

DESCRIPTION OF THE PRODUCT

Tositumomab & iodine I 131 tositumomab RadiolImmunoTherapy

Iodine I 131 tositumomab is a radioimmunotherapeutic agent developed for the treatment of patients with multiply relapsed/refractory, CD20-positive B-cell, low-grade non-Hodgkin's lymphoma (NHL), with or without transformation.

The product consists of unlabeled and radiolabeled murine monoclonal antibodies, referred to as anti-B1 antibody and iodine I 131 anti-B1 antibody, respectively. The approved USAN names are:

- tositumomab for the unlabeled anti-B1 antibody
- iodine I 131 tositumomab for the labeled antibody.

Tositumomab (anti-B1 antibody) is an IgG_{2a}, murine monoclonal antibody that binds to the CD20 antigen on the surface of normal and malignant human B cells. Iodine I 131 tositumomab therapy is believed to produce its cytotoxic effect through the effects of ionizing radiation; the extent to which immune-mediated cytotoxic activity contributes to this effect is unknown.

Composition of Tositumomab & iodine I 131 tositumomab RadiolImmunoTherapy

Bexxar therapy is the Corixa's proposed trade name for a treatment regimen that includes the combination of the unlabeled IgG_{2a} anti-CD20 murine monoclonal antibody (tositumomab), and the same IgG_{2a} anti-CD20 antibody radiolabeled with iodine 131 (iodine I 131 tositumomab).

Dosing Regimen

Description of Dosing Regimen

In clinical studies, the selection of the iodine I 131 tositumomab dose was individualized; each patient's dose was based upon a patient-specific biodistribution profile and the dose needed to deliver 65-76 cGy to known tumor sites.

The stated goal of this dosing method was to achieve an improved therapeutic index by maximizing the radiation dose to the lymphoma and controlling toxicity.

Figure 1 is a schematic presentation of the dosing methodology for iodine I 131 tositumomab therapy.

Figure 1: Iodine I 131 Tositumomab Therapy

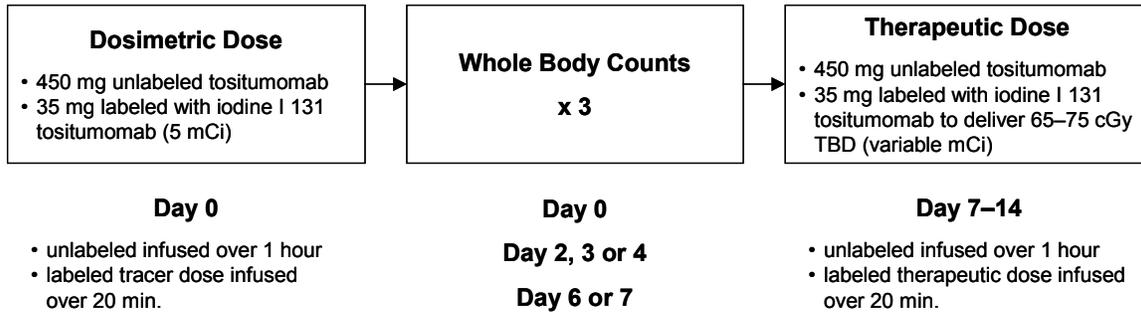


Figure 2: Calculation of Patient-Specific Dose for Iodine I 131 Tositumomab Therapy

A patient-specific activity of iodine I 131 tositumomab therapy is calculated for each patient using the following equation.

$$\text{Dose (mCi)} = \frac{\text{Activity Hours (mCi h)}}{\text{Residence Time (h)}} \times \frac{\text{Prescribed Total Body Dose (cGy)}}{75 \text{ cGy}}$$

The methodology for determining the activity of iodine I 131 tositumomab in millicuries (mCi) to be administered to the patient involves the following steps:

1. Administration of the dosimetric dose of iodine 131 tositumomab therapy.
2. Acquisition of total body radiation counts on three separate days (Day 0, Day 2–4, and Day 6–7) with a gamma camera and using the information to determine individual patient clearance rate of iodine 131.
3. Determination of the Area-under-the-Curve using tables provided by Corixa.
4. Determination of the Residence Time using worksheets provided by Corixa.
5. Determination of the patient-specific activity (total mCi dose) using the formula.

