



DATE: April 4, 2010

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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L. Austin Doyle

SUBJECT: IMC-A12 (HuMAb IGF-1R) and CCI-779 (temsirolimus, Torisel®) IND Safety Report, AE# **1586021**

TO: Investigators Using Temsirolimus (NSC 683864) and IMC-A12 (NSC 742460)

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 INDs 61010 and 100947

- 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 100947, 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 IMC-A12, 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 57-year-old female with metastatic uterine carcinoma experienced grade 4 renal failure, grade 4 pleural effusion and death NOS while on a phase 1 trial utilizing the investigational agents temsirolimus and IMC-A12.

and ordered to continue dialysis on an outpatient basis. Hospice services were contacted at the time of discharge. According to family members, the patient expired on August 5, 2009.

Pertinent laboratory values are shown in the table below.

	4/27/09 Baseline	5/5/09 C1, D8	6/11/09	6/16/09	6/26/09	6/30/09 C3, D7	7/6/09 Admission C3, D14	7/11/09 Dialysis C3, D19	7/24/09 Off- study
BUN (reference range: 10-20 mg/dL)	23	35	19	29	28	40	52	25	45
Creatinine (reference range: 0.5-1.1 mg/dL)	1.3	2.4	1.5	1.3	1.2	2.5	2.2	3.2	4.0
Carbon dioxide (reference range: 25-30 mEq/L)	23	22	20	31	22	22	18	28	26
Potassium (reference range: 3.5-5 mmol/L)	4.5	5.1	5.5	4.3	5.2	5.2	5.7	3.8	4.4

The patient's past medical and surgical history include type 2 diabetes mellitus and morbid obesity. Medications taken at the time of the event included Tessalon Perles[®], Lovenox[®], Nexium[®], TriCor[®], Hycodan[®], detemir insulin, regular insulin, ipratropium bromide, levalbuterol, ciclesonide, Omega-3[®], pilocarpine, Actos[®], ropinirole, magnesium protein complex, voriconazole, Ambien[®], and Bactrim[®]. Note that the patient was on Diovan[®] from June 16, 2009, to July 7, 2009, and on Bactrim[®] from June 9, 2009, to July 7, 2009.

There have been 20 other cases of renal failure, 20 other cases of death NOS, and 5 cases of sudden death reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND, and 2 other cases of renal failure and 2 other cases of death NOS reported to the NCI as serious adverse events through AdEERS under the IMC-A12 NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Temsirolimus		
Death, NOS (n=20)	5	10 Unrelated, 7 Unlikely, 3 Possible
Sudden death (n=5)	5	1 Unrelated, 3 Unlikely, 1 Possible
Renal failure (n=20)	5	1 Unrelated, 1 Unlikely
	4	3 Unrelated, 1 Probable
	3	4 Unrelated, 8 Unlikely, 1 Possible, 1 Probable
IMC-A12		
Death, NOS (n=2)	5	1 Unlikely, 1 Possible
Renal failure (n=2)	4	1 Unlikely, 1 Possible

To date, a total of 1935 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC, and a total of 345 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC.

In this case, it is felt that death was likely due to renal failure and progressive disease, and that a possible causal relationship exists between the renal failure and the investigational therapy.

	Death, NOS	Renal failure	Pleural Effusion
Temsirolimus	Unlikely	Possible	Unlikely
IMC-A12	Unlikely	Possible	Unlikely
Solid tumor, NOS: Uterine	Possible	Unlikely	Definite

Atherosclerosis	Possible	Possible	NA
Dehydration	N/A	Possible	NA
Renal Failure	Probable	N/A	Possible
Concomitant medication	Unlikely	Possible	NA

Date: 4/7/10

Signature: 

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

Date: 4/5/10

Signature: 

Helen Chen, M.D.
(IDB Monitor for IMC-A12)

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

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