THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Pilot Phase II Study of Erlotinib for the Treatment of Patients with Refractory/Relapsed AML
2012-0060

Core Protocol Information

Short Title	Pilot Phase II - Erlotinib for AML
Study Chair:	Jorge Cortes
Additional Contact:	Jane A. Autry Rachel R. Abramowicz Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-794-5783
Unit:	428
Full Title:	A Pilot Phase II Study of Erlotinib for the Treatment of Patients with Refractory/Relapsed AML
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Terminated 10/25/2018
Version:	09
Submitted by:	Rachel R. Abramowicz--2/27/2018 3:50:31 PM
OPR Action:	Accepted by: Melinda E. Gordon -- 3/2/2018 1:41:38 PM

Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

2012-0060 Protcol Body - FINAL VERSION (09-19-13).docx

A Pilot Phase II Study of Erlotinib for the Treatment of Patients with Refractory/Relapsed AML

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1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the efficacy of erlotinib in patients with refractory or relapsed AML.

1.1.2 To determine the safety and tolerability of erlotinib in this patient population.

1.2 Secondary Objectives

1.2.1 To investigate inhibitory effect of this drug on SYK and its down-stream targets such as JNK, MAPK and Erk.
1.2.2 To evaluate its role in Jak/STAT pathway and to investigate erlotinib-mediated cell death and/or differentiation.
1.2.3 To quantitate concentrations of plasma erlotinib.

2.0 BACKGROUND

Acute myeloid leukemia (AML) is a malignancy of immature granulocytes or monocytes. Malignancy is characterized by accumulation of leukemic blastocytes and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. In the U.S., approximately 11,930 new cases of AML are expected to be diagnosed in 2006, with an estimated 9,040 deaths occurring in the same time period. Almost all newly diagnosed cases, as well as deaths, will be in adults.[1] Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a maintenance phase. Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. Remission rates in adult AML are inversely related to age, with an expected remission rate of >65% for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age.[2]

Standard therapy for hematologic malignancies, particularly acute leukemias, has changed little over the past 20-30 years. This is in part due to the lack of understanding, until recently, of the biology of the disease which has led to little change in the management of these patients. The treatment has been based on combination therapy with standard chemotherapy agents. In acute myeloid leukemia, typically with an anthracycline and cytarabine, and in acute lymphoblastic leukemia with multi-agent therapy. Recent advances in the discovery of important molecular abnormalities has led to the development of new agents that are likely to change the outcome of patients and the standard approach to the treatment of these patients. Some examples are already in clinical practice (eg, the use of all-trans retinoic acid-based therapy for patient with PML/RARα rearrangements) and others are in development with great possibilities of

being approved in the near future (eg, FLT3 inhibitors, alone or in combination with chemotherapy). However, there is urgent need for identification of new therapeutic targets and agents that may be used for these patients.

2.1 Erlotinib

Erlotinib, a potent, selective, and reversible inhibitor of tyrosine kinase activity associated with the HER1/EGFR, has demonstrated tumor growth inhibition both in vitro and in vivo. Erlotinib was designed to target the signaling pathway that mediates the effects of EGFR activation on cell proliferation.

Erlotinib 150 mg orally once daily for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen was approved in the US on 18 November 2004 and in the EU on 19 September 2005, based on data from the randomized, placebo-controlled Study BR.21. This trial demonstrated a statistically significant and clinically meaningful survival benefit, as well as delayed time to deterioration of lung cancer symptoms, in patients who received erlotinib. This indication has now been approved in multiple countries worldwide.

Also, erlotinib 150 mg daily has been approved by European regulatory authorities for use as maintenance therapy in patients with advanced or recurrent NSCLC who had stable disease following 4 cycles of a platinum-based doublet chemotherapy. In the US, erlotinib 150 mg daily is approved for use as maintenance therapy in patients with advanced or recurrent NSCLC who have not progressed after 4 cycles of first-line platinum-based doublet chemotherapy. These indications are based on results from the SATURN study, a multicenter, double-blind, randomized phase 3 study that demonstrated statistically significant and clinically relevant improvement in progression-free survival (PFS) and overall survival (OS).

Two additional phase 3 clinical trials of erlotinib have been completed in NSCLC patients:

- First-line treatment of NSCLC, concurrently administered in combination with carboplatin/paclitaxel (Study OSI2298g); this trial showed no benefit of the addition of erlotinib to first-line chemotherapy for NSCLC.

- First-line treatment of NSCLC, concurrently administered in combination with cisplatin/gemcitabine (Study BO16411); this trial showed no benefit of the addition of erlotinib to first-line chemotherapy for NSCLC.

2.1.1 Adverse Events

As of 15 November 2010, more than 33,000 healthy subjects and cancer patients have participated in company-sponsored and investigator-

sponsored studies; more than 22,000 of these subjects or patients are estimated to have received erlotinib.

The Global Drug Safety Database contains approximately 9243 unique clinical study serious adverse events assessed as related to erlotinib in a total of 5846 patients (see table below).

