



DATE: June 25, 2009

FROM: *L. Austin Doyle mo*
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SUBJECT: CCI-779 (Temsirolimus, Torisel[®]) and Bryostatin IND Safety Report, AE# 1450004

TO: Investigators Using CCI-779 (Temsirolimus, Torisel[®]) (NSC 683864) and Bryostatin (NSC 339555)

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 temsirolimus and bryostatin.

The following must be completed by all investigators using temsirolimus under NCI IND 61010 and bryostatin under NCI IND 42780:

- 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 or 42780, 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 and bryostatin, there does not appear to be a change in the risk-benefit ratio for combination studies of temsirolimus and bryostatin; 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 55-year-old male with metastatic renal cell carcinoma experienced grade 3 renal failure and a grade 3 elevated creatinine while on a phase 1 study utilizing the investigational agents temsirolimus and bryostatin.

ADVERSE EVENTS ASSESSMENT

IND 42780	61010	ADVERSE EXPERIENCE REPORT NO.
NSC 339555	683864	IND Safety Report: # 1
Bryostatin	CCI-779	Event: Gr. 3: Renal failure
	(temsirolimus, Torisel®)	Gr. 3: Creatinine
AE: 1450004		Protocol: 5785

The patient is a 55-year-old male with renal cell carcinoma who experienced an elevated creatinine and renal failure while on a phase 1 trial utilizing the investigational agents bryostatin and temsirolimus. He began the first course of the investigational therapy on March 3, 2009, receiving bryostatin 20 mcg/m² IV over 1 hr on Day 1, bryostatin 20 mcg/m² IV over 1 hr on Days 8, 15, and 22, and temsirolimus 37.5 mg IV over 30 minutes on Days 8, 15, and 22 for Cycle 1 which was 35 days. Starting with Cycle 2, he was to receive Bryostatin 20 mcg/m² IV over 1 hour on Days 1, 8, and 15 and temsirolimus 37.5 mg IV over 30 minutes on Days 1, 8, and 15, every 28 days. The patient received his last doses of temsirolimus and bryostatin on March 24, 2009 (Cycle 1, Day 22).

The patient was initially diagnosed with metastatic clear cell renal carcinoma with metastases to the right scapula, mediastinum, and left clavicle in July 2008, and is status post left nephrectomy, adrenalectomy, lymph node dissection and chemotherapy. An MRI of the brain performed in August 2008 showed an extra-axial left parietal mass, most likely a meningioma. He began the investigational therapy on March 3, 2009.

On March 24, 2009 (Cycle 1, Day 22), the patient presented to the clinic for evaluation when laboratory findings showed a creatinine of 2.58 mg/dL (reference range: 0.64-1.27 mg/dL), BUN of 24 mg/dL (reference range: 9-20 mg/dL), and GFR of 26 mL/min/1.73 m² (reference range: >59 mL/min/1.73 m²), increased from his baseline of 0.98 mg/dL, 14 mg/dL, and >60 mL/min/1.73 m² respectively in February 2009. A renal ultrasound showed an unremarkable solitary right kidney. It was felt that his increased usage of ibuprofen over the last month may have contributed to his rise in creatinine. The patient was instructed to discontinue all ibuprofen and instead use Percocet® to manage his pain. If he felt the need to use Extra Strength Tylenol®, he should limit the total dose to less than 3 grams daily.

On March 31, 2009 (Cycle 1, Day 30), the patient was admitted to the hospital complaining of fatigue, chills, weight loss, and pruritus. The laboratory results showed the following: BUN of 48 mg/dL, creatinine of 4.52 mg/dL, and a GFR of 14 mL/min/1.73 m². The renal ultrasound was essentially unremarkable showing a right kidney of 13.9 cm in size likely due to compensatory hypertrophy. All non-steroidal anti-inflammatory drugs were held, and he was treated aggressively with IV hydration and bicarbonate. Dialysis was considered an option if the patient's condition did not improve. His condition did improve, however, and the patient was discharged home on April 3, 2009 with a BUN of 35 mg/dL, creatinine of 3.22 mg/dL, and GFR of 20 mL/min/1.73 m². He was advised to discontinue the Percocet, ACE inhibitor (Altace®), and ibuprofen, and was given information on low potassium diets and medications which can precipitate renal failure. Dilaudid® was prescribed to control the pain.

The patient was seen for follow-up on April 7, 2009 (Cycle 1, Day 36), complaining of pain and fatigue. He was unable to fill the Dilaudid® prescription. His BUN was 21 mg/dL, creatinine 2.57 mg/dL, and GFR 26 mL/min/1.73 m². The investigational therapy was held with the intention of doing serial creatinines. If the creatinine levels normalized within 2 weeks the patient would restart the treatment as per protocol; otherwise he might have to be taken off the study.

The patient's past medical/surgical history is significant for tobacco abuse for the past 35 years, tachycardia, hypertension, hypercholesterolemia, status post excision of a lipoma on the right anterior chest, and vasectomy. The patient's family history is significant in that his maternal grandmother had breast cancer and his mother had metastatic breast cancer and died shortly thereafter. Medications taken

at the time of the event included Zometa[®], Altace[®], lovastatin, metoprolol, ibuprofen, Senokot[®], and Percocet[®].

There have been 19 other cases of renal failure and 35 other cases of creatinine reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND, and 6 other cases of renal failure and 20 other cases of creatinine reported to the NCI as serious adverse events through AdEERS under the bryostatin NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Temsirolimus		
Renal failure (n=19)	5	1 Unrelated, 1 Unlikely
	4	3 Unrelated, 1 Probable
	3	3 Unrelated, 9 Unlikely, 1 Possible
Creatinine (n=35)	4	2 Unlikely
	3	4 Unrelated, 6 Unlikely, 1 Probable
	2	1 Unrelated, 10 Unlikely, 8 Possible, 2 Probable
	1	1 Unrelated
Bryostatin		
Renal failure (n=6)	5	1 Unrelated
	4	1 Unlikely
	3	2 Unrelated, 2 Unlikely
Creatinine (n=20)	3	2 Unrelated, 3 Unlikely
	2	3 Unrelated, 8 Unlikely
	1	4 Unlikely

To date, a total of 1678 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC, and a total of 1310 patients have been enrolled in NCI-sponsored clinical trials under the bryostatin IND and/or NSC.

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

	Renal failure	Creatinine
Temsirolimus	Possible	Possible
Bryostatin	Unlikely	Unlikely
Renal cell carcinoma	Unrelated	Unrelated

Date: 6/26/09

Signature: L. Austin Doyle MD

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

Date: 06.29.09

Signature: S. Percy Ivy, M.D.

S. Percy Ivy, M.D.
(IDB Monitor for bryostatin)

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

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