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APPLICATION NUMBER:

125011

MEDICAL REVIEW(S)

Clinical Review

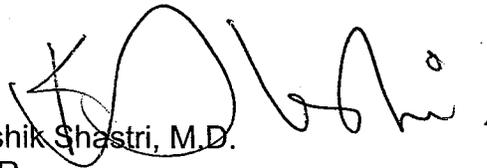
Date: June 26, 2003

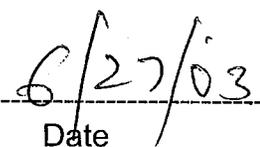
Type: BLA

FDA/STN Number: 125011

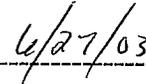
Product: BEXXAR™ therapeutic regimen
(Tositumomab and Iodine I 131 tositumomab)

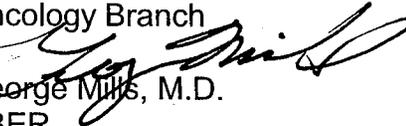
Sponsor: Corixa

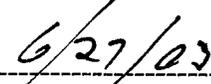

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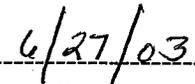

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Primary Clinical Review

Cover Sheet

Submission Type	BLA
Submission Number	BL 125011
Letter Date	
Stamp Date	
Review Completion Date	June 27, 2003
Established Name	Tositumomab and Iodine I-131 Tositumomab
Trade Name or Proposed Trade Name	Bexxar
Therapeutic Class	
Sponsor	Corixa Corporation
Priority Designation (S or P)	P

Sponsor's Proposed:

Formulation

The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is an anti-neoplastic radioimmunotherapeutic regimen composed of the monoclonal antibody, Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131 Tositumomab. Tositumomab is a murine IgG_{2a} lambda monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Tositumomab is produced in an antibiotic-free culture of mammalian cells and is composed of two murine gamma 2a heavy chains of 451 amino acids each and two lambda light chains of 220 amino acids each. The approximate molecular weight of Tositumomab is 150 kD.

Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent, colorless to slightly yellow, preservative-free liquid concentrate. It is supplied at a nominal concentration of 14 mg Tositumomab/ml in 35-mg and 225-mg single use vials. The formulation

contains 10% (w/v) maltose, 145 mM sodium chloride, 10 mM phosphate, and Water for Injection, USP. The pH is approximately 7.2.

Iodine I 131 Tositumomab is a radio-iodinated derivative of Tositumomab that has been covalently linked to Iodine-131. Unbound radio-iodine and other reactants have been removed by chromatographic purification steps. Iodine I 131 Tositumomab is supplied as a sterile, clear, preservative-free liquid for IV administration. The dosimetric dosage form is supplied at nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at date of calibration), respectively. The therapeutic dosage form is supplied at nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL (at date of calibration), respectively. The formulation for the dosimetric and the therapeutic dosage forms contains 5.0%–6.0% (w/v) povidone, 1–2 mg/mL maltose (dosimetric dose) or 9–15 mg/mL maltose (therapeutic dose), 0.85–0.95 mg/mL sodium chloride, and 0.9–1.3 mg/mL ascorbic acid. The pH is approximately 7.0.

Dosing Regimen

The BEXXAR therapeutic regimen is intended as a single course of treatment, administered in two discrete steps: the dosimetric and therapeutic steps. Each step consists of a sequential infusion of Tositumomab followed by Iodine I 131 Tositumomab. The dosimetric step consists of Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes, followed by Iodine I 131 Tositumomab (containing 5.0 mCi I-131 and 35 mg tositumomab) intravenously in 30 ml 0.9% Sodium Chloride over 20 minutes. The therapeutic step is administered 7-14 days after the dosimetric step and consists of Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes followed by Iodine I 131 Tositumomab containing the activity of Iodine-131 calculated to deliver 75cGy total body irradiation and 35 mg Tositumomab, administered intravenously over 20 minutes.

Indication

The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is indicated for the treatment of patients with CD20

positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. The BEXXAR therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin's lymphoma.

The BEXXAR therapeutic regimen is intended as a single course of treatment. The safety of multiple courses of the BEXXAR therapeutic regimen, or combination of this regimen with other forms of irradiation or chemotherapy, has not been evaluated.

Intended Population

Bexxar therapeutic regimen is indicated in patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.

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1.0 Executive Summary

1.1 Recommendation on Clinical Approvability

From a clinical perspective, I recommend approval of Bexxar therapeutic regimen for the treatment of patients with CD20 positive follicular, non-Hodgkin's lymphoma, with or without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. This recommendation is based on a clinical benefit of durable responses (median duration of 16 months; overall response rate of 68%) without evidence of an effect on survival in a multi-center, single-arm study in forty patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months.

The recommendation for approval is also consistent with the advice of the Oncology Drug Advisory Committee, which met on December 17, 2002 to deliberate on the clinical studies utilizing Bexxar described in this document.

1.2 Recommendation on Postmarketing Actions

The sponsor has agreed to have a training program with certification requirement for physicians who plan to administer this agent. The boxed warning in the package contains the following wording:

Special requirements: The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) contains a radioactive component and should be administered only by physicians and other health care

professionals qualified by training in the safe use and handling of therapeutic radionuclides. The BEXXAR therapeutic regimen should be administered only by physicians who are in the process of being or have been certified by Corixa Corporation in dose calculation and administration of the Bexxar therapeutic regimen.

In addition, the sponsor has agreed to a continuing monitoring and quality assurance program for the sites that are involved in administering Bexxar therapy.

The sponsor has also agreed to several post-marketing studies, which are discussed in detail elsewhere in this review. Briefly, the sponsor has agreed to conduct the following post-marketing studies: (1) To conduct an open-label efficacy trial of Rituximab versus Bexxar therapeutic regimen in patients with lymphoma who have received at least one, and no more than two prior chemotherapy regimens, and who are appropriate candidates for systemic therapy with the primary objective of demonstrating a longer event free-survival in patients treated with Tositumomab and Iodine I 131 Tositumomab as compared to those receiving Rituximab (2) To conduct an open-label trial of Zevalin versus the Bexxar® therapeutic regimen in patients with lymphoma who have failed at least 3 regimens, one of which was Rituximab with the primary endpoint of overall safety and non-inferiority of Bexxar therapeutic regimen with regard to efficacy (3) To conduct a single arm, open label, multicenter, Phase 2 trial evaluating the pharmacokinetics, safety, and efficacy of retreatment with the Bexxar® therapeutic regimen in patients who have had duration of response of at least 6 months in the post-marketing commitments outlined in 1 and 2 above with the primary objective of comparing the pharmacokinetics associated with retreatment and with initial treatment and assessing the safety and efficacy of retreatment with the Bexxar® therapeutic regimen (4) To conduct a companion study to evaluate the use of prophylactic vaccines in patients with relapsed, follicular, B- cell non- Hodgkin's lymphoma receiving Bexxar® or Rituximab while participating in the trial described in Commitment 1 above. This study will assess the impact of the anti-

lymphoma therapies on development of protective antibody titers to recall and new antigens (5) To collect information on patients who become seropositive for HAMA after treatment on studies described in the post-marketing commitments outlined in 1 and 2 above regarding the impact of HAMA on the ability of patients to receive subsequent therapy in which a component of the therapy was a murine or partially murine protein, alteration in the safety and/ or efficacy of subsequent therapy, interference with in vivo or in vitro diagnostic assays that utilize murine monoclonal antibodies, and ability of patients to undergo in vivo diagnostic procedures. (6) To conduct a retrospective study of stored HAMA positive samples from clinical studies and a prospective study from sera from patients in the trials described in the post-marketing commitments outlined in 1 and 2 above who become HAMA seropositive following treatment, to determine the prevalence of interference of HAMA with diagnostic *in vitro* assays and the relationship, if any, between interference and level of HAMA (7) To collect information regarding the occurrence of myelodysplasia/acute leukemia in studies involving Bexxar®, including studies in BL 125011/0; other studies not contained in the BLA; and those studies that are being designed to address post-marketing commitments or other regulatory requirements (8) To conduct a quality assurance (QA) assessment to determine the level of compliance with the training program.

