



DATE: March 29, 2010

FROM: Howard Streicher, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: CC-5013 (Lenalidomide, Revlimid®) and Bevacizumab (rhuMab VEGF), NCI IND Safety Report, AE# 1277486

TO: Investigators Using Lenalidomide (NSC 703813) and Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents bevacizumab and lenalidomide.

The following must be completed by all investigators using bevacizumab under NCI IND 7921 and lenalidomide under NCI IND 70116:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 7921 and IND 70116, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab and lenalidomide, there does not appear to be a change in the risk-benefit ratio for bevacizumab and lenalidomide studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC:

A 67-year old male with multiple myeloma developed grade 3 pneumonitis/pulmonary infiltrates, atrial fibrillation and left ventricular diastolic dysfunction while on a phase 2 study using the investigational agents lenalidomide and bevacizumab in combination with dexamethasone.

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ADVERSE EVENTS ASSESSMENT

IND 70116 7921	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Gr. 3: Pneumonitis/pulmonary infiltrates Gr. 3: Atrial fibrillation Gr. 3: Left ventricular diastolic dysfunction
NSC 703813 704865 CC-5013 Bevacizumab (lenalidomide, (rhuMAB VEGF) Revlimid)	
AE: 1277486	Protocol: 7313

The patient is a 67-year-old male with multiple myeloma who developed pneumonitis/pulmonary infiltrates, atrial fibrillation, and left ventricular diastolic dysfunction (LVDD) while on a phase 2 study using the investigational agents bevacizumab and lenalidomide in combination with dexamethasone. He began his first course of the investigational therapy on August 11, 2008, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, lenalidomide 25 mg PO QD on Days 1-21, and dexamethasone 40 mg PO on Days 1, 8, 15, and 22, every 28 days. The patient received the last dose of bevacizumab on March 9, 2009 (Cycle 8, Day 15), the last dose of dexamethasone on March 2, 2009 (Cycle 8, Day 8), and the last dose of lenalidomide on March 13, 2009 (Cycle 8, Day 19).

The patient was diagnosed with multiple myeloma in September 2004, and is status post chemotherapy and stem cell transplantation (July 2005). He began the investigational study on August 11, 2008.

On March 14, 2009 (Cycle 8, Day 20), the patient presented to the ER with dyspnea and a dry cough. Vital signs upon admission were as follows: temperature 98.2° F, pulse 82 bpm, respiratory rate 22 breaths/minute, blood pressure 171/89 mmHg and oxygen saturation 92% on room air. On examination, the patient was tachypneic, had expiratory wheezing, and his thighs were mottled in appearance. He stated that before coming to the hospital, he had severe mid scapular pain, a fever of 101°F which lasted for a couple of days, then dyspnea. In the ER, the patient was placed on a heart monitor and given oxygen and IV fluids. An ECG revealed normal sinus rhythm with a right bundle branch block with no significant changes since February 2008. A portable chest X-ray was negative for acute cardiopulmonary process. Laboratory reports were significant for: troponin 0.25 ng/mL (reference range of 0.03-0.09 ng/mL) suggestive of myocardial damage with greater levels consistent with MI, BUN 26 mg/dL (reference range: 7-23 mg/dL), creatinine 1.74 mg/dL (reference range: 0.46-1.44 mg/dL), and glucose was 106 mg/dL (reference range: 65-100 mg/dL). Upon admission to the hospital, the patient was started on IV Avelox®, pain medications, antihypertensive medications, aspirin, Lasix®, nebulizer, steroid, and inhaler treatments. Shortly after admission, the patient developed atrial fibrillation, and was started on an amiodarone drip and Ranexa®, and converted to normal rhythm. He was then started on Lovenox® and Coumadin®, and a cardiac consult was ordered.

On March 15, 2009 (Cycle 8, Day 21), the patient's laboratory reports were significant for: potassium 5.1 mEq/L (reference range: 3.5-5.0 mEq/L), BUN 39 mg/dL, creatinine 4.07 mg/dL, glucose 152 mg/dL, and his troponin was 0.41 ng/mL (great than .09 ng/mL is consistent with MI).

A CT scan the next day revealed subtle alveolitis in the upper lobes, an increase in the fine nodular pattern of the lung fields, and coronary artery calcifications. A transthoracic echocardiogram on March 17, 2009, showed mild left ventricular concentric hypertrophy, mild mitral regurgitation, mild aortic valvular insufficiency, and mild tricuspid regurgitation with mild pulmonary hypertension. The left ventricular systolic function was normal, with an ejection fraction of 60%. The left ventricular diastolic function could not be evaluated due to atrial fibrillation. On March 20, 2009 (Cycle 8, Day 26), the patient's cardiac and renal status improved and the patient was discharged to home on oxygen.