MeDRA System Organ Class **Preferred Terms**	**Fatal Events**	**Total Events**
Infections and infestations		
Pneumonia, pneumonia primary atypical, lung infections, upper/lower respiratory tract infection, bronchitis	56	230
Cellulitis, infection, abscess, localized infection, folliculitis, skin infection	8	137
Sepsis, staphylococcal sepsis, bacteremia, sepsis syndrome	26	64
Neutropenic sepsis	2	5
Pharyngitis, herpangina, tonsillitis	-	4
Cellulitis orbital	-	1
Endometritis	-	1
Blood and lymphatic system disorder		
Neutropenia, leucopenia, agranulocytosis	5	104
Febrile neutropenia	-	69
Anemia	3	158
Thrombocytopenia	4	73
Pancytopenia, bone marrow failure	2	10
Coagulopathy, disseminated intravascular coagulation, hemorrhagic diathesis	8	15
Hemolytic uremic syndrome, TTP	-	3
Leukocytosis	-	1
Metabolism and nutrition disorders		
Dehydration	7	294
Anorexia, failure to thrive, malnutrition, cachexia	1	243
Hypokalemia	-	34
Other electrolyte imbalance (Na+, Ca++, Mg++, phosphate)	-	86
Hyperglycemia, hypoglycemia	1	18
Psychiatric disorders		
Confusional state, mental status changes, disorientation	-	37
Anxiety	-	2
Depression	-	4
Nervous system disorders		
CVA, cerebral infarction, hemorrhagic stroke, TIA, hemiparesis, cerebral artery embolism	29	93
Headache	1	19
Neuropathy peripheral, paraesthesia	-	14

Lethargy, depressed consciousness	1	19
Aphasia	-	4
Coordination abnormal	-	1
Dizziness, vertigo	-	34
Syncope	-	17
Myasthenia gravis	-	1
Eye disorders		
Keratitis, keratoconjunctivitis sicca/dry eye, punctuate keratitis	-	12
Conjunctivitis	-	14
Ectropion	-	1
Uveitis, iridocyclitis	-	5
Vision blurred, visual disturbance, blindness	1	14
Corneal erosion/ulceration/perforation	-	6
Cardiac disorders		
Acute myocardial infarction, acute coronary syndrome, angina	15	57
Cardiac arrest, cardio-respiratory arrest	15	17
Cardiovascular disorder	2	2
Atrial fibrillation/supraventricular tachycardia/tachycardia	-	27
Cardiac failure acute, cardiac failure congestive, left ventricular failure, left ventricular systolic dysfunction	5	29
Bradycardia	1	4
Vascular disorders		
Deep vein thrombosis, phlebothrombosis, thrombosis, jugular vein thrombosis	-	81
Hypotension, orthostatic hypotension	4	33
Vasculitis, vasculitis necrotizing	-	7
Peripheral embolism, embolism	-	9
Hypertension, hypertensive crisis	-	18
Peripheral ischemia	-	3
Respiratory, thoracic, and mediastinal disorders		
Pneumonitis, interstitial lung disease, bronchiolitis obliterans and organizing pneumonia (BOOP), lung infiltration, alveolitis	198	621
Dyspnea	34	218
Pulmonary embolism	17	107
Respiratory distress, acute respiratory distress syndrome	14	25
Respiratory failure, respiratory arrest	30	37
Anemic hypoxia, hypoxia	3	26
Hemoptysis, pulmonary hemorrhage	18	48
Epistaxis	-	20
Pharyngolaryngeal pain	-	3
Pulmonary fibrosis	1	21
Cough	1	20
Respiratory acidosis	1	1

Gastrointestinal disorders		
Diarrhea	16	873
Vomiting	2	332
Nausea	1	269
Gastrointestinal hemorrhage, melena, hematemesis, rectal bleeding	21	188
Mouth hemorrhage	-	2
Pancreatitis	1	24
Stomatitis, mouth ulceration, glossitis	-	98
Colitis, enterocolitis, cecitis	2	18
Abdominal pain, dyspepsia	2	103
Diarrhea hemorrhagic	-	4
Intestinal ischemia	1	4
Gastric Ulcer/Duodenal Ulcer	1	34
Esophagitis, gastritis	-	33
Intestinal perforation, gastrointestinal perforation, gastrointestinal ulcer perforation, diverticular perforation	14	37
Constipation	-	30
Dysphagia	-	27
Pneumoperitoneum	1	4
Hepatobiliary disorders		
Hyperbilirubinemia	-	51
Cholecystitis	-	8
Jaundice	-	8
Hepatic function abnormal, liver disorder	7	112
Hepatic steatosis	1	2
Hepatitis, hepatic failure, hepatotoxicity	15	31
Skin and subcutaneous tissue disorders		
Rash, dermatitis acneiform, exanthematous pustulosis, dermatitis, exanthema, acne, rash pustular, skin toxicity	-	698
Dermatitis exfoliative	-	31
Dermatitis bullous, blister	1	2
Stevens Johnson syndrome, erythema multiforme, skin necrosis	2	9
Dactylitis	-	2
Pruritus	-	14
Urticaria	-	8
Eczema	-	14
Hyperhidrosis	-	2
Paronychia	-	22
Palmar plantar erythrodysesthesia syndrome	-	14
Alopecia	-	2
Dry skin	-	8