1.3 Summary of Clinical Findings

1.3.1 Overview of Clinical Review

The primary efficacy data supporting the indication for the treatment of Rituximab-refractory patients with low grade and follicular NHL, with or without transformation, are derived from Study CP-97-012, a single-arm study in forty patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation,

who had relapsed following or were refractory to chemotherapy. In these studies.

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

1.3.2 Efficacy

The following table summarizes the five clinical trials that were used to support the licensing application. Of these, study CP-97-12 is the primary study to support the indication, while the other studies showing similar response rates and duration of response are used to support the clinical benefit.

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TABLE 1: Summary Of Clinical Studies:

Study Number	Median # of Prior Chemotherapy Regimens (range)	Overall Response Rate % (95% CI)	Complete (CR + CCR) Response Rate	Median Duration of Response (months)
CP-97-012 (N = 40)	4 (1-11)	68% (51%, 81%)	30%	16
RIT-II-004 (N = 60)	4 (2-13)	47% (34%, 60%)	20%	12
RIT-I-000 (N=22)	3 (1-11)	64% (41%, 83%)	27%	18
RIT-II-001 (N = 47)	4 (1-8)	49% (34%, 64%)	26%	14
RIT-II-002 (N = 42+19)	2 (1-4)	59% (46%, 71%)	33%	13

Study CP-97-012 was a multi-center, single-arm study in patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. Determination of clinical benefit of the BEXXAR therapeutic regimen was based on evidence of durable responses without evidence of an effect on survival. All patients in the study were required to have received prior treatment with at least four doses of Rituximab without an objective response, or to have progressed following treatment. Patients were also required to have a platelet count $\geq 100,000/\text{mm}^3$; an average of $<25\%$ of the intratrabecular marrow space involved by lymphoma, and no evidence of progressive disease arising in a field irradiated with >3500 cGy within 1 year of completion of irradiation.

Forty patients initiated treatment with the BEXXAR therapeutic regimen. The median age was 57 (range: 35-78); the median time from

diagnosis to protocol entry was 50 months (range: 11–70); and the median number of prior chemotherapy regimens was 4 (range: 1–11). Twenty-four patients had disease that did not respond to their last treatment with Rituximab, 11 patients had disease that responded to Rituximab for less than 6 months, and five patients had disease that responded to Rituximab, with a duration of response of 6 months or greater. Overall, 35 of the 40 patients met the definition of “Rituximab refractory”, defined as no response or a response of less than 6 months duration. Table 2 summarizes efficacy outcome data from this study, as determined by an independent panel that reviewed patient records and radiologic studies. The median duration of follow-up was 35 months and 34 months for all patients and for the Rituximab-refractory subset, respectively.

Table 2
Efficacy Outcomes Patients (CP-97-012)

	Objective Responses to the BEXXAR Therapeutic Regimen in patients refractory to Rituximab		Objective Responses to the BEXXAR Therapeutic Regimen in all Patients	
	Response Rate (%) (95% CI ^a) (n=35)	Median duration of response (Mos) (Range)	Response Rate (%) (95% CI ^a) (n=40)	Median Duration of Response (Mos) (Range)
Overall Response	63% (45% - 79%)	25 (4+ - 35+)	68% (51% - 81%)	16 (1+ - 35+)
Complete response ^c	29% (15% - 46%)	NR ^b (4 - 35+)	33% (19% - 49%)	NR (4 - 35+)

^a C.I. = Confidence Interval
^b NR = Not reached
^c Complete response rate = Pathologic and clinical complete responses

The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin’s lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response

rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months.

The results of the studies were discussed at the Oncology Advisory Committee meeting on December 17, 2002. And they also opined that the objective response rate and the response duration supported by other clinical studies in Rituximab -naïve patients with chemotherapy-refractory disease, constitute substantial evidence of clinical benefit.

The other marketed drug Zevalin has comparable response rates in low grade non-Hodgkin's lymphoma.

1.3.3 Safety

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

The most common and prolonged adverse event was in hematologic parameters. Per patient incidence of platelet counts < 50,000/mm³, absolute neutrophil count <1000 cell/mm³, and hemoglobin < 8 gm/dl was 53%, 63% and 29% respectively. The median duration of platelet counts < 50,000/mm³, absolute neutrophil count <1000 cell/mm³, and hemoglobin < 8 gm/dl was 32,31 and 23 days respectively. Infectious Events occurred in one hundred and four of the 230 (45%) patients of which 19 (8%) were considered serious. Documented infections included pneumonia, bacteremia, septicemia, bronchitis, and skin infections. Twenty-eight (12%) patients experienced hemorrhagic events; the majority were mild to moderate.

Hypersensitivity Reactions as described by the following adverse events: allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus, and serum sickness occurred in fourteen patients (6%). An infusional toxicity as evident from a constellation of symptoms, including fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea, have been reported during or within 48 hours of infusion. Ninety-two patients (40%) reported fever, rigors/chills, or sweating. The infusional adverse events were managed by adjustment of the rate of infusion or temporary discontinuation in 14 patients and permanent discontinuation of infusion in 2 patients. Gastrointestinal toxicity was observed in eighty-seven patients (38%) and included nausea, emesis, abdominal pain, and diarrhea.

Delayed Adverse Reactions

The most significant delayed adverse reactions included hypothyroidism, HAMA, myelodysplasia/leukemia. The overall incidence of MDS/secondary leukemia among the patients included in the clinical studies, was 8.3%, with a median follow-up of 35 months and a median time to development of MDS of 30 months. The cumulative incidences of MDS/secondary leukemia were 4.2% and 10.7% at 2 and 4 years, respectively. Among the 765 patients included in the expanded access programs, where the median duration of follow-up was shorter (20 months), the overall incidence of MDS/secondary leukemia was 1.7% (13/765) and the median time to development of MDS was 23 months. The cumulative incidences of MDS/secondary leukemia were 1.37% and 4.8% at 2 years and 4 years, respectively, in the expanded access population. The overall incidence of hypothyroidism, in the absence of competing risks, in the clinical study patients was 14% with cumulative incidences of 4.2% at 6 months and 8.1%, 12.6%, and 15.0% at 1, 2, and 4 years, respectively. New events have been observed up to 72 months post treatment. In the expanded access program experience, with a median observation period of 18 months, 54 patients (9%) became hypothyroid as determined by elevated TSH. The cumulative incidence of hypothyroidism in the combined populations was 9.1% and 17.4% at 2

and 4 years, respectively. Regarding HAMA, of the patient in the clinical trials, 11% seroconverted to HAMA positivity. The median time to development of HAMA was 6 months. In a study of 77 patients who were chemotherapy-naïve, the incidence of conversion to HAMA seropositivity was 70%, with a median time to development of HAMA of 27 days. Of the 978 patients in the expanded access program who were seronegative for HAMA prior to treatment, 785 (80%) had at least one post-treatment HAMA value obtained. With a median observation period of 6 months, a total of 76 patients (10%) became seropositive for HAMA post-treatment. The median time of HAMA development was 148 days; with 45 (59%) patients seropositive for HAMA by 6 months. No patient became seropositive for HAMA more than 30 months after administration of the BEXXAR therapeutic regimen.

