



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: January 16, 2009
To: NCCTG Primary Clinical Research Associates
From: Janis Wobschall
Re: N027D, "A Phase I Study of CCI-779 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme"

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with CCI-779 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1203511_F1

Please note that all risks currently cited in the NCCTG consent form can not be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Wobschall at wobschall.janis@mayo.edu or 507-284-4852.

JW/kjm
enclosure



DATE: January 5, 2009
FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (Temsirrolimus, Torisel®) IND Safety Report, AE# 1203511
TO: Investigators Temsirolimus, 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 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 73-year-old female with primary peritoneal carcinoma experienced grade 3 dehydration while on a phase 2 trial utilizing the investigational agent temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 61010	ADVERSE EXPERIENCE REPORT NO.
NSC 683864	IND Safety Report: #1
CCI-779 (temsirolimus, Torisel®)	Event: Gr. 3: Dehydration
AE: 1203511	Protocol: GOG-0170I

The patient is a 73-year-old female with primary peritoneal carcinoma who experienced dehydration while on a phase 2 trial utilizing the investigational agent temsirolimus. She began the first course of the investigational therapy on July 31, 2008, receiving temsirolimus 25 mg IV over 30 minutes weekly, every 28 days. The patient received her last dose of temsirolimus on October 22, 2008 (Cycle 4, Day 1).

The patient was initially diagnosed with primary peritoneal carcinoma of the pelvis in February 2007, and is status post multiple systemic agent chemotherapy. She began investigational therapy on July 31, 2008.

On October 22, 2008 (Cycle 4, Day 1), the patient presented for her scheduled treatment in a wheelchair complaining of weakness, fatigue, tooth and ear pain, and urinary symptoms which included dysuria, frequency, and urgency. During the physical examination, she was weak and found it difficult to sit up. Her performance status was grade 2, and she had a Karnofsky performance score (KPS) of 60%. It was felt that a recent tooth extraction may have contributed to her pain and weakness. Her family reported some mental status changes. Urinalysis results showed a urinary tract infection, and she was started on Macrobid® for 10 days. The patient received her treatment as scheduled and was also hydrated with an extra liter of IV fluid.

On October 31, 2008 (Cycle 4, Day 10), the patient was seen in the outpatient oncology clinic complaining of a dry, constant cough and fever, and was observed to be dehydrated. Her laboratory results from the previous day showed a potassium level of 2.6 mEq/L (reference range: 3.5-5.1 mEq/L) and 3.3 mEq/L on this visit. (Please see the table below.) She was admitted to the hospital with a temperature of 102.4° F, pulse 101 bpm, blood pressure 147/81 mmHg, and an oxygen saturation of 100% on room air. A noncontrast CT scan of the head, performed to evaluate the patient's mental status changes, was negative. A CT angiography of the chest on November 2, 2008, showed intermittent sites of ill-defined infiltrates throughout both lungs; bilateral pleural effusions; ground-glass mid-upper lung infiltrate; and a few, nonspecific <1 cm lymph nodes in the mediastinum. The patient was treated with IV antibiotics, IV fluids with potassium replacement, and Tylenol® for her fever. She also received 2 units of packed red blood cells. The patient was afebrile on November 1, 2008, but had another temperature spike on November 5, 2008. A CT scan of the chest, abdomen and pelvis on November 6, 2008, revealed an interval decrease in the bilateral pleural fluid and no acute abdominal abnormalities; there was also an interval decrease in the size of the periaortic lymph node when compared to a September 2008 study. Her condition improved, her potassium was stable at 3.8 mEq/L, and she was discharged home on November 8, 2008 (Cycle 4, Day 18). The patient was seen for follow-up on November 26, 2008 (Cycle 4, Day 36), and was found to be doing well; as she had apparent complete radiological response to treatment, it was decided that she would discontinue treatment at this point and follow-up in 3 months.

The patient's past medical/surgical history is significant for ovarian cancer, appendectomy, left breast biopsy, and port placement. The patient's brother has colon cancer. Medications taken at the time of the event included Coumadin®, Zofran®, Lasix®, Compazine®, Atarax®, and multivitamins.

Pertinent laboratory values are shown in the table below:

	7/24/08 Baseline	10/30/08	10/31/08 Admission	11/2/08	11/4/08 C4, D14	11/7/08 C4, D17	11/8/08 C4, D18
WBC (reference range: 4.8-10.8 × 1000/mm ³)	3.6	*	5.0	5.9	5.8	6.8	6.8
Hemoglobin (reference range: 12.0-16.0 g/dL)	11.7	*	8.5	11.6	11.2	11.2	10.6
Chloride (reference range: 98-107 mEq/L)	101	96	104	105	100	102	*
BUN (reference range: 7-18 mg/dL)	16	18	10	4	6	7	*
Creatinine (reference range: 0.51-0.95 mg/dL)	1.0	1.10	0.99	0.80	1.07	0.85	0.8
Sodium (reference range: 136-145 mEq/L)	136	136	138	138	139	135	*
Potassium (reference range: 3.5-5.1 mEq/L)	3.8	2.6	3.3	3.6	2.9	4.0	3.8

* = Not Done

There have been 51 other cases of dehydration reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC as shown in the table below.

Adverse Event	Grade	Attribution
Dehydration (n=51)	4	1 Possible, 1 Unrelated
	3	5 Possible, 20 Unlikely, 10 Unrelated, 1 Probable
	2	1 Possible, 10 Unlikely, 2 Unrelated

To date, a total of 1437 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus NSC.

In this case, it is felt that a possible causal relationship between the dehydration and temsirolimus therapy cannot be excluded.

	Dehydration
Temsirolimus	Possible
Primary peritoneal carcinoma	Unlikely

Date: 1/6/09

Signature: *L. Austin Doyle*

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.
Elizabeth Watts
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Wyeth Pharmaceuticals, Inc.