Rationale for Dosing Regimen

The use of iodine I 131 tositumomab and the dosing regimen were based on preclinical and clinical data summarized below.

Preclinical Information

Preclinical studies demonstrated that

- Localization of iodine I 131 tositumomab was B-cell specific, based upon data from preclinical toxicology studies (repeat dose study in -----) and the open literature.
- Iodine 131 was excreted primarily in the urine based upon from general knowledge and published literature. No specific study conducted by the sponsor.
- B cells were decreased after treatment with iodine I 131 tositumomab based upon data from preclinical toxicology studies (repeat dose study in -----).
- There were no significant drug-related effects on the number of T cells based upon data from preclinical toxicology studies (repeat dose study in -----).
- Tumor uptake of iodine I 131 tositumomab was increased after predosing with unlabeled tositumomab based upon data published in from reference 29 (Cancer Research '92) used anti-B1 antibody.

Clinical Data in Support of proposed dosing regimen

Maximum tolerated, non-myeloablative, total-body dose (TBD)

The **maximum tolerated, non-myeloablative, total-body dose (TBD)** was established in the Phase 1 Study RIT-I-000 using a standard dose-escalation schedule evaluating doses beginning at 25 cGy and increasing by 10-cGy increments until the dose-limiting toxicity (DLT) was reached. Two of three patients had DLT at 85 cGy TBD. Thus, the maximum tolerated total body dose was determined to be 75 cGy. This dose (75 cGy) was further attenuated for obese patients and patients with lower pre-therapy platelet counts.

Dose Adjustment for obese patients

Summary: The **dose for obese patients** was adjusted to 137% of their calculated lean body mass. The adjustment was introduced to account for the fact that obese patients can be modeled as an outer shell of fat with little radioantibody accumulation in the region surrounding the lean body mass.⁶⁴ Clinical data were consistent with this model in that 2 of 3 obese patients who received an unattenuated dose of 75 cGy developed Grade IV thrombocytopenia and Grade IV neutropenia. By comparison, of 14 obese patients who received an attenuated dose of 75 cGy to the lean body mass, only 2 (14%) developed Grade IV thrombocytopenia and 3 (21%) developed Grade IV neutropenia.

TBD Reduction for Obesity

Identification of a higher incidence of hematologic toxicity in obese patients and patients with baseline thrombocytopenia led to dose (TBD) reduction for these two groups of subjects. These two TBD reductions were introduced in Amendment 3 of study RIT-II-001 in -----.

To examine the effect of these dose reductions, hematologic data were analyzed from subjects in studies RIT-I-000, RIT-II-001, RIT-II-002 (Arm A and crossover), and RIT-II-004 who received the relevant TBD. It is noted that subjects from RIT-II-003 were excluded from analyses because they had not received

chemotherapy and, therefore, would not be expected to have a comparable incidence of hematologic toxicity.

The following table summarizes the hematologic toxicity observed (by NCI CTC grade) for obese patients who received a 75 cGy TBD as an adjusted or unadjusted dose. Obesity was defined as exceeding 137% of the lean body mass (Ref. 2). The weight limit by height was defined by the following equations:

Gender	Definition
Males	Obese if weight (kg) $>65.76 + 1.452 (\text{height in cm} - 152)$
Females	Obese if weight (kg) $>62.34 + 1.247 (\text{height in cm} - 152)$

Seventeen subjects dosed at 75 cGy TBD were classified as obese. Fourteen subjects received an attenuated dose based on 137% of their calculated lean body mass and 3 subjects did not receive an attenuated dose but were dosed based on the total body mass.