Any limitations imposed by missing data in evaluation of early hematologic toxicity was overcome by using a worst case analysis, imputing grade III/IV toxicities for the missing values. For the delayed toxicities of myelodysplasia, hypothyroidism and HAMA development, data from expanded access program supplemented the findings from clinical studies.

The safety profile of this drug is acceptable for the indicated population and is comparable to the other marketed product of Zevalin.

1.3.4 Dosing, Regimen, and Administration

The tositumomab therapeutic regimen consists of a two-part administration of the tositumomab antibody administered 7 to 14 days apart. The first step is administration of the dosimetric dose, consisting of 450 mg of unlabeled tositumomab antibody intravenously over one hour followed by 35 mg of tositumomab labeled with 5 mCi of ¹³¹Iodine. A series of at least 5 gamma camera scans are obtained over the next 5-7 days to derive the dose of ¹³¹Iodine antibody required to deliver 75 cGy to the whole body. The therapeutic dose is administered as the second step, consisting of sequential infusions of 450 mg of unlabeled tositumomab antibody followed by 35 mg of tositumomab labeled with a patient-specific dose of ¹³¹Iodine.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies have been performed.

1.3.6 Special Populations

Because of the radioligand of I-131, Bexxar is characterized as pregnancy category X; mothers should not nurse if they are administered this drug, and it has not been studied in pediatric population.

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2.0 Background

2.1 Clinical Context of Application

General

Non-Hodgkin's lymphomas (NHLs) encompass several unique malignant lymphoid disease entities that vary in clinical behavior, morphologic appearance, immunologic, and molecular phenotype. The various types represent neoplastic lymphoid cells arrested at different stages of normal differentiation. Based on their natural history, NHLs can be clinically classified as indolent, aggressive, and highly aggressive.

Epidemiology

NHLs are the fifth most common cause of cancer in the United States, with an estimated incidence of 63,600 cases in 2001ⁱ. Follicular center cell lymphomas are the second most common subtype, comprising approximately 40% of all non-Hodgkin's lymphomas. Since 1950, the incidence of NHL has steadily increased at approximately 4% per year.

Classification

Several histologic classifications of NHLs exist. Commonly used systems are the 1982 International Working Formulation (IWF)ⁱⁱ and the 1994 Revised European-American (REAL) classificationsⁱⁱⁱ. These classification systems group lymphoid neoplasms according to clinical behavior (low grade/indolent, intermediate grade/aggressive, or high grade/very aggressive). Historically, this grouping often served as a basis for choosing a first line therapy.

IWF and REAL Classification by Proposed Clinical Grouping	
IWF	REAL
<u>Low Grade Lymphomas</u>	<u>Indolent (low-risk) lymphoma</u>
Small lymphocytic (A)	Small lymphocytic
Follicular small cleaved (B)	Lymphoplasmacytic
Follicular mixed (C)	Marginal zone
	Splenic
<u>Intermediate-grade lymphomas</u>	MALT B-cell (extranodal)
Follicular large (D)	Monocytoid B-cell (nodal)
Diffuse small cleaved (E)	Follicle center, small grade I
Diffuse mixed (F)	Follicle center, mixed small/large grade II
Diffuse large cell (G)	
<u>High grade lymphoma</u>	<u>Aggressive (intermediate-risk) lymphomas</u>
Immunoblastic, large cell (H)	Mantle cell
Lymphoblastic convoluted and nonconvoluted (I)	Follicle center, large grade III
Lymphoblastic small noncleaved (J)	Diffuse large B-cell
	Primary mediastinal (thymic), large B-cell
	Burkitt-like, high grade B-cell
	<u>Very Aggressive (high risk) lymphomas</u>

More recently, the World Health Organization (WHO) proposed a new classification system^{iv}. Unlike the IWF and REAL classifications, the WHO committee felt that grouping lymphoid neoplasms according to clinical behavior was neither necessary nor desirable^v. The committee recognized that specific disease entities could be defined by a combination of morphology, immunology, genetic features, and clinical features. Each entity had distinct clinical behavior and outcome predictable by applicable prognostic factors (e.g.; the international Prognostic Index) and related to the type of initial therapy administered. The committee concluded that each lymphoma type needed to be treated as distinct entities. Therefore, rather than depending on clinical grouping (i.e.; low grade/indolent, etc.), the committee emphasized that clinical decisions should be based on the specific lymphoid neoplasm.

Proposed WHO Classification of B-Cell Neoplasms

- Precursor B-cell neoplasm
 - Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
- Mature (peripheral) B-cell neoplasms*
 - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
 - B-cell prolymphocytic leukemia
 - Lymphoplasmacytic lymphoma
 - Splenic marginal zone B-cell lymphoma (1/2 villous lymphocytes)
 - Hairy cell leukemia
 - Plasma cell myeloma/plasmacytoma
 - Extranodal marginal zone B-cell lymphoma of MALT type
 - Nodal marginal zone B-cell lymphoma (1/2 monocytoid B cells)
 - Follicular lymphoma
 - Mantle-cell lymphoma
 - Diffuse large B-cell lymphoma
 - Mediastinal large B-cell lymphoma
 - Primary effusion lymphoma
 - Burkitt's lymphoma/Burkitt cell leukemia

Natural History

The median age prevalence of indolent lymphoma is in the sixth decade. B-cell indolent (low-risk group) NHL is not curable with standard treatment. First line therapy is commonly associated with a high rate of clinical response followed by relapse. Subsequent remissions may occur but at a progressively lower rate and with progressively shorter durations with a median progression-free survival (PFS) frequently less than 6 months^{vi} using traditional chemotherapeutic regimens. However, recent studies suggest that treatment using unconjugated monoclonal antibodies directed against CD20 antigen may yield a prolonged median PFS greater than 6 months^{vii} in relapsed or refractory indolent NHL populations.

Over time, indolent NHL may transform to aggressive (intermediate risk) or very aggressive (high-risk) lymphomas that have a more aggressive clinical course. The incidence of transformation ranges from 40% to 70% and is associated with disease progression and known adverse prognostic factors^{viii}. In general, transformation has a poor prognosis and frequently results in a rapidly fatal outcome. However, some patients

can have complete responses to salvage chemotherapy regimens and achieve durable complete remissions^{ix}. Overall survival following transformation is poor with an estimated median survival ranging from 7 to 22 months.

Prognostic Indicators

The most valuable and widely used prognostic indicator system for NHL is the International Prognostic Index (IPI)^x. The IPI is a prognostic index that was developed to predict outcome in patients with aggressive NHL, based on patients' clinical characteristics before treatment. However, the IPI has been shown to apply to indolent (low-risk) lymphoma^{xi}.

