

IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA

FAX: 301-796-9845

1. IND NUMBER
61010

2. AGENT NAME
CCI-779 (temsirolimus, Torisel®)

3. DATE
October 28, 2011

4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION
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8a. PROTOCOL NUMBER (AE #)
N038H (AE# 1057393)

8b. AE GRADE: AE
Grade 3: Treatment related secondary malignancy

9. PATIENT IDENTIFICATION
9042784

10. AGE
72 years

11. SEX
Male

12. PROTOCOL SPECIFIED

Cycle = 28 days:

Temsirolimus: 25 mg IV over 30 minutes on Days 1, 8, 15, and 22

Rituximab: 375 mg/m² IV at an initial rate of 50 mg/hour increasing by 50 mg/hour every 30 minutes for a maximum of 400 mg/hour on Day 1

Rituximab: 375 mg/m² IV at an initial rate of 100 mg/hour increasing by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour on Days 8, 15, and 22

Cycles 2+

Temsirolimus: 25 mg IV over 30 minutes on days 1, 8, 15, and 22

Rituximab: 375 mg/m² IV at an initial rate of 100 mg/hour increasing by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour on Day 1 of Cycles 3, 5, 7, 9, and 11 only

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on January 11, 2007, and received the last dose of temsirolimus on December 6, 2007 (Cycle 12, Day 22) and the last dose of rituximab on October 18, 2007 (Cycle 11, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 72-year-old male with mantle cell lymphoma who experienced grade 3 myelodysplastic syndrome after completing a phase 2 trial utilizing the investigational agent temsirolimus in combination with rituximab. In January 2008, the patient began treatment with lenolidomide achieving a complete response after 6 cycles. In August 2010, a bone marrow biopsy confirmed a diagnosis of therapy-related myelodysplastic syndrome without excess blasts. The cytogenetics revealed a deletion 13q and deletion 20q. His hemoglobin was 10.8 g/dL (reference range: 13.5-17.5 g/dL), his MCV was 98 μm³ (reference range: 81.2-95.1 μm³), his WBC was 4.7 x10⁹/L (reference range: 3.5-10.5 x10⁹/L), his ANC was 2.9 x10⁹/L (reference range: 2.5-8.0 x10⁹/L), and his platelet count was 48 x10⁹/L (reference range: 150-450 x10⁹/L). On September 20, 2010, lenolidamide therapy was discontinued. On June 1, 2011, a bone marrow biopsy showed near eradication of the deletion 13q clone. On September 13, 2011, the patient's hemoglobin was 12.8 g/dL, his WBC was 3.4 x10⁹/L, his ANC was 1.61 x10⁹/L, his platelet count was 95 x10⁹/L, and his peripheral smear was without any abnormality and was free of circulating blasts. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using temsirolimus = 3041.

There has been 1 other case of a treatment related secondary malignancy (grade 3, possibly related) and 1 other case of myelodysplasia (grade 3, unlikely related) reported to the NCI through AdEERS as serious adverse events for temsirolimus.

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16. ASSESSMENT

In this case, it is felt that a possible relationship exists between the event and the investigational agent.

	<u>Myelodysplastic syndrome</u>
<u>Temsirolimus</u>	<u>Possible</u>
<u>Rituximab</u>	<u>Possible</u>
<u>Lenolidomide</u>	<u>Possible</u>
<u>Mantle cell lymphoma</u>	<u>Possible</u>

17. COMMENTS

Medications taken at the time of the event included aspirin, vitamin B complex, cranberry extract, cruciferous, curcumin, Dexilant[®], gamma globulin, ipratropium, melatonin, omega 3 fish oil, Paxil[®], Synthroid[®], silymarin, vitamin C with dehydroquercetin, vitamin D3, cimetidine, clonazepam, coenzyme Q10, ferrous gluconate, green tea leaf extract, lutein, magnesium, multivitamin, niacin, potassium, and vitamin E.

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32 (d) (2).

DISCLAIMER per 21 CFR 312.32 (e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.