



DATE: 6/1/11

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: IMC-A12 (HuMAb IGF-1R; A12; Cixutumumab) and CCI-779 (temsirolimus, Torisel®)
NCI IND Safety Report, AE# **1413345**

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.

An 18-year-old male with metastatic epithelioid sarcoma of the right forearm experienced grade 4 non-infectious wound complication while on a phase 1 trial utilizing the investigational agents IMC-A12 and CCI-779.

ADVERSE EVENTS ASSESSMENT

IND	100947	61010	ADVERSE EXPERIENCE REPORT NO.
NSC	742460	683864	IND Safety Report: # 1
IMC-A12 (HuMab IGF-1R; A12; Cixutumumab)	CCI-779	(temsirolimus, Torisel [®])	Event: Gr. 4: Wound complication, non-infectious
AE:	1413345		Protocol: ADV L0813

The patient is an 18-year-old male with metastatic epithelioid sarcoma of the right forearm who experienced non-infectious wound complication while on a phase 1 trial utilizing the investigational agents IMC-A12 and CCI-779. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 28 Days

IMC-A12: 6 mg/kg IV over 1 hour on Days 1, 8, 15, and 22

CCI-779: 15 mg/m² IV over 30 minutes on Days 1, 8, 15, and 22

The patient was diagnosed with metastatic epithelioid sarcoma of the right forearm in August 2008. He is status post multiple-agents systemic chemotherapy from August to November 2008; radiation therapy from December 2008 to January 2009, and July 2009; and incisional biopsy of the right forearm mass, excisional biopsy of right upper arm skin lesion, and axillary lymph node biopsy in September 2008. The patient began the investigational treatment on March 10, 2010, and received his last doses of IMC-A12 and CCI-779 on April 1, 2011 (Cycle 11, Day 1).

Of note, the patient started the study with lesions/soft tissue necrosis on the right forearm. Throughout the course of the study, the lesions progressively worsened. On February 4, 2011, (Cycle 10, Day 15), the patient underwent wound exploration, debridement, and dressing change of the right forearm open wound. The investigational treatments were held. On February 11, 2011, he had wound debridement of the right arm and two Apligraf[®] placements on the right forearm lesion. The study drugs continued to be held to allow for graft healing. On March 11, 2011, he was re-instated on the investigational therapies, and continued on to Cycle 11.

On April 11, 2011 (Cycle 11, Day 11), a MRI of the right proximal upper extremity revealed increasing T2 signal and enhancement in the soft tissues along the distal aspect of the humeral shaft and elbow. Another MRI of the forearm that day was consistent with cellulitis and osteomyelitis. On April 19, 2011, the patient underwent a debridement of the necrotic bone, jet irrigation, and a dressing change of the open wound on the right forearm, which was repeated 3 days later. On April 29, 2011, he had an irrigation and debridement of his right forearm lesion. It was felt that the best course of action regarding the non-healing wound would be to amputate the patient's arm which was recommended after a discussion with his family. He was removed from the protocol that day. The patient was scheduled to undergo amputation on May 20, 2011. The operative and follow-up notes are not available at this time.

The patient's past medical/surgical history is significant for left subclavian venous port insertion in October 2008 and removal in November 2009, and a re-insertion in April 2010. Medications taken at the time of the event included Tylenol[®], Norco[®], nystatin, codeine, gabapentin, pentamidine, silver-hydrocolloid dressing, vitamin D-3, multivitamin, K-Phos[®] Neutral, and Zofran[®].

There has been one other case of non-infectious wound complication (grade 3, possibly related) reported to the NCI as a serious adverse event through ADEERS under the IMC-A12 NSC and/or IND. Non-infectious wound complications are expected events for CCI-779.

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 2727 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and/or NSC.

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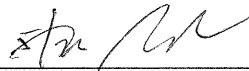
AE #1413345

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Although the wound complication was thought to be related to the patient's disease and radiation therapy, possible attributions to the investigational agents IMC-A12 and CCI-779 cannot be ruled out.

	Wound complication, non-infectious
CCI-779	Possible
IMC-A12	Possible
Epithelioid sarcoma	Definite
Radiation Therapy	Definite

Date: 5/25/11

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

Date: 6/1/11

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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