International Prognostic Index

The Tumor Score system divides the population into two risk groups by assigning one point for the presence of each of five variables:

- Age (less than or equal to 60 vs. >60 years),
- Tumor stage (stage I or II [localized disease] vs. stage III or IV [advanced disease]),
- Number of extranodal sites of disease (less than or equal to 1 vs. >1),
- Performance status (0 or 1 vs. greater than or equal to 2),
- Serum LDH level (less than or equal to 1 times normal vs. >1 times normal)

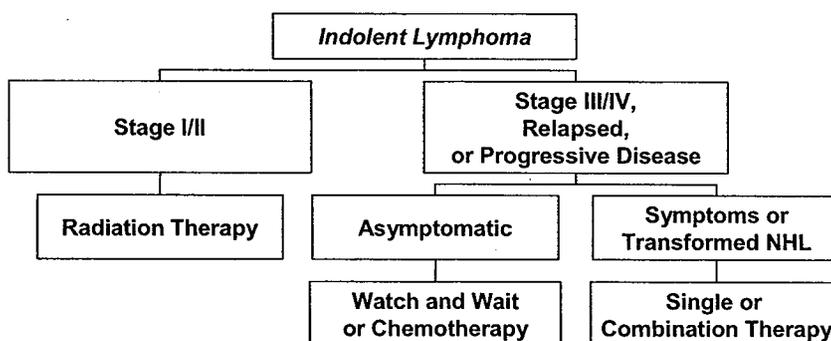
Patients with scores of < 1 are low risk; 2 low-intermediate risk; 3 high-intermediate risk; and > 3 high risk.

IPI Score and Clinical Outcome (Follicle Center Cell NHL)

IPI	CR (%)	5-yr FFS (%)	5-yr OS (%)	Median OS (mo)
Low	92	75	85	160
Low-Int	81	64	69	108
High-Int	77	38	28	35
High	0	0	0	12

Cytogenetics, gene rearrangement, and oncoproteins are important molecular markers of histologic subtype and mechanisms of lymphomagenesis. BCL2 oncogene (t14;18) overexpression is characteristic of follicular center cell NHLs. However, the use of biomarkers to predict clinical outcome in indolent NHL is investigational and need to be validated in prospective trials.

Treatment Strategy



Localized indolent lymphoma at initial presentation is unusual and represents less than 5% of the population. Patients with early-stage indolent lymphomas are potentially curable with radiation therapy (46% to 68% 10-year DFS)^{xii, xiii, xiv}. The addition of chemotherapy to radiotherapy as primary treatment has not convincingly prolonged remission duration or survival.

The majority of patients with indolent NHL present with advanced disease. For the majority of patients, selection of initial treatment is based on the clinical situation, prognostic indicators, physician bias, and patient choice. There is no single standard initial therapy for indolent NHL.

In general, alkylating agents are useful palliative treatment options that can result in improved well-being for most patients, often for long periods. Although commonly used, combinations of chemotherapy have not convincingly resulted in longer or greater number remissions. There is no proof that initial combination chemotherapy will prolong survival in comparison with single drugs. The addition of interferon to initial combination chemotherapy may increase the response rate, significantly prolong remission duration, but prolonged survival has not been unequivocally proven. In the absence of disease-related symptoms, treatment can safely be deferred without adversely impacting survival.

Distinguishing follicular lymphoma into those with predominantly small cells (follicle small, grade I), those with an intermediate number of small and large cells (follicle center, mixed small/large grade II), and those with more large cells (Follicle center, large grade III) is difficult^{xv}. However studies that have assessed the clinical behavior or these lymphomas have shown that patients with follicular large cell lymphoma have a shorter remission duration and overall survival than patients with the other subtypes. For these patients, the incorporation of an anthracycline into the initial treatment regimen appears to improve outcome^{xvi}.

**FDA Approved
Drugs in NHL**
BCNU
Blenoxane
Leukeran
Velban
Oncovin
Cytosar
Adriamycin
Methotrexate
Intron A
Rituxan

Overall response rates to therapy for low-grade lymphomas at the later stages (Stage III or IV) are between 80% to 90% with different chemotherapeutic regimens. The rate of complete response to initial therapy ranges from 23% to 83% in various studies. The median duration of response for therapy is 2 years for most studies. Less than 10% of patients remain in remission for more than 5 years. However, median survival exceeds 9 years in many series. The choice for either (a) a conservative approach or (b) an aggressive approach exists because there is still no evidence that one is more effective than the other in terms of overall survival.

**Commonly Used First Line
Treatment of Indolent NHL**

Watch and wait

Radiation

Localized

Low-dose total body

Irradiation

Oral alkylating agents

CVP

CHOP

CHOP + Rituxan

Mitoxantrone

Second and third generation
anthracycline-based regimens

Fludarabine

Cladribine

Transplantation

Interferon alpha-2b

Second Line Treatment

Patients with relapsed indolent lymphoma may repeatedly respond to alkylating agents or combinations containing an alkylating agent, although the proportion responding decreases with each relapse. Patients relapsing after or who are refractory to treatment with alkylating agents often respond to treatment with combinations containing an anthracycline. Responses are also often seen in patients treated with purine analogues alone or in combination with other drugs. High dose chemotherapy followed by autologous or allogeneic reestablishment of bone marrow function can induce long-term remissions but it is not proven whether they are more frequent or of longer duration than with conventionally dosed therapy. The impact of the novel treatment strategies including high-dose therapy on overall survival is still uncertain.

Recent Regulatory Approvals

There are two agents who have received marketing approval for the treatment of relapsed and refractory, low grade NHL. They are Rituxan (Rituximab) and the Zevalin therapeutic regimen. Rituxan is a chimeric monoclonal antibody directed against the CD20 antigen. The Zevalin therapeutic regimen, which is a two stage treatment involving administration of Rituxan plus ibritumomab (a murine monoclonal antibody directed against the CD20 antigen) labeled with 111-Indium, followed one week later by

Rituxan plus ibritumomab (a murine monoclonal antibody directed against the CD20 antigen) labeled with 90-Yttrium.

Rituxan is indicated for the treatment of relapsed or refractory, low grade or follicular NHL. Marketing approval was based on 3 single arm trials with a total of 242 registered participants. The ORR was 48% (6% CR and 42% PR) and the median duration of response ranged from 10-12 months. Serious adverse events were uncommon (<5%). In addition, the toxicity profile of Rituxan was mild, dominated by infusional toxicity most notable on the first dose and grade 3 or 4 toxicity occurring in less than 5% of the study population. Based on the very favorable toxicity profile indicating that Rituxan would be very unlikely to impair survival, the BRMAC recommended standard approval of Rituxan.

Zevalin was licensed in Feb. 19, 2002 based upon the results of two efficacy trials conducted in related populations. The first study was conducted in 143 patients with heavily pretreated low-grade follicular NHL, with or without transformation, in which patients were randomized to Rituxan or Zevalin. The results of this study showed a significantly higher response rate for Zevalin (73% vs. 47%), higher complete response rates (20% vs. 9%) and similar durations of response (14.2 vs. 12.1 mos) and times-to-progression (11.2 vs. 10.1 mos), as determined by a masked, independent review panel. There was also substantially greater hematologic toxicity for Zevalin-treated patients. The ODAC recommended accelerated approval for Zevalin in this population based upon the surrogate endpoint of higher response rate but felt that full approval would require additional data to establish the overall risks and benefits of Zevalin as compared to Rituxan. A confirmatory trial will be conducted to establish the superiority of Zevalin (over Rituxan) on progression-free survival.

The second efficacy study was a single arm trial conducted in 57 patients, 52 of whom had follicular NHL, who were refractory to prior Rituxan. In the subset of 52 patients, the overall response rate to Zevalin was 58% (95% CI 43%, 71%) with a median duration of response of 7.7 months. Toxicity in this population was qualitatively and quantitatively similar to that observed in randomized study. Based upon the anti-tumor activity in the Rituxan-refractory population together with the information absence of impairment in survival in the Rituxan-controlled study, the ODAC considered the risk-benefit ratio to have been adequately addressed for this patient population and recommended full approval. Zevalin received standard approval for treatment of follicular NHL that had relapsed from or was refractory to standard therapy, including Rituxan. Zevalin received accelerated approval for treatment of treatment of follicular or low grade NHL, with or without transformation, that had relapsed from or was refractory to standard chemotherapy but no prior Rituxan.