Nail disorder, ingrowing nail, hair growth abnormal	-	8
Musculoskeletal and connective tissue disorders		
Muscular weakness	-	20
Joint swelling	-	1
Myalgia	-	9
Osteonecrosis	-	2
Renal and Urinary disorders		
Renal insufficiency, renal failure, nephrotic syndrome	15	96
Reproductive system and breast disorders		
Vaginal hemorrhage, menorrhagia	-	3
General disorders and administration site conditions		
Fatigue, asthenia, malaise, health deterioration, performance status decreased	16	325
Pyrexia	1	190
Mucosal inflammation	1	53
Pain, chest pain	2	52
Edema, peripheral edema	-	17
Rigors, chills	-	12
Enanthema	-	1
Investigations		
Prothrombin time or INR prolonged	-	34
Liver function test (eg, transaminases, AP) abnormal/increased	-	114
Blood creatinine abnormal/increased	-	24
Blood bilirubin increased	-	26
Weight decreased	1	26
Blood urea increased	-	3
Ejection fraction decreased	-	2
Fecal occult blood positive	-	1
Hemoglobin decreased	-	20
Neutrophil count decreased	-	18
Amylase/Lipase increased	-	7
Injury, poisoning, and procedural complications		
Radiation pneumonitis	2	12

2.2 Rationale for Erlotinib in AML

Recently anecdotal reports have suggested that erlotinib can induce complete remission in patients with acute myeloid leukemia being treated for a concomitant non-small cell lung cancer.[3,4] This was assumed to be an off target effect of erlotinib, but the exact mechanism was not clear. Previous reports had suggested that both gefitinib and erlotinib induced apoptosis in leukemic cell lines and cells obtained from patients with acute myeloid leukemia and myelodysplastic

syndromes, while sparing normal CD34+ cells.[5-8] Gefitinib was also found to have a differentiation effect.[8] Using proteomic and RNA1-based approaches Syk was identified as the off target for these agents in AML.[9] This effect was confirmed using a somewhat specific Syk inhibitor, R406 which demonstrated that Syk inhibition can trigger differentiation of AML and MDS cells.[9] A similar effect was observed with gefitinib.[9] Importantly, Syk mRNA and protein is widely expressed in AML,[10] during B-cell development[11], in myeloid and other hematopoietic cells[12], and in primary CLL lymphocytes[13]. Inhibition of Syk with fostamatinib has also demonstrated significant antileukemia activity in chronic lymphocytic leukemia[14,15] and acute lymphoblastic leukemia[16]. We thus hypothesize that erlotinib may have significant clinical activity in patients with AML, possibly through inhibition of Syk.

3.0 STUDY DESIGN

- This will be a phase II, single-arm, open-label study.

- All patients will receive therapy with erlotinib administered orally as a continuous daily dose in 28-day cycles. Patients will continue therapy until clinically significant progression of the disease or unacceptable toxicity.

- The historical experience in this patient population is that response with standard therapy, when available, is less than 1%. In many instances (eg, patients with myelodysplastic syndrome failing hypomethylating agents), no standard therapy is even available. Thus, an overall response rate of 20% will be considered significant.

4.0 PATIENT SELECTION

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to initiating treatment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion Criteria

4.1.1 Patients with AML who have either been refractory to prior therapy or have relapsed after prior therapy. Patients with MDS or CMML who received therapy with a hypomethylating agent and progress to AML are eligibleif they have received any therapy for MDS and failed (i.e., lack or loss of response) regardless of whether they have received therapy for AML or not. The WHO classification will be used for AML.

4.1.2 Age ≥18 years

4.1.3 ECOG Performance Status ≤2

4.1.4 Adequate liver (total bilirubin ≤2x ULN, ALT ≤2.5x ULN) and renal (creatinine ≤2x ULN) function.

4.1.5 Patients must provide written informed consent.

4.1.6 Patients must have been off chemotherapy for 2 weeks prior to entering this study, unless there is evidence of rapidly progressive disease, and must have recovered from the clinically significant toxic effects of that therapy to at least grade 1. Use of hydroxyurea for patients with rapidly proliferative disease is allowed before the start of study therapy and for the first four weeks on therapy.

4.1.7 Patients – both males and females – with reproductive potential (ie, menopausal for less than 1 year and not surgically sterilized) must practice effective contraceptive measures throughout the study. Women of childbearing potential must provide a negative pregnancy test (serum or urine) within 14 days prior to initiation of study.

4.2 Exclusion Criteria

4.2.1 Patients with known allergy or hypersensitivity to erlotinib.

4.2.2 Patients with any other known disease (except carcinoma in-situ) concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes; cardiovascular disease including congestive heart failure NYHA Class III or IV, myocardial infarction within 6 months, and poorly controlled hypertension; chronic renal failure; or active uncontrolled infection) which, in the opinion of the investigator could compromise participation in the study.

4.2.3 Patients unwilling or unable to comply with the protocol.

4.2.4 Significant gastrointestinal disorders that may interfere with absorption of erlotinib.

4.2.5 Patients who can receive a stem cell transplant within 4 weeks.

5.0 TREATMENT PLAN

5.1 General: All patients should be registered in CORe.

5.2 Treatment Plan: Patients will receive erlotinib therapy according to the suggested guidelines below. Individual minor variations in the initiation of therapy, are acceptable as indicated by patient condition and physician judgment. These variations should be documented in the patient's medical record.

