



DATE: **OCT 26 2010**

FROM: Howard Streicher, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
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SUBJECT: CC-5013 (lenalidomide, Revlimid®) and PS-341 (bortezomib, Velcade®), NCI IND Safety Report, AE# **1628411**

TO: Investigators Using Lenalidomide (NSC 703813) and Bortezomib (NSC 681239)

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 lenalidomide and bortezomib.

The following must be completed by all investigators using lenalidomide under NCI IND 70116 and/or bortezomib under NCI IND 58443:

- 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 70116 and/or IND 58443, 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 lenalidomide and bortezomib, there does not appear to be a change in the risk-benefit ratio for lenalidomide and bortezomib 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs:

A 35-year-old male with multiple myeloma died unexpectedly while on a phase 3 trial utilizing the investigational agents lenalidomide and bortezomib in combination with dexamethasone.

## ADVERSE EVENTS ASSESSMENT

IND <b>70116</b> NSC <b>703813</b> CC-5013 (lenalidomide, Revlimid®) AE: <b>1628411</b>	58443 681239 PS-341 (bortezomib; Velcade®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # <b>1</b> Event: <b>Gr. 5: Death: NOS</b> Protocol: <b>S0777</b>
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The patient was a 35-year-old male with stage III multiple myeloma who died unexpectedly while on a phase 3 trial utilizing lenalidomide and bortezomib in combination with dexamethasone. He began his first course of treatment on January 16, 2009, and was to receive lenalidomide 25 mg PO daily on Days 1-14, bortezomib 1.3 mg/m<sup>2</sup> IVP on Days 1, 4, 8 and 11, and dexamethasone 20 mg PO on Days 1, 2, 4, 5, 8, 9, 11, and 12, every 21 days. He received the last dose of lenalidomide on February 22, 2009 (Cycle 2, Day 14), the last dose of bortezomib on February 19, 2009 (Cycle 2, Day 11), and the last dose of dexamethasone on February 20, 2009 (Cycle 2, Day 12).

The patient was diagnosed with plasma cell myeloma by bone marrow biopsy in October 2008, after lytic lesions were found on CT scan in September 2008. On December 28, 2008, the patient underwent another bone marrow biopsy which showed hypercellular marrow with overall cellularity greater than 95% and a diffuse atypical mononuclear cell infiltrate. Plasma cells accounted for approximately 61% of nucleated marrow elements by morphologic differential count. A pulmonary function test performed on December 30, 2008, was significant for both mild obstructive and mild restrictive lung defects and a mild decrease in diffusing capacity. On January 2, 2009, he had a normal ECG. He received no prior treatment before starting the investigational treatment on January 16, 2009.

On February 22, 2009 (Cycle 2, Day 14), a call from an unknown source was placed to paramedics reporting that the patient was short of breath. When the paramedics arrived at the patient's home, they found him unresponsive. They initiated cardio-pulmonary resuscitation and transported the patient to the hospital emergency room. Once in the emergency room, copious amounts of gastric contents were suctioned from the patient's airway before the patient could be intubated. Resuscitative efforts were continued but were unsuccessful. The patient was pronounced dead at 10:39 pm and his family was notified. No autopsy was performed.

The patient's past medical/surgical history is significant for cholecystectomy secondary to gallstones, sickle cell trait, gout, and a solitary kidney. Medications taken at the time of the event included morphine, oxycodone, and Lortab®.

There have been 10 other cases of death NOS, and 5 other cases of sudden death reported to the NCI as serious adverse events through AdEERS under the lenalidomide NSC and/or IND, and 47 other cases of death NOS and 9 other cases of sudden death reported to the NCI as serious adverse events through AdEERS under the bortezomib NSC and/or IND, which are summarized in the following table:

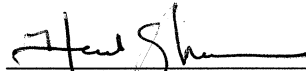
Adverse Event	Grade	Attribution
<b>Lenalidomide (NSC 703813)</b>		
Death: NOS (n=10) Death: Sudden (n=5)	5	8 Unlikely, 2 Probable 3 Unlikely, 2 Possible
<b>Bortezomib (NSC 681239)</b>		
Death: NOS (n=47) Death: Sudden (n=9)	5	18 Unrelated, 28 Unlikely, 1 Possible 8 Unlikely, 1 Possible

A total of 2,240 patients have been enrolled in NCI-sponsored clinical trials under the lenalidomide IND and/or NSC, and a total of 3,231 patients have been enrolled under the bortezomib IND and/or NSC.

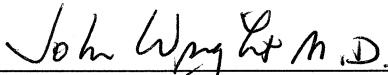
In this case, it is felt that a possible causal relationship between the event and lenalidomide or bortezomib therapy cannot be excluded.

	<b>Death: NOS</b>
<b>Lenalidomide</b>	Possible
<b>Bortezomib</b>	Possible
<b>Dexamethasone</b>	Possible
<b>Myeloma, NOS</b>	Probable
<b>Undiagnosed pulmonary embolism, cardiac arrhythmia, or sepsis</b>	Possible

Date: 10/13/10

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

Date: 10/22/10

Signature:   
John Wright, M.D., Ph.D.  
(IDB Monitor for bortezomib)

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

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