2.2 Pre-submission Activity

The current recommendation for approval of Bexxar therapeutic regimen is based on Study CP-97-012, which was a multi-center, single-

arm study in patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. Determination of clinical benefit of the BEXXAR therapeutic regimen was based on evidence of durable responses without evidence of an effect on survival. The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months. The results of the studies were discussed at the Oncology Advisory Committee meeting on December 17, 2002. And they were of the opinion that the objective response rate and the response duration supported by other clinical studies in Rituximab -naïve patients with chemotherapy-refractory disease, constitute substantial evidence of clinical benefit.

The original development plan for the tositumomab therapeutic regimen consisted of a single major efficacy trial (RIT-II-004) supported by evidence of anti-tumor activity in a single Phase 1, several Phase 2 trials and additional safety information obtained from a large expanded access experience. RIT-II-004 was a single arm, multicenter trial conducted in patients with chemotherapy-refractory, CD20 positive, low grade and follicular non-Hodgkin's lymphoma. The original goal of the major efficacy trial was to demonstrate that the tositumomab therapeutic regimen had an effect on the surrogate endpoint of response rate. The sponsor intended to show that the tositumomab therapeutic regimen could provide an overall response rate $\geq 30\%$, a complete response rate of $\geq 10\%$, and a median duration of response of 8 months in patients whose disease was no longer responding chemotherapy or who had short (<6 months) response durations. In order to put these data in perspective, the sponsor was urged to conduct a controlled trial.

In response to this request, the sponsor noted that, historically, objective response rates and the durations of response decrease with each subsequent

chemotherapy. Therefore, the trial was designed also to incorporate comparisons of the response rate and duration with the tositumomab therapeutic regimen to that achieved with the most recent chemotherapy regimen. Using this design, activity (durable tumor responses) would be demonstrated if a higher proportion of patients achieved responses and/or more durable responses after treatment with the tositumomab therapeutic regimen than they had achieved with an adequate trial (as least two cycles) of a standard chemotherapeutic regimen (defined in the protocol as the last qualifying chemotherapy [LQC]). To minimize the potential effects of bias in assessing the results in this open label, single arm trial, the response and duration of response to the LQC and to the tositumomab therapeutic regimen were determined by an independent review panel that was masked to the investigator's assessment of response. Masking to the treatment regimen was unlikely to have been maintained since the frequency and type of evaluations for response were uniform (specified in the protocol) following the tositumomab therapeutic regimen whereas the same evaluations for the LQC were performed according to the individual treating physician's standard medical practice.

This study design, which utilized the patient's response to recent prior chemotherapy as an historical control, was identified by the Biological Response Modifiers Advisory Committee (BRMAC) as an acceptable study design for drugs intended to treat patients with "chemotherapy-refractory" NHL and as an acceptable alternative to a concurrently controlled trial, using best standard of care or alternative therapy of physician choice, as requested by FDA.

The Investigational New Drug Application (IND) for Bexxar was received on October 13, 1989.

Milestones prior to submission of BLA

01/10/95	End-of-Phase 1/Pre-Phase 2 Meeting
02/28/97	Request for Subpart E Designation Submitted
03/13/97	Pre-Phase 3 Meeting (Clinical)
05/05/97	FDA AI Letter Issued: Subpart E Designation Denied
05/09/97	Request for Clarification of Subpart E Designation Submitted
06/03/97	Pre-Phase 3 Meeting (CMC)
10/02/97	FDA AI Letter Issued re: Pivotal Study; Subpart E Designation Denied
02/26/98	FDA AI Letter Issued re: Pivotal Study
07/28/98	End-of-Phase 3 Meeting
10/15/98	Pre-BLA Meeting (Clinical)

11/25/98 FDA Letter Issued: Fast Track Status Granted for Transformed Patients
12/15/98 Pre-BLA Meeting (CMC- Product Comparability)
06/25/99 FDA AI Letter Issued re: BLA Content and Format
06/29/99 BLA Application (STN 103906/0) Submitted
08/27/99 FDA Refusal-to-file (RTF) Letter Issued

Milestones for BLA STN 125011/0

09/14/00 BLA Application (STN 125011/0) Submitted
11/14/00 FDA Filing Notification Letter Issued
12/14/00 Safety Update Submitted
12/22/00 Proposed Manufacturing Change Submitted
02/01/01 FDA Discipline Review Letter (DR) Issued (Clinical)
03/16/01 FDA Complete Review (CR) Letter Issued
04/09/01 Type A Meeting (re: 3/16/01 CR Letter [Clinical])
05/31/01 Type A meeting (re: 3/16/01 CR Letter [CMC])
09/10/01 Class 2 Resubmission
12/11/01 Final Study Report for RIT-II-004 Submitted
03/04/02 Safety Update Submitted
03/12/02 FDA Complete Review Letter Issued
04/24/02 Type A Meeting (re: 03/12/02 CR letter [clinical])
05/13/02 FDA Advice Letter Issued
05/31/02 Request for Dispute Resolution Submitted
06/26/02 FDA Other Letter re: Dispute Resolution Issued
07/09/02 Revised Indication Submitted
07/19/02 Telecon re: Status of Dispute Resolution
07/23/02 Telecon re: Dispute Resolution/ODAC
07/24/02 Type A Meeting (re: 03/12/02 CR letter [CMC])
07/26/02 Telecon re: Dispute Resolution/ODAC
07/31/02 Telecon re: Dispute Resolution (Corixa chooses December ODAC as forum)
10/04/02 Incomplete Response to 03/12/02 CR Letter (Clinical Only)
10/31/02 Class 2 Resubmission
12/17/02 ODAC (Formal Dispute Resolution)
03/03/03 DR letter
05/21/03 CR letter

3.0 Integrated Review of Clinical Data

3.1 Data Sources and Review Method

The efficacy study for the indication considered for approval was based on CP-97-012, a multi-center, single-arm study in forty patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. The following table describes the source of the data considered.

Table 3: Number of Patients in Clinical Studies

Study	Enrolled Initiated	Number Enrolled	Number Integrated Efficacy Analysis (ISE)	Number of Patients in Safety (ISS-E) Efficacy Population (see notes)	Number of Patients in Safety (ISS-A) All	Number of Patients in Efficacy Population (ITT Analysis)	Number of Patients in Durable Response Population Durpop
RIT-I-000	24 Apr 90	59	42 ^a	22 ^{aa}	22	59	16
RIT-II-001	5 Dec 95	47	47	47	47	47	10
RIT-II-002 Arm A	18 Sep 96	42	42	42	42	42	12
RIT-II-002 Arm B	18 Sep 96	36	0	0	0	0	0
RIT-II-002 Arm X	18 Sep 96	19	19	19	19	19	8
RIT-II-003		77	0	0	0	0	0
RIT-II-004	22 Nov 96	61	60	60	60	61	15
CP-97-012	17 Jul 98	43	40	40	40	43	17
CP-98-020		796	0	0	765	0	0
Total		1180	250	230	995	271	78

^a Excludes 17 patients with intermediate grade lymphoma and also received total body doses other than 65 or 75 cGy

^{aa} 20 patients received total body doses other than 65 or 75 cGy.

Data Cutoff Date for Safety -- February 01, 2003

An updated safety database with an updated Integrated Safety Summary (ISS) for the 995 patients enrolled in Studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, CP-97-012, and CP-98-020 with a data cutoff date of 01 February 2003 was submitted to FDA on April 03, 2003.