5.2.1 Therapy: Patients will receive erlotinib at a dose of 150 mg orally, once daily in 28-day cycles.

5.2.2 Dose Adjustments: Dose adjustments will be done as described below using the following dose-levels:

Dose Level*	Erlotinib daily dose
0	150 mg
-1	100 mg
-2	50 mg

* Dose escalations/reductions different than those described in this table should be discussed with PI or Co-PI and documentation of the discussion made in the patient's medical record.

6.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITES

6.1 Dose Reduction Criteria for Hematologic Toxicity at Least Possibly Related to Erlotinib

Patients with AML usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemias. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 weeks of therapy unless an adjustment or interruption is considered by the investigator to be in the best interest of the patient. The reason for the variation should be documented in the patient's medical record. After this time, treatment interruptions and dose adjustments may be considered on an individual basis. The following guidelines can be used to consider treatment:

6.1.1 Patients with neutropenia or thrombocytopenia as a consequence of the disease do not require treatment interruptions for myelosuppression. Dose-reductions in these patients should be considered in an individual case and discussed with the PI. The following guidelines can be used for these patients:

6.1.1.1 Patients with a response and pre-cycle counts of neutrophils $>1x10^9$/L and platelets >50 $x10^9$/L who have sustained low counts of neutrophils <0.5 $x10^9$/L or a platelet count <20 x $x10^9$/L (eg, for more than 5 consecutive days) may have treatment interrupted. Upon recovery of counts to neutrophils $>1x10^9$/L and platelets to >50 $x10^9$/L treatment may be re-started with a 1 dose level reduction. A reduction of 2 dose levels may

be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.

6.1.1.2 If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts, may continue treatment regardless of neutrophil and platelet count and give supportive care as needed.

6.1.1.3 If no marrow evidence of leukemia, may hold therapy until recovery of granulocytes to ≥1 $x10^9$/L and platelets ≥ 50 $x10^9$/L, then resume at same or 1 lower dose level according to guidelines mentioned above.

6.2 Dose Reduction Criteria for Non-Hematologic Toxicity at Least Possibly Related to Erlotinib

Toxicity (NCI CTCAE v4.0)	Dose Modification[a]
Diarrhea	
Grade 1 or 2	None. May initiate therapy with loperamide or alternate antidiarrheal. See Section 6.3 for treatment details.
Grade 3[b] or 4[b]	[a)] Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower. If the event does not resolve to ≤grade 2 within 14 days, erlotinib will be discontinued.
Rash	
Grade 1	None
Grade 2	None. *Initiate treatment as outlined in Section 6.3.* If rash persists and is intolerable or worsens over 10 – 14 days, then reduce by 1 dose level.
Grade 3[b]	Reduce by 1 dose level. If rash persists or worsens over 10 – 14 days, then interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower. If the event does not resolve to ≤grade 2 within 14 days, erlotinib will be discontinued.
Grade 4	Permanently discontinue erlotinib.
Interstitial Lung Disease (ILD)	
Any Grade	If ILD possibly related to study drug is suspected, erlotinib should be interrupted immediately pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued permanently and appropriate treatment instituted as necessary.
Other Non-Hematologic Toxicities	
Grade 1 or 2	None
Grade 3[b, c]	Interrupt erlotinib until resolution to ≤ grade 2 and then restart 1 dose level lower.
Grade 4	Permanently discontinue erlotinib

a) Doses that have been reduced 1 dose level for toxicity may be re-escalated to the previous

dose level only if the toxicity abates or returns to baseline severity and the investigator believes it is in the best interest of the patient. Doses that have been reduced 2 dose levels for toxicity may only be re-escalated to the previous dose level (ie, dose level at first reduction) and only if the toxicity abates or returns to baseline severity and the investigator believes it is in the best interest of the patient. Doses that have been reduced 2 or more dose levels for toxicity may not be re-escalated to the starting dose level (or dose-escalated dose for tobacco smokers). Any patient who fails to tolerate treatment at 50 mg/day will be discontinued from the study.

[b] If not responding to optimal treatment within 48 hrs.

[c] Only if ≥ 2 grade level change from baseline

6.3 Suggested Management of Toxicity: The following guidelines are offered as suggestions for the management of toxicity. Variations of these are acceptable based on the patient's individual circumstances and physician preference.

If a patient experiences several toxicities, dose adjustments are to be made based on the greatest degree of toxicity (ie, reducing the dose to the lowest level). If significant toxicity is still apparent, the dose may be reduced a second time. Any patient who fails to tolerate treatment of 50 mg/day will be withdrawn from the study.

Antidiarrheal and antirash medications may be introduced at any time if clinically indicated. Previous phase 1 and 2 studies have demonstrated that the frequency and severity of diarrhea can be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea resolves for 12 hours. Other antidiarrheal medications may be used as clinically indicated.

In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration due to erlotinib therapy, erlotinib should be interrupted and appropriate measures should be taken to intensively treat the dehydration.

Patients may be informed that skin toxicity is to be expected during treatment with erlotinib. Skin toxicity may take the form of dry skin, rash, acneiform eruption, or hair or nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib. Creams and ointments are recommended because they have a greater ability to retain moisture than lotions. Examples of suitable emollient creams include: Neutrogena® Norwegian formula, SARNA® Ultra, Vanicream™, Aveeno® (fragrance-free formulation), and Eucerin® cream. Other over-the-counter aqueous creams or emulsifying ointments may also provide symptomatic benefit. Lotions are not recommended because they often contain alcohol, which may dry the skin. Patients may also be encouraged to use a titanium dioxide or zinc oxide-based sunscreen product applied to sun-exposed areas twice per day.

