology & Laboratory Medicine CLIA Certified Laboratory

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