During a clinic visit on March 23, 2009 (Cycle 8, Day 29), the patient continued to complain of dyspnea on exertion; his oxygen saturation was 98% on 2 liters of oxygen. A CT scan of the lungs showed

improvement in the alveolar infiltrates. He was removed from the protocol due to his multiple medical problems.

On March 24, 2009, the patient returned to the ER with dyspnea on exertion, a non-productive cough, and complaints of fatigue and occasional nausea. He denied chest pain. Vital signs upon admission were as follows: temperature 97.4° F, pulse 56 bpm, respiratory rate 24 breaths/minute, blood pressure 167/85 mmHg and oxygen saturation was 96%. The patient was given IV Solu-Medrol® and nebulizer treatments which alleviated his symptoms. He was given IV Solu-Medrol® and both albuterol and Atrovent® via nebulizer.

On March 27, 2009, a myocardial perfusion scan was performed which showed an equivocal small zone of reversible ischemia involving the cardiac apex with some fixed thinning of the inferior wall region, with an ejection fraction of 62%. The patient was then discharged home on oxygen. By March 31, 2009, the patient's pulmonary, cardiac, and renal symptoms had improved.

The patient's past medical/surgical history is significant for spinal fractures to thoracic region, prostate carcinoma with radical prostatectomy, tobacco abuse, chronic obstructive pulmonary disease, congestive heart failure, hypertension, transient ischemic attacks, and lung nodules of unknown etiology. Medications taken at the time of the event included metoprolol, Os-Cal®, Bayer aspirin®, and Norvasc®.

There have been and 52 other cases of pneumonitis/pulmonary infiltrates, 27 other cases of atrial fibrillation, and 4 other cases of LVDD reported to the NCI as serious adverse events through ADEERS under the lenalidomide NSC and/or IND as shown in the table below. There have been 156 other cases of pneumonitis/pulmonary infiltrates and 109 other cases of atrial fibrillation reported to the NCI as serious adverse events through ADEERS under the bevacizumab NSC and/or IND as shown in the table below. LVDD is an expected event for bevacizumab.

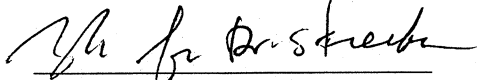
Adverse Event	Grade	Attribution
Lenalidomide (NSC 703813)		
Pneumonitis (n=52)	5	1 Possible, 2 Unlikely
	4	5 Possible, 1 Unlikely
	3	7 Possible, 15 Unlikely, 7 Unrelated
	2	2 Possible, 2 Unlikely
Atrial fibrillation (n=27)	5	1 Possible
	4	2 Possible, 2 Unlikely
	3	1 Probable, 7 Possible, 6 Unlikely
	2	7 Possible, 1 Unlikely
LVDD (n=4)	5	1 Unlikely
	3	1 Possible, 1 Unlikely, 1 Unrelated
Bevacizumab (NSC 704865)		
Pneumonitis (n=156)	5	3 Possible, 11 Unlikely
	4	1 Probable, 8 Possible, 14 Unlikely
	3	1 Definite, 4 Probable, 43 Possible, 41 Unlikely, 13 Unrelated
	2	1 Probable, 3 Possible, 7 Unlikely, 5 Unrelated
Atrial fibrillation (n=109)	1	1 Possible
	4	1 Probable, 16 Possible, 10 Unlikely, 1 Unrelated
	3	4 Probable, 36 Possible, 14 Unlikely, 3 Unrelated
	2	10 Possible, 8 Unlikely, 4 Unrelated
1	2 Unrelated	

To date, a total of 25,481 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC and 2054 patients have been enrolled in NCI-sponsored clinical trials under the lenalidomide IND and/or NSC.


In this case, it is felt that a causal relationship exists between the events and lenalidomide and bevacizumab.

	Pneumonitis/pulmonary infiltrates	LVDD	Atrial fibrillation
Bevacizumab	Possible	Probable	Possible
Lenalidomide	Possible	Probable	Possible
Dexamethasone	Unlikely	Probable	Possible
Multiple myeloma	Unlikely	Unlikely	Unlikely
Coronary artery disease	Unrelated	Probable	Probable

Date: 3/31/10

Signature: 
 Howard Streicher, M.D.
 (IDB Monitor for lenalidomide)

Date: 3/31/10

Signature: 
 Helen Chen, M.D.
 (IDB Monitor for bevacizumab)

If this assessment is changed, we will notify your office.

cc: Arthur Cannon
 Drug Safety: onc_drug.safety@gene.com
 Genentech, Inc.

cc: Twyla Franco
 Neda Bell
 Drug Safety: drugsafety@celgene.com
 Celgene Corporation