Patients who develop skin toxicity and are symptomatic may be treated with topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with the topical therapy. A topical immodulating cream such as Elidel could also be considered. For more severe rash, oral corticosteroids may be beneficial. Patients who fail to respond to these measures may have the dose of erlotinib interrupted or reduced. See Annex 5 for more information on skin toxicity management.

Minocycline may interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives should be monitored accordingly.

There have been infrequent reports of serious ILD, including fatal events, in patients receiving erlotinib for the treatment of NSCLC and other advanced solid tumors. In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, where ILD is suspected, study drug should be interrupted pending diagnostic evaluation. If ILD is diagnosed, study drug should be permanently discontinued and appropriate treatment instituted as necessary.

Treatment with erlotinib should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with erlotinib.

Gastrointestinal perforation (including fatalities) has been reported in patients receiving erlotinib. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration ordiverticular disease are at increased risk. Permanently discontinue erlotinib in patients who develop gastrointestinal perforation.

Bullous, blistering and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Interrupt or discontinue erlotinib treatment if the patient develops severe bullous, blistering, or exfoliating conditions.

Ocular Disorders, including corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal ulceration/perforation. Interrupt or discontinue erlotinib therapy if patients present with acute/worsening ocular disorders such as unexplained eye pain.

Erlotinib dosing should be discontinued for any severe toxicity that does not respond to treatment or failure to recover within 14 days from hematological toxicity attributable to erlotinib.

6.4 Dose Escalation

Patients who have had a prior dose reduction of erlotinib and who have no toxicity for at least 1 month of therapy may increase the dose of erlotinib provided they have experienced no grade ≥3 erlotinib-related toxicity. Dose escalation may be done by one dose level at a time and dose escalations should not be done more often than every 28 days. Patients may not escalate to a dose level they received earlier where the patient experienced grade 4 toxicity.

6.5 Supportive Care Guidelines

Supportive measures including erythropoietin, analgesics, blood transfusions, antimicrobials, and hematopoietic colony stimulating factors for treatment of cytopenias are permitted.

Prophylactic use of hematopoietic colony stimulating factors is not permitted.

Other chemotherapy, investigational cytotoxic agents, radiation, or biologic therapy is prohibited while the patient is on study with the following exceptions during cycle 1: During the first 7 days of study only, patients may receive leukaphereses to control elevated blast and/or platelet counts and hydroxyurea is allowed for a maximum of the first 28 days on study. Intrathecal chemotherapy to treat isolated CNS involvement of leukemia is allowable.

6.6 Patients may be taken off study at any time to receive a stem cell transplant as clinically indicated.

7.0 AGENT FORMULATION AND PROCUREMENT

7.1 Formulation

The pharmaceutical preparations of erlotinib are formulations containing the hydrochloride salt. Erlotinib is supplied as tablets containing erlotinib hydrochloride equivalent to 150 mg, 100 mg, and 25 mg of erlotinib. All tablets are round, white, film-coated, bi-convex tablets without markings. Additional information regarding erlotinib can be found in the Tarceva Package Insert. Erlotinib for this trial will be provided as investigational product.

7.2 Packaging and Labeling

Erlotinib tablets are supplied in blue-white, high-density polyethylene (HDPE) bottles of 30 tablets each.

7.3 Storage and Handling

Erlotinib tablets should be stored at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F).

7.4 Administration

Erlotinib tablets should be taken at approximately the same time of day. Each erlotinib dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water, and should be taken 1 hour before or 2 hours after meals. Erlotinib should not be taken with grapefruit or grapefruit juice. The entire dose must be taken at one time. If the patient vomits after taking the tablet(s), the dose is replaced only if the tablet(s) can actually be seen and counted. Missed doses will not be made up. Unused study drug returned by patients should be destroyed in accordance with the institution's policy. Patients will document self-administration by using the MDACC pill diary.

8.0 PATIENT EVALUATION

8.1 Pre-Treatment Evaluation: All pretreatment studies should be obtained within 14 days (±3 days) of entry into the trial, unless otherwise stated.

8.1.1 A complete history and physical, including assessment of baseline adverse events.

8.1.2 CBC, platelet count, differential (differential can be omitted if WBC is $\leq 0.5 \times 10^9$/L).

8.1.3 Creatinine, total bilirubin, ALT.

8.1.4 Pregnancy test (urine or plasma) in females of childbearing potential should be performed within 14 days of initiation of study.

8.1.5 Bone marrow aspirate during the last 14 days preceding study initiation. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose).

8.1.6 Pretreatment optional correlative studies (Appendix A). Every effort will be made to collect all samples at all time points for all patients; however, missing collection in one or more of these time points in occasional patients will not be considered a protocol deviation/violation.

8.1.7 Chest x-ray

8.2 Evaluation During Treatment: All tests are ±5 days unless otherwise specified.

8.2.1 Physical exam after 28 days of therapy (± 7 days), then every 2-3 months.

8.2.2 Assessment of adverse events.

8.2.3 CBC, platelet count, differential once weekly for the first 3 months, then every 2-4 weeks (differential can be omitted if WBC is ≤0.5 $x10^9$/L) until 6 months of therapy, then every 6-8 weeks.

