

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125011

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review of Tositumomab (Bexxar)

STN 125011

Product: Tositumomab (Bexxar)

Sponsor: Corixa

Study RIT-II-003 was titled "Phase II Trial of Iodine-131 Anti-B1 Antibody for Previously Untreated, Advanced Stage, Low-Grade Non-Hodgkin's Lymphoma"). In this study patients had CD20 positive low-grade non-Hodgkin's lymphoma (NHL), Ann Arbor stage III or IV disease, and no more than 25% bone marrow involvement. Patients had not received prior therapy for NHL including radiation therapy or chemotherapy, could be newly diagnosed or observed following diagnosis and could be either symptomatic or asymptomatic.

Study RIT-II-003 was used to establish the pharmacokinetic comparability of site-radiolabeled Coulter Corp Material, Centrally-radiolabeled Lonza/CYTOGEN material and BI Pharma KG produced material.

To establish the comparability of various changes in the type of radiolabeling and sources of manufacture, a series of patients were enrolled in protocol RIT-II-003. The first series of patients were used to study the change from Coulter to Lonza/CYTOGEN generated material and site of radiolabeling. Subsequent series of patients were used to compare Lonza/CYTOGEN to material made at BI Pharma KG.

The relevance of the patient population used in study RIT-II-003 to the patient population used in the Phase 3 study was determined by a pharmacokinetic comparison to patients used in RIT-I-000. Specifically, data from relapsed/refractory NHL patients in RIT-I-000 were compared to data from previously untreated NHL patients in RIT-II-003.

In the first phase of the study RIT-II-003, patients were infused with 450 or 475 mg of unlabeled anti-B1 antibody over 70 minutes followed by a 30 minute infusion of 10 to 35 mg of Anti-B1 antibody radiolabeled with 5 mCi of I-131. Whole body dosimetry was collected with 1 hour and selected time points to determine total body residence time. Using the dosimetry data along with the patient height and mass, a specific therapeutic dose of I-131 was determined and infused in the second phase of the study. In this phase, patients were given 450 to 475 mg of unlabeled anti-B1 antibody over 70 minutes followed by a 30 minute infusion of 10 to 35 mg of anti-B1 antibody radiolabeled with a patient specific dose of I-131 (45 to 75 cGy TBD). Obese patients were given a dose that was calculated using 137% of their lean body mass. Blood samples were collected immediately after infusion and at 0.5, 1, 2, 4, 12, 24, 48, 72, 96 and 120 hours after infusion. Data were recorded as counts per minute per ml and converted to a percentage-injected activity per gram based on the counter efficiency and the injected activity. Blood was assumed to have a density of 1 gram/ml.

For each patient the predose of unlabeled Anti-B1 Antibody and the dosimetric and therapeutic doses of I-131 labeled antibody were from the same sources.

The Phase 3 trial (RIT-II-004) is composed of patients with low-grade or transformed low-grade NHL and is refractory to chemotherapy whereas patients from RIT-II-003 have not been given prior therapy. The relevance of the patients in RIT-II-003 to RIT-II-004 is established under RIT-I-000 as a subset of these patients received on average four poor regimens of chemotherapy for NHL. Additionally, these patients in RIT-I-000 were similarly treated in terms of infusions of anti-B1 antibody.

Pharmacokinetic endpoints were computed using WinNonlin. Area under the curve was computed as the sum of the intercepts divided by the macro constants for each compartment. With the exception of 1 patient a 1-compartment model was used, a 2-compartment model was utilized to analyze the data. Terminal half-life was defined as the natural log of 2 divided by λ . Volume of distribution at time 0 was 100 divided by the intercept (C_0) and volume at steady state (V_{dss}) was equal to 100 multiplied by (I^2/λ^2) divided by AUC^2 . The results of the study are summarized below: