



**DATE:** November 10, 2009  
*L. Austin Doyle*  
**FROM:** L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
**SUBJECT:** CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# 1699372  
**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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 64-year-old female with endometrioid endometrial adenocarcinoma suddenly expired while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with hormonal therapy.

**ADVERSE EVENTS ASSESSMENT**

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®) AE: 1699372	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 5: Death not associated with CTCAE term: Sudden death Protocol: GOG-0248
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The patient was a 64-year-old female with endometrioid endometrial adenocarcinoma who suddenly expired while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with hormonal therapy. She began the first course of the investigational therapy on June 15, 2009, receiving megestrol acetate 80 mg by mouth twice daily for 3 weeks followed by, tamoxifen 20 mg by mouth twice daily for 3 weeks plus temsirolimus 25 mg IV over 30 minutes weekly, every 6 weeks. She received her last dose of temsirolimus on August 31, 2009 (Cycle 2, Day 36), the last dose of megestrol acetate on August 17, 2009 (Cycle 2, Day 22), and the last dose of tamoxifen on September 1, 2009 (Cycle 2, Day 37).

The patient was initially diagnosed with endometrioid endometrial adenocarcinoma in May 2006, and is status post debulking surgery and multiple-agent systemic chemotherapy. She began the investigational therapy on June 15, 2009.

On August 31, 2009 (Cycle 2, Day 36), the patient presented to the infusion clinic for treatment. Her vital signs were 37.2° C, pulse 62 bpm, respiration 18 breaths per minute, blood pressure 145/65 mmHg, and oxygen saturation 91% on room air. The patient offered no complaints and denied nausea, vomiting, and diarrhea. She was assessed as being in good condition and able to receive treatment. The patient tolerated the treatment without incident and was discharged ambulatory in a stable condition, accompanied by her family. On September 1, 2009, the patient had dinner with her brother and was observed to be tired. On September 2, 2009 (Cycle 2, Day 38), the research staff received a call from the Salt Lake Police Department informing them that the patient was found dead in her bed by a family member. There is no further information about the cause of the patient's death. The family has declined an autopsy.

The patient's past medical/surgical history is significant for hypertension, diabetes, diabetes- and chemotherapy-induced bilateral neuropathy in feet, hyperlipidemia, glaucoma, cataracts, deep venous thrombosis, osteoarthritis in multiple joints, bilateral total hip replacement, and bilateral vitrectomy secondary to diabetic retinopathy. Medications taken at the time of the event included Benadryl®.

There have been 4 other cases of sudden death and 20 other cases of death NOS reported as serious adverse events through ADEERS under the temsirolimus NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Death not associated with CTCAE term: Sudden death (n=4)	5	3 Unlikely 1 Unrelated
Death not associated with CTCAE term: Death NOS (n=20)	5	3 Possible 7 Unlikely 10 Unrelated

To date, a total of 1,782 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

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

	<b>Death not associated with CTCAE term: Sudden death</b>
<b>CCI-779 (temsirolimus, Torisel®)</b>	Possible
<b>Megestrol acetate</b>	Possible
<b>Tamoxifen</b>	Possible
<b>Endometrioid endometrial adenocarcinoma</b>	Possible

Date: 11/12/09

Signature: L. Austin Doyle MD  
L. Austin Doyle, M.D.  
(IDB Monitor for CCI-779)

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

cc: Rafael E. Curiel, Ph.D.  
Wyeth GSSE Triage, [WASDTRI@wyeth.com](mailto:WASDTRI@wyeth.com)  
Wyeth Pharmaceuticals, Inc.