8.2.4 Creatinine, total bilirubin, ALT weekly for the first 3 months, then every 2-4 weeks until 6 months of therapy, then every 6-8 weeks.

8.2.5 Bone marrow aspiration on day 28 (± 7 days), then every 2-3 months for 1 year; then as clinically indicated. Bone marrow aspirations to be performed at MDACC.

8.2.6 Correlative studies (Appendix A). Every effort will be made to collect all samples at all time points for all patients; however, missing collection in one or more of these time points in occasional patients will not be considered a protocol deviation/violation.

8.2.7 For patients that remain on study with no significant toxicity for more than 12 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of correlative studies and other laboratory tests to once every one to three cycles.

8.2.8 For patients receiving concomitant warfarin, PT at least every 4 weeks for the first 6 months or more frequent if clinically indicated; after the first 6 months, PT as clinically indicated.

8.3 End of Treatment Visit

8.3.1 To be completed 30 days (+/- 7 days) after the last dose of study drug.

8.3.2 This visit will consist of a review of symptoms and adverse events. This visit can be done by phone if patient unwilling or unable to do at MDACC.

9.0 CRITERIA FOR RESPONSE

9.1 Response criteria will be modified from the International Working Group for AML (JCO 2003; 21: 4642-9). Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

9.1.1 Complete Remission (CR):

- **Peripheral blood counts:**
  No circulating blasts
  Neutrophil count ≥1.0 $x10^9$/L
  Platelet count ≥100 $x10^9$/L

- **Bone marrow aspirate and biopsy:**
  ≤5% blasts
  No Auer rods
  No extramedullary leukemia

9.1.2 Complete remission with incomplete blood count recovery (CRi):

- **Peripheral blood counts:**
  No circulating blasts
  Neutrophil count <1.0 $x10^9$/L, or
  Platelet count <100 $x10^9$/L

- **Bone marrow aspirate and biopsy:**
  ≤ 5% blasts
  No Auer rods
  No extramedullary leukemia

9.1.3 Partial Remission (PR):

- All CR criteria if abnormal before treatment except:
- ≥50 % reduction in bone marrow blast but still >5%

9.1.4 Morphologic Leukemia-Free State (MLF):

- Bone marrow: ≤5% myeloblasts

9.1.5 Hematologic Improvement (HI): Hematologic response must be described by the number of positively affected cell lines.

- **Erythroid response (E)** (pretreatment Hgb <11 g/dL)
  Hgb increase by ≥1.5 g/dL

- **Platelet response (P)** (pretreatment platelets <100 $x10^9$/L)
  Absolute increase of ≥30 x 10^9/L for patients starting with >20 x 10^9/L platelets, or
  Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%

- **Neutrophil response (N)** (pretreatment ANC <1.0 x10^9/L)
  At least 100% increase and an absolute increase >0.5 x 10^9/L

- **Blast response (B):** at least 50% reduction in blast percentage.

9.1.6 Overall Response: An adequate response, included in the overall response rate (ORR) for this trial will include all of the following obtained within the first 3 months of therapy: CR, CRi, PR, MLF, HI.

10.0 ADVERSE EVENT REPORTING

10.1 Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

10.2 Adverse Events (AEs) will be evaluated according to the CTC AE version 4.0 and documented in medical record. Only unexpected AEs will be recorded in the Case Report Form (CRF). PDMS/CORe will be used as the electronic case report form for this protocol. Adverse events and protocol specific data will be entered into PDMS/CORe. Expected events during leukemia therapy are:

10.2.1 Myelosuppression related events (due to disease or leukemia therapy)

10.2.1.1 febrile or infection episodes not requiring management in the intensive care unit

10.2.1.2 epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage

10.2.1.3 anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia

10.2.2 Disease Related Events

10.2.2.1 Symptoms associated with anemia

10.2.2.1.1 fatigue

10.2.2.1.2 weakness

10.2.2.1.3 shortness of breath

10.2.2.2 electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)

10.2.2.3 chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

10.2.2.4 coagulation abnormalities

10.2.2.5 disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

10.2.2.6 alopecia

10.2.2.7 bone, joint, or muscle pain

10.2.2.8 liver function test abnormalities associated with infection or disease progression

10.2.2.9 disease progression

10.2.2.10 abnormal hematologic values

10.2.3 General Therapy Related Events

10.2.3.1 catheter related events

10.2.3.2 renal failure related to tumor lysis syndrome or antibiotic/ antifungal therapy

10.2.3.3 rash related to antibiotic use

10.2.4 Hospitalization for the management of any of the above expected events

10.3 Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

10.4 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Company:

Serious adverse event will be reported by FAX concurrently to OSI Drug Safety (Fax number: 303-546-7706). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. **Hospitalizations for the management of any expected adverse events (previously described) will not have an expedited report but it will be included in the annual report via the SAE log.**

Pregnancies: Any pregnancy that occurs during study participation or within 4 weeks of the patient's last study drug administration should be reported using the MD Anderson SAE Form. To ensure patient safety each pregnancy must also be reported to OSI and the IND Office within 24 hours of learning of its occurrence.