Primary Study:

CP-97-012 Rituxan-failure patients

Supportive Studies:

RIT-I-000 Dose finding (predose unlabeled antibody and MTD) and safety

RIT-II-001 Reproducibility of whole body dosimetry, as well as safety and efficacy

RIT-II-004 Chemotherapy-refractory patients; patient-as-own control

RIT-II-002 Randomized comparison of the safety and efficacy of the labeled antibody versus the unlabeled antibody -- 42 patients received iodine I 131 tositumomab (Arm A), 36 patients received unlabeled antibody (Arm B) and 19 patients received iodine I 131 tositumomab (Arm X - Arm B Crossover after progressing on Arm B)

Notes on Efficacy/Safety Database:

- (1) The sponsor submitted information on 1180 patients enrolled or receiving iodine I 131 tositumomab in the 5 clinical efficacy/activity trials and additional experience in expanded access studies. Safety data are provided for 995 patients enrolled in the 5 clinical efficacy/activity trials and data from the expanded access experience. FDA has chosen to conduct analyses primarily in the data derived from 230 in the clinical studies and to utilize the expanded access data only to supplement targeted analyses of specific toxicities. The primary safety database is derived from the 5 clinical studies. The reasons for exclusion of patients from the database are summarized in the table below.

- (2) **Study - RIT-I-000:** 37 patients received total body doses other than 65 or 75 cGy. 17 patients out of 37 patients also had intermediate grade lymphoma). 17 patients are excluded from the efficacy database and 37 patients are excluded from the safety database

- (3) **Study - RIT-II-002:** Study 002 data included 42 patients from Arm A (hot antibody, Iodine I-131 Tositumomab) 36 from Arm B (cold antibody unlabeled Tositumomab) and 19 patients cross-over (Patients in Arm B who had documentation of disease progression were crossed over to be treated in Arm A (labeled antibody)). When they crossed over, they were re-enrolled with a unique patient ID number. Thus safety efficacy database has 61 (42+19) patients and excludes 17 patients who only received cold antibody unlabeled Tositumomab .

- (4) **Study - RIT-II-004:** 1 patient received dose = 0 cGy and is excluded. There was one patient (004-021-001 51M I75C) in RIT-II-004 with Mantle Cell NHL. This patient was White Male, 51 years old, Intermediate Grade, 75 cGy total body dose, IPI=2, Ann Arbor Stage at Study Entry = 4, Tumor

Grade at Study Entry = 4, Study Day of Diagnosis of NHL = 2.1 years, no prior bone marrow transplant, maximum diameter = 7, Number of prior chemotherapy received = 3, Number of prior radiotherapy received = 0, Response = SD, Maximum ANC Toxicity Grade (NCI criteria) = 2, Maximum PLT Toxicity Grade (NCI criteria) = 3, died on day 298 from dose.

- (5) **Study CP-97-012 Rituxan-Failure Study:** 3 patients did not receive any dose (dose=0 cGy) and are excluded from efficacy/safet database.
- (6) **Study CP-98-020 Expanded Access Study** – 31 patients on study had less than 13 weeks of follow up as data cut-off date or 2 patients in single patient studies (out of 6 single patient studies) received total body doses other than 65 or 75 cGy These patients are excluded
- (7) **Durpop** is patients who had durable response. This population includes all integrated efficacy patient population MIRROR-panel assessed confirmed responders with MIRROR panel-assessed time to progression of at least one year.
- (8) **ISE- Durpop** is patients in the ISE population who did not have durable response.
- (9) **Tran Pop** = Transformed low-grade patient population- includes all integrated efficacy population patients with transformed low-grade NHL

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of

delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

In describing hematologic toxicity of cytopenias, missing data was imputed as showing grade III/IV toxicity thereby depicting the worst case scenario.

3.2 Clinical Pharmacology

Please see detailed reviews by Dr. Green (Pharmacology/toxicology review) and Dr. Mills (nuclear Medicine aspects in section 3.5.1)

General Pharmacology

Tositumomab binds specifically to the CD20 (human B-lymphocyte–restricted differentiation antigen, Bp 35 or B1) antigen. This antigen is a transmembrane phosphoprotein expressed on pre-B lymphocytes and at higher density on mature B lymphocytes. The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL). CD20 is not expressed on hematopoietic stem cells, normal plasma cells, or other non-lymphoid cells. The recognition epitope for Tositumomab is found within the extracellular domain of the CD20 antigen. CD20 does not shed from the cell surface and does not internalize following antibody binding.

Mechanism of Action: Possible mechanisms of action of BEXXAR include induction of apoptosis, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC) mediated by the antibody. Additionally, cell death is associated with ionizing radiation from the radioisotope.

Pharmacokinetics/Pharmacodynamics

The phase 1 study of Iodine I 131 Tositumomab determined that a 475 mg predose of unlabeled antibody decreased splenic targeting and increased the terminal half-life of the radiolabeled antibody. The median blood clearance following administration of 485 mg of Tositumomab in 110 patients with non-Hodgkin's lymphoma was 68.2 mg/hr (range: 30.2–260.8 mg/hr). Patients with high tumor burden, splenomegaly, or bone marrow involvement were noted to have a faster clearance, shorter terminal half-life, and larger volume of distribution. The total body clearance, as measured by total body gamma camera counts, was dependent on the same factors noted for blood clearance. Patient-specific dosing, based on total body clearance, provided a consistent radiation dose, despite variable pharmacokinetics, by allowing each patient's administered activity to be adjusted for individual patient variables.

Elimination of Iodine-131 occurs by decay and excretion in the urine. Urine was collected for 49 dosimetric doses. After 5 days, the whole body clearance was 67% of the injected dose. Ninety-eight percent of the clearance was accounted for in the urine. (Please see detailed review by Dr. Mills section 3.5.1 regarding dosimetry and other nuclear medicine issues).

3.3 Integrated Review of Efficacy

3.3.1 Approach to Review of the Efficacy

The data sources are described in section 3.3.1.

The efficacy study for the indication considered for approval was based on CP-97-012, a multi-center, single-arm study in forty patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy.

3.3.2 Review of Trials by Indication

The following describes the *Study CP-97-012*, which is described in greater detail in section 6.1. The other clinical trials that support the approval of Bexxar are described in section 6.1 under the individual study reports.

Title: Phase II Study of Iodine I 131 tositumomab for Non-Hodgkin's Lymphoma Patients who Have Previously Received Rituximab.

Design: Phase 2, single-arm, open-label, multicenter study of iodine I 131 tositumomab in the treatment of non-Hodgkin's lymphoma patients who were previously treated with rituximab therapy without an objective response or who relapsed/progressed during or within 6 months following therapy.

Objectives

1. To assess the response rate and duration of response of iodine I 131 tositumomab therapy in patients who were previously treated with at least 4 doses of rituximab and failed to achieve a response (CR, CCR, or PR) or relapsed/progressed during treatment or following completion of rituximab therapy.
2. To assess the safety of Iodine I 131 -tositumomab therapy in patients who were previously treated with at least 4 doses of Rituximab and failed to achieve a response (CR, CCR, or PR) or relapsed/progressed during treatment or following completion of rituximab therapy.

Inclusion Criteria (verbatim from protocol after the inclusion of amendments 1-4)

1. Patients must have a histologically confirmed initial diagnosis of low grade non-Hodgkin's B-cell lymphoma according to International Working Formulation (i.e., small lymphocytic [with or without plasmacytoid

differentiation]; follicular, small-cleaved; or follicular, mixed small-cleaved lymphoma), low-grade lymphoma that has transformed to higher grade histology, or *de novo* follicular large cell lymphoma.

