



**DATE:** March 17, 2010  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
*L. Austin Doyle MD*  
**SUBJECT:** CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1963044  
**TO:** Investigators Using CCI-779 (temsirolimus, Torisel®) (NSC 683864)

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 agent temsirolimus.

The following must be completed by all investigators using temsirolimus under NCI IND 61010.

- 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 61010, 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 temsirolimus, there does not appear to be a change in the risk-benefit ratio for temsirolimus, 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 63-year-old female with endometrioid endometrial adenocarcinoma developed grade 3 decreased carbon monoxide diffusion capacity ( $DL_{CO}$ ) and grade 2 decreased forced expiratory volume ( $FEV_1$ ) while on a phase 2 trial utilizing the investigational agent temsirolimus.

**ADVERSE EVENTS ASSESSMENT**

IND <b>61010</b> NSC <b>683864</b> CCI-779 (temsirrolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> Event: <b>Gr. 3: Carbon monoxide diffusion capacity (DL<sub>CO</sub>)</b> <b>Gr. 2 FEV<sub>1</sub></b> Protocol: <b>GOG-0248</b>
AE: <b>1963044</b>	

The patient is a 63-year-old female with endometrioid endometrial adenocarcinoma who developed decreased carbon monoxide diffusion capacity (DL<sub>CO</sub>) and decreased forced expiratory volume (FEV<sub>1</sub>) while on a phase 2 trial utilizing the investigational agent temsirolimus. She began the first course of the investigational therapy on June 26, 2009, receiving temsirolimus 25 mg IV over 30 minutes weekly, every 6 weeks. She received her last dose of temsirolimus on July 31, 2009 (Cycle 1, Day 36).

The patient was initially diagnosed with endometrioid endometrial adenocarcinoma in May 2009, and is status post total abdominal hysterectomy and bilateral salpingo-oophorectomy. She began the investigational therapy on June 26, 2009.

On August 3, 2009 (Cycle 1, Day 39), a restaging CT scan of the chest with contrast revealed interval development of the lower lobe predominant lung disease which was thought to represent drug reaction, aspiration, or infection. The patient presented to the clinic on August 6, 2009 (Cycle 1, Day 42), and reported dyspnea on exertion when climbing 1 flight of stairs and with walking 1.5 blocks since the initiation of the investigational therapy. She also reported the beginning of an upper respiratory illness with a 5-day history of productive cough. The patient denied chest pain, wheezing, and problems with breathing prior to her diagnosis with cancer. Physical examination revealed good respiratory effort and diffuse mild crackles with decreased breath sound at the lung bases. The study drug was held pending results of a pulmonary function test (PFT).

On August 10, 2009 (Cycle 1, Day 46), a PFT showed: an FEV<sub>1</sub> that was 70% of predicted value; a DL<sub>CO</sub> that was 58% of predicted value which could reflect interstitial lung disease, emphysema, pulmonary vascular disease, or anemia; reduced forced vital capacity; and a significant underestimation of the total lung capacity which suggested that airflow obstruction was present. Another possibility was that the pattern of lung volumes represented respiratory muscle weakness. At a follow-up evaluation on August 20, 2009, she complained of fatigue, chills, and continued dyspnea on exertion. On physical examination, she appeared to be in no apparent distress despite decreased breath sounds at her lung bases. The study drug was further held. A repeat PFT on August 21, 2009 (Cycle 1, Day 57), showed an FEV<sub>1</sub> that was 69% of predicted value, a DL<sub>CO</sub> that was 47% of predicted value, and declining total lung capacity. It was thought that the patient had mild restrictive lung disease with at least moderate obstructive airway disease and a pattern consistent with respiratory muscle weakness. The patient was removed from the protocol. PFTs from October 5, 2009, revealed an FEV<sub>1</sub> 63% of predicted value and a DL<sub>CO</sub> at 47% of predicted value; it was felt that there was a restrictive defect based on the lung volumes indicating parenchymal involvement possible from drug toxicity. She returned on October 8, 2009, reporting a significant increase in her symptoms (becoming very short of breath at work) and a 4 pound weight loss since her last visit. The patient had recently completed a course of Medrol Dosepak® prior to this visit. Her oxygen saturation was 90-91% on room air, and she desaturated to 79% after walking 600 feet in the clinic. She was given an influenza vaccination, and started on home oxygen at 3 liters and prednisone for 4 weeks. A repeat CT scan of the chest with contrast on October 14, 2009, showed significant progressive interval increase in the lower zone hypersensitivity and drug-related interstitial pneumonitis.

On October 22, 2009, her oxygen saturation was 87-94% on room air. The patient was able to perform her activities of daily living without dyspnea, except that she required periods of rest after these activities.

She had gained 4 pounds, and her appetite was improved. The prednisone dose was decreased and she was started on Bactrim<sup>®</sup> prophylaxis. On November 5, 2009, the patient was noted to be improving on the prednisone and oxygen therapy. The plan was to continue the treatment for 3 to 6 months with continuing evaluation.

The patient's past medical/surgical history is significant for hypertension, 11 years of constant second-hand tobacco exposure, and ex-smoker of 1½ packs per day for 5 years. The patient worked in a metal factory for 10 years and she has occupational exposure given that she works in environmental services. Medications taken at the time of the event included Norvasc<sup>®</sup>, hydrochlorothiazide, aspirin, and iron sulfate.

There have been no other cases of decreased DL<sub>CO</sub> and FEV<sub>1</sub> reported as serious adverse events through AdEERS under the temsirolimus NSC and/or IND.

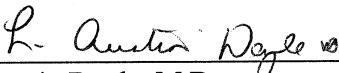
To date, a total of 1,935 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a probable relationship exists between the events and the investigational agent.

	Decreased DL <sub>CO</sub>	Decreased FEV <sub>1</sub>
<b>Temsirolimus</b>	Probable	Probable
<b>Endometrioid endometrial adenocarcinoma</b>	Unlikely	Unlikely

Date: 3/18/10

Signature:

  
L. Austin Doyle, M.D.  
(IDB Monitor for temsirolimus)

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

cc: Rafael E. Curiel, Ph.D.  
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Wyeth Pharmaceuticals, Inc.