The Investigator will follow the pregnant female until completion of the pregnancy. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs.

11.0 STATISTICAL CONSIDERATIONS[17]

This is an open-label, to assess the efficacy and safety of erlotinib in patients with AML. The primary efficacy endpoint is overall response as defined in section 9.3.

The historical experience in this patient population is that response with standard therapy, when available, is less than 1%. In many instances (eg, patients with myelodysplastic syndrome failing hypomethylating agents), no standard therapy is even available. Thus, an overall response rate of 20% will be considered significant. For the purpose of this analysis, a response will be considered if occurring after 3 months of therapy (or earlier).

The Simon's optimal two-stage design will be used to implement the study. A total of 29 patients will be enrolled to this study. These sample sizes are based on Simon's optimal 2-stage designs of alpha=0.05 with power of 95% (beta=0.05) to test the null hypothesis that the ORR will be $\leq 1\%$ versus the alternative hypothesis that ORR will be ≥ 20. At the first stage, 14 patients will be enrolled. If no response is observed among the 14 patients, the trial will be terminated early for futility. If one or more patients have response, 15 more patients will be enrolled at the 2^{nd} stage. If at least 2 responses achieved after the completion of the 2^{nd} stage, the study will conclude that the treatment improves the response rate from 1% to 20%. The probability of early termination under the null hypothesis is 87%. The probability of seeing at least 2 responses under the null (ORR = 1%) is 3% while the probability of seeing at least 2 with an event rate of 20% is 94.8%.

Further enrollment will continue during the interim analysis unless no responders (CR+PR+HI) have been reported by the time of enrollment of the 14th subject being analyzed. In this event, enrollment will be suspended and these 14 subjects will be followed to further assess their responses. During this follow-up period, as soon as one response is observed, enrollment will resume. If no response is observed after the 14 subjects have been fully assessed, the trial will be terminated for futility.

11.1 Safety Monitoring

Toxicities will be monitored using the method of Thall, Simon, and Estey [1]. Toxicity is defined as clinically significant, non-hematologic grade 3 or 4 toxicities at least possibly related to erlotinib. We would like to control the rate of clinically significant, non-hematologic grade 3 or 4 toxicities at least possibly

related to erlotinib to be lower than 30% during the 1st 28 days. Using this information a non-informative flat prior distribution of Beta (0.6, 1.4) was chosen for the new combination treatment.

The interim monitoring will be first conducted after the first 10 patients have been evaluated and then be repeated continuously. The monitoring rule for toxicity is $Pr(\theta_{E, Tox} > 0.3 \mid data) > 0.90$, where $\theta_{E, Tox}$ is the proportion of any grade 3 or 4 clinically significant, non-hematologic toxicities at least possibly related to erlotinib. That is, the trial will be terminated if at any time during the study there is a more than 90% chance that the average rate of grade 3 or 4 non-hematologic adverse events is more than 30%.

The stopping boundaries, based on these assumptions and monitoring conditions are shown in Table 1. For example, accrual will be stopped if 6 or more patients experience toxicity among the first 10 patients treated or if 7 or more patients experience toxicity in the first 13 patients.

Table 1: Stop accrual if the number of grade 3 or 4 non-hematologic adverse events is equal to or greater than indicated (i.e., # Grade 3 or 4 toxicity) among the number of patients accrued (i.e., # Patients)

# Grade 3 or 4 toxicity	6	7	8	9	10	11	12
# Patients	10	13	15	18	21	23	26

Table 2 shows the operating characteristics for this stopping rule based on 10000 simulations.

Table 2: Operating characteristics of toxicity monitoring (Based on 10000 simulations)

True Toxicity Probability	**Stop Probability**	**Trial Sample Size Percentile**		
		25%	50%	75%
0.2	3%	29	29	29
0.3	21.50%	29	29	29
0.4	57.50%	11	22	29
0.5	88.50%	10	11	19

11.2 Statistical Analysis

The primary efficacy endpoint is the overall response (ORR) as assessed by investigators and defined in section 9.3. The overall response rate (ORR) will be calculated for Using the intent-to-treat (ITT) data. The corresponding 95% confidence interval will be derived.

Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported.

Additional AE summaries will include AE frequency by AE severity and by relationship to study drug. Adverse events requiring discontinuation of study drug will be summarized separately, both overall and by AE severity and by relationship to study drug. Subjects found to have abnormal values considered clinically significant will be summarized. Laboratory shift tables containing counts and percentages will be prepared by laboratory parameter and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, disease burden, and number of prior therapies) will be summarized. Summary statistics will include: means, standard deviations, and medians for continuous variables and proportions for categorical variables.

For secondary endpoints, descriptive statistics will be used to summarize the expression of biomarkers and the concentrations of plasma erlotinib. The Wilcoxon rank sum test will be used to compare the expressions of biomarkers and concentrations of plasma erlotinib between patients with and without response.

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Appendix A: Pharmacodynamic Investigations During Erlotinib Oral Therapy in Patients with AML Who Have Failed Prior Therapy.