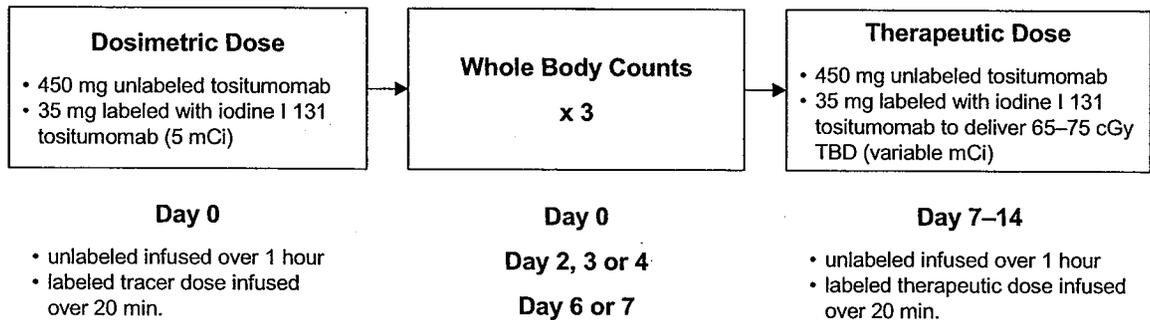
2. Patients must have evidence that their tumor tissue expresses the CD20 antigen. Immunoperoxidase stains of paraffin-embedded tissue showing positive reactivity with L26 antibody or immunoperoxidase stains of frozen tissue showing positive reactivity with Anti-B1 Antibody or evidence of CD20 positivity by flow cytometry are acceptable evidence of CD20 positivity.
3. Patients must have been treated with at least 4 doses of rituximab at any time and failed to achieve an objective response (CR, CCR, PR), or relapsed/progressed during treatment or following the completion of rituximab therapy.
4. Patients must have a performance status of at least 60% on the Karnofsky Scale and an anticipated survival of at least three months.
5. Patients must have an absolute granulocyte count $>1500/\text{mm}^3$ (US) or $>1500 \times 10^9/\text{l}$ (UK) and a platelet count $>100,000/\text{mm}^3$ (US) or $>100,000 \times 10^9/\text{l}$ (UK) within 14 days of study entry. These blood counts must be sustained without support of hematopoietic cytokines or transfusion of blood products.
6. Patients must have adequate renal function (defined as serum creatinine $<1.5 \times$ upper limit of normal) and hepatic function (defined as total bilirubin $<1.5 \times$ upper limit of normal and hepatic transaminases [AST and ALT] $<5 \times$ upper limit of normal) within fourteen days of study entry.
7. Patients must have bi-dimensionally measurable disease. At least one lesion must be 2 x 2 cm (by CT scan).
8. Patients must be at least 18 years of age.
9. Patients must give written informed consent and sign an Institutional Review Board/Ethics Committee (IRB/EC)-approved informed consent form prior to study entry.

Exclusion Criteria (verbatim from final protocol which includes amendments 1-4)

1. Patients with more than an average of 25% of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens as assessed microscopically within 42 days of study entry. Bilateral posterior iliac crest core biopsies are required if the percentage of intratrabecular space involved exceeds 10% on a unilateral biopsy. The mean of bilateral biopsies must be no more than 25%.
2. Patients who have received cytotoxic chemotherapy, radiation therapy, immunosuppressants, or cytokine treatment within 4 weeks prior to study entry (6 weeks for nitrosourea compounds) or who exhibit persistent clinical evidence of toxicity. The use of systemic steroids must be discontinued at least 1 week prior to study entry.
3. Patients with prior hematopoietic stem cell transplant following high dose chemotherapy or chemo/radiotherapy.
4. Patients with active obstructive hydronephrosis.
5. Patients with evidence of active infection requiring intravenous (IV) antibiotics at the time of study entry.
6. Patients with New York Heart Association class III or IV heart disease (see Appendix D) or other serious illness that would preclude evaluation.
7. Patients with prior malignancy other than lymphoma, except for adequately treated skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for 5 years.
8. Patients with known HIV infection.
9. Patients with known brain or leptomeningeal metastases.
10. Patients who are pregnant or breastfeeding. Patients of childbearing potential must undergo a pregnancy test within 7 days of study entry and radiolabeled antibody is not to be administered until a negative result is obtained. Males and females must agree to use effective contraception for 6 months following the radioimmunotherapy.
11. Patients with previous allergic reactions to iodine. This does not include reacting to IV iodine-containing contrast materials.
12. Patients who previously received radioimmunotherapy.

13. Patients with progressive disease within 1 year of irradiation arising in a field that has been previously irradiated with >3500 cGy.
14. Patients who are HAMA positive.
15. Patients who are concurrently receiving either approved or non-approved (through another protocol) anti-cancer drugs or biologics.

Treatment Plan



Patient Monitoring Plan

Data were collected in three different phases.

1. During the initial study period, patients had data collected during outpatient visits
 - Imaging at several time points over days 0-7 to collect dosimetry data
 - AE data was collected at each visit.
 - Hematologic values were required to be obtained at baseline, weeks 3 through 9, weeks 13 and 25 and thereafter every 26 weeks during the follow-up phase.
 - HAMA values were obtained at baseline, day 5, weeks 7, 13, and 25.
 - Thyroid function (including TSH) data were obtained at baseline, week 25 and during follow up and long-term follow up (after amendment 4) visits.
 - Tumor response was evaluated at baseline and at weeks 7, 13, 25, and during follow-up visits.

2. At week 52, the follow up [FU] phase of visits began every 26 weeks until two years or until the patient withdrew from the study or two years elapsed. Follow up visits included physical examination and history, hematology and serum chemistry and thyroid function tests, radiographic evaluations, information on AEs and medication experience, and bone marrow studies if baseline biopsy was positive for lymphoma.
3. The last phase of monitoring was long-term follow up [LTFU]. LTFU began either after a patient withdrew from study for progressive disease or concomitant therapy or after two years post therapeutic dose. Data was collected every six months. LTFU data initially included only vital status, cancer status, and thyroid function but was expanded in amendment four to include HAMA, TSH sampling and thyroid disease information, second malignancy information and subsequent therapy for NHL by history.

Original Analytic plan

No primary endpoint was identified. The following endpoints were listed: response rate, complete response rate, response duration, time to progression, time to treatment failure, and survival. The sample size of 20 patients was selected to enable the response rate to be estimated with a maximum standard error of 0.112 and an expected standard error of 0.10. (The sample size was subsequently increased to 40 patients via amendment.) Point estimates with two-sided 95% confidence intervals would be generated for response rates; patients withdrawing due to death or toxicity before their [response] status could be assessed were considered to have progressive disease (intent-to-treat analysis). Additional analyses of response rates in patients who completed protocol-specified therapy would also be conducted. Kaplan-Meier curves would be generated for time to event analyses (response duration, time to progression, time to treatment failure and overall survival) and mean and median durations for the time to event analyses reported. Adverse events would be summarized by relationship to study drug, organ system and severity. Summaries of patient

discontinuations would be provided. The use of supportive care such as CSFs and transfusions would be provided.

Results

Patient Enrollment and Disposition

Forty-three patients were enrolled between July 17, 1998 and November 19, 1999. Three patients did not receive either the dosimetric or therapeutic dose (012-035-005; 012-036-011; and 012-037-013). Forty patients received both the dosimetric and therapeutic dose.

