



**DATE:** OCT 12 2010

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

**SUBJECT:** IMC-A12 (HuMAb IGF-1R; A12) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1097524

**TO:** Investigators Using IMC-A12 (NSC 742460) and 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 agents IMC-A12 and temsirolimus.

The following must be completed by all investigators using IMC-A12 under NCI IND 100947 and 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 INDs 100947 or 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 IMC-A12 and temsirolimus, there does not appear to be a change in the risk-benefit ratio for IMC-A12 and 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 78-year-old male with metastatic adrenal leiomyosarcoma developed grade 3 dysphagia while on a phase 2 trial utilizing the investigational agents IMC-A12 and temsirolimus.

## ADVERSE EVENTS ASSESSMENT

IND <b>100947</b> NSC <b>742460</b> <b>IMC-A12 (HuMAb</b> <b>IGF-1R)</b> AE: <b>1097524</b>	<b>61010</b> <b>683864</b> <b>CCI-779</b> <b>(temsirolimus, Torisel®)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 3: Dysphagia</b> Protocol: <b>8121</b>
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The patient is a 78-year-old male with metastatic adrenal leiomyosarcoma who developed dysphagia while on a phase 2 trial utilizing the investigational agents IMC-A12 and temsirolimus. He began the first course of the investigational therapy on May 27, 2010, receiving temsirolimus 25 mg IV over 30 minutes weekly and IMC-A12 6 mg/kg IV over 1 hour weekly, every 6 weeks. He received his last doses of temsirolimus and IMC-A12 on June 17, 2010 (Cycle 1, Day 22).

The patient was diagnosed with adrenal leiomyosarcoma in July 2006, and is status post right adrenalectomy; single-agent systemic chemotherapy from October 2008 to January 2009 and from August 2009 to April 2010; and multiple-agent systemic chemotherapy from February to July 2009. Liver and lung metastases were noted in 2008. He started the investigational treatment on May 27, 2010.

On June 24, 2010 (Cycle 1, Day 29), the patient presented to the clinic with failure to thrive and pain in the abdomen, back, and scalp. The study drugs were held, and he was treated with IV hydration, oxycodone, and Tylenol®.

On June 28, 2010 (Cycle 1, Day 33), the patient was admitted to the hospital for early satiety, difficulty in swallowing, nausea, and vomiting. He reported a 1-week history of intermittent lower abdominal pain, anorexia, a 4-day history of non-bloody diarrhea, and worsening abdominal gas. He had mild epigastric tenderness on examination. An abdominal X-ray showed no evidence of obstruction. He was started on IV fluids, and low-dose Marinol®.

On June 29, 2010 (Cycle 1, Day 34), normal swallow study was unremarkable, and regular diet as tolerated was recommended. Later that day, an upper gastrointestinal endoscopy revealed a normal esophagus, hiatus hernia, and diffuse mild mucosal abnormality characterized by erythema in the duodenal bulb, which was considered unrelated to the study drugs. However, the dysphagia was deemed possibly related to the investigational treatments, and the patient was removed from the protocol on June 30, 2010.

By July 2, 2010, the patient was on a regular diet, and he was discharged home that day in stable condition. On August 5, 2010, during a follow-up visit at the clinic, the patient was noted to have gained weight. The plan at this time was for the patient to follow up in 2 weeks.

The patient's past medical and surgical history is significant for transient ischemic attack versus lacunar infarcts, hypertension, hypercholesterolemia, GERD, peripheral neuropathy, pulmonary nodules, lower back pain, 4.6 cm abdominal aortic aneurysm, bilateral common iliac aneurysms, type 2 diabetic mellitus, benign prostatic hypertrophy, hernia repair in 2005, and tonsillectomy as a child. His social history is significant for prior tobacco use (quit 30 years ago). Medications taken at the time of the event included metoprolol, simvastatin, terazosin, finasteride, Protonix®, Lyrica®, oxycodone, Tylenol®, metformin, Multi-Vitamin Infusion (MVI), fish oil, vitamin B6, Oscal®, and mushroom pills.

There have been 5 other cases of dysphagia reported to the NCI as serious adverse events through AdeERS under the temsirolimus NSC and/or IND, and no other cases of dysphagia 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
<b>Temsirolimus</b>		
Dysphagia (n=5)	3	1 Unlikely, 1 Possible
	2	1 Possible, 1 Probable, 1 Definite

To date, a total of 2,247 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC, and a total of 594 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the temsirolimus therapy, and that there is no relationship between the event and IMC-A12.

	<b>Dysphagia</b>
<b>Temsirolimus</b>	Possible
<b>IMC-A12</b>	Unrelated
<b>Leiomyosarcoma</b>	Unrelated
<b>Inflamed duodenum</b>	Possible

Date: 10/6/10

Signature: \_\_\_\_\_

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

Date: 10/11/10

Signature: \_\_\_\_\_

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

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

cc: Rafael E. Curiel, Ph.D.  
Wyeth GSSE Triage: WASDTRI@wyeth.com  
Wyeth Pharmaceuticals, Inc.

Jocelyn Ulrich, R.Ph.  
Pfizer, Inc.

Naseem Zojwalla, M.D.  
Clinical Safety: mailindata\_GSM TINDY@lilly.com  
ImClone LLC