



**DATE:** 6/8/11

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
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**SUBJECT:** IMC-A12 (HuMAb IGF-1R; A12; Cixutumumab<sup>®</sup>) and CCI-779 (temsirolimus, Torisel<sup>®</sup>)  
NCI IND Safety Report, AE# **1116728**

**TO:** Investigators Using IMC-A12 (NSC 742460) and CCI-779 (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 CCI-779.

The following must be completed by all investigators using IMC-A12 under NCI IND 100947 and CCI-779 under NCI IND 61010:

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your 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 CCI-779, there does not appear to be a change in the risk-benefit ratio for IMC-A12 and CCI-779 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 71-year-old male with metastatic scrotal leiomyosarcoma experienced grade 2 bilateral paronychia of the great toes while on a phase 2 trial utilizing the investigational agents IMC-A12 and CCI-779.

## ADVERSE EVENTS ASSESSMENT

IND <b>100947</b> NSC <b>742460</b> <b>IMC-A12 (HuMab</b> <b>IGF-1R; A12;</b> <b>Cixutumumab<sup>®</sup>)</b> AE: <b>1116728</b>	<b>61010</b> <b>683864</b> <b>CCI-779</b> <b>(temsirolimus, Torisel<sup>®</sup>)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # <b>1</b> Event: <b>Gr. 2: Paronychia</b>  Protocol: <b>8121</b>
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The patient is a 71-year-old male with metastatic scrotal leiomyosarcoma who experienced bilateral paronychia of his great toes while on a phase 2 trial utilizing the investigational agents IMC-A12 and CCI-779. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 42 Days (6 weeks)  
 IMC-A12: 6 mg/kg IV over 60 minutes weekly  
 CCI-779: 25 mg IV over 30 minutes weekly

The patient was diagnosed with left scrotal leiomyosarcoma in September 2005. He is status post tumor resection (September 2005) and multiple-agent systemic chemotherapy (March 2010-April 2010). The patient began the investigational treatment on July 20, 2010, and received his last doses of IMC-A12 and CCI-779 on October 26, 2010 (Cycle 3, Day 15).

On October 26, 2010 (Cycle 3, Day 15), the patient reported experiencing a sore left great toe, which became increasingly red and tender, and developed into paronychia. On November 1, 2010, the patient was seen by a podiatrist who removed pus-like exudate from the left great toe, and prescribed Keflex<sup>®</sup> for 8 days. Laboratory results revealed his white blood cell (WBC) count was 10.3 K/uL (reference range 3.5-11 K/uL), glucose was 186 mg/dL (reference range: 60-109 mg/dL) and hemoglobin was 10.1 g/dL (reference range: 13.5-17.5 g/dL).

By November 9, 2010 (Cycle 3, Day 29), the patient's paronychia had not resolved and he was prescribed Augmentin<sup>®</sup> for 10 days. On November 15, 2010 the paronychia had not worsened, but remained unresolved, and it was recommended that the patient follow up with the podiatrist. At that time, the oncologist felt that the paronychia was unlikely related to the investigational therapy.

On November 23, 2010 (Cycle 4, Day 1), an X-ray of the left great toe revealed soft tissue swelling and mild osteoarthritis of the metatarsophalangeal joint; however, there was no specific radiographic evidence of osteomyelitis. The patient was prescribed Cipro<sup>®</sup> and clindamycin for 14 days. He later reported that he had stopped taking the clindamycin after 2-3 days due to stomach irritation. On this day, the patient also had a consultation for management of his diabetes with medications and nutritional instructions. On December 7, 2010 (Cycle 4, Day 15), the patient was seen by an orthopedic surgeon who noted bilateral serous drainage from the left great toenail with slight redness; however, the toenail appeared stable and not grossly loose. The patient underwent trimming of the mediolateral nail fold and additional nail material. He was prescribed Silvadene<sup>®</sup> dressing changes twice daily and his Cipro<sup>®</sup> medication was continued twice daily for 7 days. He continued to receive the investigational agents as scheduled, with no dose reductions. At a follow-up visit on December 14, 2010, the orthopedic surgeon noted that the patient's toe looked much better, with no signs of inflammation or infection. He was instructed to complete his antibiotics along with the toe soakings and the Silvadene<sup>®</sup> dressings.

On February 15, 2011 (Cycle 6, Day 1), the patient reported that the infection of the left great toe had recurred, and the dermatologist prescribed econazole 1% topical cream twice daily and mupirocin 2% topical ointment three times a day.

On March 15, 2011 (Cycle 6, Day 29), the patient had a surgical consultation for bilateral paronychia of the great toes. Surgical removal of his bilateral toenails was recommended.

On April 12, 2011 (Cycle 7, Day 15), the patient was seen at the clinic and reported having good results with continued treatment of the paronychia with Epsom<sup>®</sup> salt soaks and Silvadene<sup>®</sup> cream. The site has since learned that this event has been seen in other patients on this protocol. As a result, it is felt that the event is possibly related to the investigational therapy.

The patient's past medical/surgical history is significant for hypertension, diabetes, stage III chronic kidney disease, gout, colonoscopy and removal of colonic polyps (2005). Medications taken at the time of the event included Lantus<sup>®</sup>, hydrochlorothiazide, propranolol SA, Exforge<sup>®</sup>, lisinopril, clonidine hydrochloride, allupurinol, hydrocodone/acetaminophen, folic acid, and multivitamins.


There has been 1 other case of paronychia and 1 other case of nail loss reported to the NCI as serious adverse events through AdEERS under the NSC and/or IND for IMC-A12, and there has been 1 other case of paronychia, and 1 other case of nail loss reported as serious adverse events through AdEERS under the NSC and/or IND for CCI-779 as summarized in the table below:


Adverse Event	Grade	Attribution
<b>IMC-A12</b>		
Paronychia (n=1)	2	1 Unrelated
Nail loss (n=1)	2	1 Probable
<b>CCI-779</b>		
Paronychia (n=1)	2	1 Definite
Nail loss (n=1)	2	1 Possible

To date, a total of 1052 patients have been enrolled in NCI-sponsored clinical trials under the IMC-A12 IND and/or NSC, and a total of 2730 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and/or NSC.

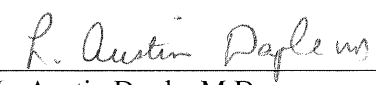
In this case, it is felt that a possible causal relationship exists between the event and the investigational agents IMC-A12 and CCI-779.

	<b>Paronychia</b>
<b>CCI-779</b>	Possible
<b>IMC-A12</b>	Possible
<b>Scrotal leiomyosarcoma</b>	Unrelated

Date: 

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

Date: 6/8/11

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

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

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