The major objectives of the pharmacokinetic and pharmacodynamic investigations during this clinical trial are as follows:

1. To unveil which one or all three distinct biologic processes are blocked by erlotinib such as cell death by apoptosis, irreversible cell cycle blockade or terminal differentiation in AML[1].
2. To determine the molecular mechanism involved in erlotinib induced off-target effect on numerous cell-cycle proteins and onco-proteins[2].
3. To determine the effect of erlotinib on Syk (a non-receptor tyrosine kinase) inhibition[3], a recently identified novel target of AML.
4. To relate plasma pharmacokinetic and cellular pharmacodynamic endpoints and to seek correlations between these measurements and response to therapy.

Only patients entering at MD Anderson Cancer Center will be studied. All patients with ≥5,000 WBC/μl of peripheral blood will be requested to participate in the cellular pharmacodynamic studies. Patients will sign consent forms to enter these investigations.

Once a patient has consented to participate in the investigation, please contact Ms Yuling Chen (pager 713 404-2550) in The Laboratory of Cellular and Molecular Pharmacology (Dr. Gandhi, phone, 713 792-3336) to coordinate scheduling of blood samples. To facilitate preparedness for laboratory studies, please plan on initiating therapy in the subsequent morning if the clinical situation allows and please inform us as soon as there is a possibility of patient entering the clinical trial.

Blood samples will be collected at the following times during Cycle 1.**

1. 0 (Pre-dose)
2. 6 hour
3. 24 hours
4. Day 5
5. Day 28

Each blood sample will be collected in a Vacutainer green top tube. The samples will be mixed and immediately put on ice-bath. Samples will be brought to Dr. Gandhi's laboratory in the Tan zone (T6.3932). The blood will be centrifuged and plasma will be separated, transferred to storage tubes and immediately frozen, and stored until analysis. After removal of plasma, the blood cells will be resuspended in PBS and CLL lymphocytes will be isolated by Ficoll-Hypaque density-gradient centrifugation procedures. Cells will be used for the following laboratory endpoints.

**Every effort will be made to collect all samples at all time points for all patients; however, missing collection in one or more of these time points in occasional patients will not be considered a protocol deviation/violation.

NOTE: We may not be able to do all studies in every patient. This will be decided based on diagnosis and number of leukemia cells recovered from the peripheral blood sample.

Plasma pharmacokinetics: Plasma will be separated from the peripheral blood samples and analyzed by a reference laboratory for concentration of erlotinib.

Cell death assay: The leukemic blast cells before and during erlotinib therapy (1×10^6 cells) from real-time will be stained with Annexin V-FITC and propidium iodide to determine induction of apoptosis using FACS calibur/flow cytometry machine[2].

Mitochondrial outer membrane permeabilization assay: The leukemic blast cells before and during erlotinib therapy (1×10^6 cells) obtained in real-time will be stained with DIOC6 and propidium iodide to determine the loss of mitochondrial outer membrane polarity using FACS calibur/flow cytometry machine[2].

Assessment of differentiation: Because preclinical studies illustrated either/or effect of apoptosis or differentiation caused by erlotinib in AML cell lines, we will determine if erlotinib can overcome the block of differentiation during erlotinib therapy[1,2]. The leukemic blasts before and during erlotinib therapy (1×10^6 cells) obtained in real-time will be washed and stained with PE-conjugated anti-CD11b antibody (myelomonocytic marker from Becton Dickinson; clone ICRF44) and Isotypic mouse IgG1 (Becton Dickinson) to measure CD11b positive cells using flow cytometry.

Measurement of cell cycle blockade: Phospho-proteome analysis revealed that off target effect of erlotinib can influence the phosphorylation status of numerous proteins including the retinoblastoma (Rb) protein which is critical for G1/S transition of the cell cycle[1]. Therefore, we plan to measure the total and phospho-Rb (Ser-807/811) before and during therapy using immunoblotting technique.

Measurement of JAK/STAT proteins: Erlotinib is known to induce apoptosis via inhibiting the phosphorylation of oncogenic JAK2 kinase on Tyr 1007/1008 in AML cell lines, which otherwise would phosphorylate STAT-5 (Tyr-694), a transcription factor and a direct target of JAK2[1]. Therefore our plan is to measure the JAK2 and STAT-5 proteins and their post-translational modification during erlotinib therapy using immunoblotting experiments.

Measurement of NPM-1 and $p14^{ARF}$: In AML cell lines, the anti-neoplastic action of erlotinib was associated with redistribution of NPM-1 (nucleophosmin-1, a myelomonocytic master regulator) and $p14^{ARF}$ (a tumor suppressor protein) from nucleus to the cytoplasm[1]. So we will be measuring these two proteins by immuno-fluorescence method and immunoblotting experiments by staining with antibodies specific for NPM-1 and $p14^{ARF}$ before and during erlotinib therapy.

Measurement of Syk and the downstream molecules: Two recent important findings, one, erlotinib has off-target effect on Syk tyrosine kinase and two, inhibition of Syk protein induced cytotoxicity in AML - identified Syk as an AML target[4,5]. Therefore our plan is to monitor Syk

phosphorylation during therapy and the consequent modulation in Syk-regulated pathways such as NFKB, PI3-K/AKT[6,7], STAT-3[8], mTOR[9] and MAPK/ERK pathways[10]. In addition, inhibition of BCR-induced Syk activation down-regulates Mcl-1[11], so we will be evaluating the expression and functional role of all the above said proteins during erlotinib therapy.

Correlative Studies References:

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