A reduction in the incidence of Grade IV hematologic toxicity was noted with the dose attenuation. Of the subjects not receiving an attenuated dose, 2 of 3 (67%) subjects developed Grade IV thrombocytopenia, 2 of 3 (67%) subjects developed Grade IV neutropenia, and 2 of 3 (67%) subjects developed Grade IV anemia. Of the subjects receiving an attenuated dose, 2 of 14 (14%) subjects developed Grade IV thrombocytopenia, 3 of 14 (21%) subjects developed Grade IV neutropenia, and 0 of 14 (0%) subjects developed Grade IV anemia.

Hematologic toxicity in obese patients according to dose (adjusted or unadjusted dose)		
NCI CTC Grade	TBD Reduced (n=14)	No TBD Reduction (n=3)
WBC (x 1000 cells/mm³)		
0 (nadir ≥4.0)	1 (7%)	0 (0%)
1 (nadir 3.0 to <4.0)	3 (21%)	0 (0%)
2 (nadir 2.0 to <3.0)	8 (57%)	1 (33%)
3 (nadir 1.0 to <2.0)	1 (7%)	0 (0%)
4 (nadir <1.0)	1 (7%)	2 (67%)
Platelets (x 1000 cells/mm³)		
0 (nadir ≥150)	1(7%)	1 (33%)
1 (nadir 75 to <150)	5 (36%)	0 (0%)
2 (nadir 50 to <75)	6 (43%)	0 (0%)
3 (nadir 25 to <50)	0 (0%)	0 (0%)
4 (nadir 10 to <25)	1 (7%)	1 (33%)
4+ (nadir <10)	1 (7%)	1 (33%)
Hemoglobin (g/dL)		
0 (nadir ≥12.0)	6 (43%)	0 (0%)
1 (nadir 10.0 to <12.0)	5 (36%)	1 (33%)
2 (nadir 8.0 to <10.0)	2 (14%)	0 (0%)
3 (nadir 6.5 to <8.0)	1 (7%)	0 (0%)
4 (nadir <6.5)	0 (0%)	2 (67%)
ANC (x 1000 cells/mm³)		
0 (nadir ≥2.0)	2 (14%)	0 (0%)
1 (nadir 1.5 to <2.0)	1 (7%)	0 (0%)
2 (nadir 1.0 to <1.5)	7 (50%)	1 (33%)
3 (nadir 0.5 to <1.0)	1 (7%)	0 (0%)
4 (nadir 0.1–0.5)	3 (21%)	0 (0%)
4+ (nadir <0.1)	0 (0%)	2 (67%)

Dose Adjustment in the prescribed TBD for patients with baseline platelet counts between 100,000 cells/mm³ and 149,999 cells/mm³

Summary: The adjustment in the prescribed TBD for patients with baseline platelet counts between 100,000 cells/mm³ and 149,999 cells/mm³ was based on data that suggested that these patients sustained a higher incidence of Grade III/IV hematological toxicity when treated with 75 cGy. Of 20 patients who received an unattenuated dose of 75 cGy, 8 (40%) developed Grade IV thrombocytopenia and 6 (30%) developed Grade IV neutropenia. Of the 38 patients who received an attenuated dose of 65 cGy, 11 (29%) developed Grade IV thrombocytopenia and 10 (26%) Grade IV neutropenia.

TBD Reduction for Thrombocytopenia

Dose reduction to 65 cGy TBD was selected by the sponsor for subjects with baseline thrombocytopenia, defined as platelet count between 100,000 cells/mm³ and 149,999 cells/mm³.

Fifty-eight subjects were enrolled with baseline platelets between 100,000 cells/mm³ and 150,000 cells/mm³ and received either a 65 or 75 cGy TBD. Thirty-eight subjects received a 65 cGy TBD, the proposed reduction in TBD for

this subgroup, and 20 subjects received a standard 75 cGy TBD. A reduction in the incidence of Grade IV hematologic toxicity was noted with the dose reduction.

The following table summarizes the maximum hematologic toxicity grade for all subjects who entered with platelet counts between 100,000 cells/mm³ and 150,000 cells/mm³ according to dose (attenuated [65cGy] or unadjusted dose).

Hematologic toxicity in thrombocytopenic patients according to dose (adjusted vs. unadjusted dose)		
NCI CTC Grade	Attenuated Dose [65 cGy] n=38	Non-Attenuated [75cGy] n=20
WBC (1000 cells/mm³)		
0 (nadir ≥4.0)	2 (5%)	0 (0%)
1 (nadir 3.0 to <4.0)	9 (24%)	2 (10%)
2 (nadir 2.0 to <3.0)	7 (18%)	5 (25%)
3 (nadir 1.0 to <2.0)	16 (42%)	9 (45%)
4 (nadir <1.0)	4 (11%)	4 (20%)
Platelets (x 1000 cells/mm³)		
0 (nadir ≥150)	0 (0%)	0 (0%)
1 (nadir 75 to <150)	6 (16%)	3 (15%)
2 (nadir 50 to <75)	10 (26%)	4 (20%)
3 (nadir 25 to <50)	11 (29%)	5 (25%)
4 (nadir 10 to <25)	8 (21%)	6 (30%)
4+ (nadir <10)	3 (8%)	2 (10%)
Hemoglobin (g/dL)		
0 (nadir ≥12.0)	10 (26%)	3 (15%)
1 (nadir 10.0 to <12.0)	11 (29%)	10 (50%)
2 (nadir 8.0 to <10.0)	7 (18%)	3 (15%)
3 (nadir 6.5 to <8.0)	9 (24%)	3 (15%)
4 (nadir <6.5)	1 (3%)	1 (5%)
ANC (x 1000 cells/mm³)		
0 (nadir ≥2.0)	6 (16%)	1 (5%)
1 (nadir 1.5 to <2.0)	5 (13%)	1 (5%)
2 (nadir 1.0 to <1.5)	8 (21%)	4 (20%)
3 (nadir 0.5 to <1.0)	9 (24%)	8 (40%)
4 (nadir 0.1–0.5)	9 (24%)	4 (20%)
4+ (nadir <0.1)	1 (3%)	2 (10%)

Effect of administering unlabeled tositumomab

The **effect of administering unlabeled tositumomab** prior to the administration of labeled antibody was evaluated in the first 25 patients in Study RIT-I-000. Patients received either 0, 95 or 475 mg of unlabeled antibody as a pre-dose with a 10-mg dose of labeled antibody. Total body residence times (TBRTs) (i.e., rate of clearance of iodine I 131 tositumomab) of radioactivity were longer in those patients who received the larger pre-dose so that a lower administered activity (mCi) of iodine I 131 tositumomab was needed to deliver the prescribed total body dose of radiation. In addition, there was a trend toward improved tumor targeting with iodine I 131 tositumomab in patients with splenomegaly or high tumor burden who received the larger pre-dose. Based on these results, all subsequent patients received a total protein dose of 485 mg (Note: the dose of the labeled antibody in the dosimetric dose was increased to 35 mg because up to a 35-mg dose of labeled antibody was required for the therapeutic dose. The majority of the patients studied received a pre-dose of 450-mg of unlabeled antibody prior to the dosimetric dose.).

Administration of a patient-specific administered activity

Administration of a patient-specific administered activity was chosen by the sponsor because the clearance of radioimmunoconjugates has been observed to be highly variable from patient to patient. The variability in TBRT correlates with known and measurable parameters, such as body weight, tumor cell mass and spleen mass. Therefore, in the sponsor's opinion, the radiation dose can only be determined from individualized, total-body dosimetry.

Figure 3. demonstrates the range in the mCi dose required to deliver a target total body dose (TBD) of 75 cGy.

Figure 3: mCi Required to Deliver 75 cGy (N = 608)