Study Population

The subjects enrolled in this study had similar baseline entry characteristics to those enrolled in other study (RIT-II-004) in terms of proportion with transformed disease, distribution of stages of disease, proportion with bulky disease, and prior treatment history, with the sole exception that all patients must have progressed following treatment with rituximab.

Table 4: Baseline Entry Characteristics for Study Population in Study CP 97-012

Baseline entry characteristic	ITT population n=43
Age (years)	
Median(range)	56 (35-78)
Q1; Q3	49; 65
Gender	
Males (%)	29 (67%)
Race	
Caucasian (%)	35 (81%)
Histologic diagnosis at entry	
W/o transformation	
Low grade	27 (63%)
Intermediate grade	3 (7%)
High grade	0
With transformation	
Low grade	1(2%)
Intermediate grade	12 (28%)
High grade	0
Stage of disease	
I	1 (2%)
II	7 (16%)
III	9 (21%)
IV	26 (61%)
Missing	0
IPI category	
0	2 (5%)
1	12 (28%)
2	15 (35%)
3	5 (12%)
4	4 (9%)
5	1 (2%)
Missing	4 (9%)
Max. tumor diameter	
< 5 cm	24 (56%)
≥ 5, ≤10 cm	14 (33%)
> 10 cm	5 (12%)
# Prior chemo regimens	
Median (range)	4 (1-11)
25 th , 75 th quartiles	3, 5
# Prior RT regimens	
Median (range)	0 (0-4)
25 th , 75 th quartiles	0, 1
No Prior BMT	42 (98%)
Time from diagnosis to entry (yrs)	
Median i(range)	4.2 (1.0, 14.2)
25 th , 75 th quartiles	2.7, 7.0

Efficacy Analyses

No primary efficacy endpoint was identified in the protocol. The analytic plan stated that analyses would be conducted in the intent-to-treat population, which was not further defined. The analytic plan also stated that additional analyses of response rates in patients who completed protocol-specified therapy would also be conducted. In addition, the proposed indicated population to be supported by this study differs from that eligible for the study. For these reasons, all pre-specified analyses were assessed in three populations:

- An intent-to-treat (ITT) population that includes all of the patients registered in the study (n=43). In the ITT analyses, patients who did not receive the tositumomab therapeutic regimen are treated as patients with no response and a response duration of 0 days.
- The “treated” population that includes all patients who received all or part of the tositumomab treatment regimen (n=40);
- The “proposed indication” population that includes patients with rituximab refractory, follicular NHL without major eligibility violations (n=30) The “indicated” population excludes 13 subjects listed below (some subjects are overlapping):
 - 3 subjects who did not receive the tositumomab therapeutic regimen (patients 012-035-005, 012-036-011 & 012-037-013)
 - 5 subjects with prior responses to rituximab that were durable for ≥ 6 months, i.e., were not rituximab-refractory (patients 012-035-001, 012-036-012, 012-037-002, 012-037-007 & 012-037-009)
 - 2 patients who lacked baseline radiographic studies (patients 012-036-002 & 012-036-006),
 - 2 patients without measurable 2 x 2 cm lesions (patients 012-035-005 & 012-037-001)

- 1 patient who had a treatment within 4 weeks prior to enrollment (012-035-008).
- 2 patients who did not have follicular histology (012-035-008 and 012-036-002)
- 2 patients with follicular histology with transformation (012-037-002 and 012-035-015)

Pre-specified Efficacy Analyses

The pre-specified study endpoints were response rate, complete response rate, response duration, time to progression, time to treatment failure, and survival. Time to treatment failure was removed as an endpoint in the fourth and final amendment to the protocol. Analyses of time to progression, time to treatment failure, and survival were not provided in FDA's analyses, because these data cannot be interpreted in a study that does not contain an internal control population.

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Table 5: Response Rates and Duration of Response for Study CP-97-012

	ITT Investigator or (n=43)	ITT MIRROR (n=43)	Treated Investigator or (n=40)	Treated MIRROR (n=40)	Indicated Invest. assess (n=30)	Indicated MIRROR (n=30)
Overall response rate (Number of responders) 95% CI	60% (26) 44%, 75%	63% (27) 47%, 77%	65% (26) 48%, 79%	68% (27) 51%, 81%	60% (18) 41%, 77%	63% (19) 44%, 80%
Median Duration (Years) (K-M Curves) 95% CI on Median IQ Range in Years Range in Years	1.9 0.9, --- 0.7, --- 0.3, 2.9+	1.3 0.8, --- 0.8, --- 0.1+, 2.9+	1.0 0.9, --- 0.7, --- 0.3, 2.9+	1.3 0.8, --- 0.8, --- 0.1+, 2.9+	--- 1.3, ... 1.3, --- 0.3, 2.9+	2.1 yrs 0.9, --- 0.9, --- 0.3+, 2.9+
CR (%) 95% CI	14% (6) 5%, 28%	26% (11) 14%, 41%	15% (6) 6%, 30%	28% (11) 15%, 44%	17% (5) 6%, 35%	23% (7) 10%, 42%
CCR (%) 95% CI	19% (8) 8%, 33%	5% (2) 1%, 16%	20% (8) 9%, 36%	5% (2) 1%, 17%	20% (6) 8%, 39%	3% (1) 0%, 17%
PR (%) 95% CI	28% (12) 15%, 44%	33% (14) 19%, 49%	30% (12) 17%, 47%	35% (14) 21%, 52%	23% (7) 10%, 42%	37% (11) 20%, 56%

--- indicates not reached
+ indicates censored

The protocol was amended four times; the last amendment, which stated that efficacy analyses would be conducted according to MIRROR panel assessment, was activated more than one year after the last patient was enrolled. Therefore, it is appropriate to present both the investigator-assessed response rates and that derived from MIRROR panel review. The FDA assessed for concordance between the investigator-assessment and the MIRROR Panel assessment of response (CR + CCR + PR) and non-response (SD + PD). There were no significant differences ($p = 1.0$, McNemar's test) with only one discrepancy in determination of objective response. However, among the categories of response, the MIRROR panel identified a higher proportion of patients with CR as compared to the investigators; the latter identified a higher proportion of patients with CCR. In analyses where CR and CCR rates are pooled, this difference would not change the analysis.

Other protocol-specified analyses

1. In amendment 1, the analytic plan was revised, stating that analyses of response would be “stratified by response to prior Rituxan.” The protocol does not provide additional details on the proposed stratification. For purposes of this analysis, the response rates are analyzed according to patients who responded to rituximab and those who failed to respond to the most recent rituximab regimen. Since rituximab has a long serum half-life and can be detected in the serum 6-9 months after receiving a single 4 weekly course, patients in whom the response to rituximab was less than 6 months should be classified as refractory and analyzed with those who fail to achieve a response. As can be seen in the next table, the response rates to the tositumomab therapeutic regimen does not appear to differ qualitatively in patients who failed to respond to rituximab as compared to those who were responsive, although the duration of response is shorter in the rituximab non-responsive patients.

Table 6: Response rate to I 131 tositumomab in subsets of the study population based on prior response to rituximab.

Prior response to most recent rituximab regimen	Response to the tositumomab therapeutic regimen	Median Duration of response to the tositumomab therapeutic regimen
Rituximab-responsive (CR, CCR, or PR)	11/18 (61%)	2.1 years
Rituximab non-responsive (PD OR SD)	16/25 (64%)	1.3 years

There were 4 patients enrolled who achieved a CR, CCR or PR to the most recent rituximab course that was durable for ≥ 6 months. The results in these patients whose disease was not refractory to rituximab are summarized as follows:

Table 7:

Patient ID	Rituximab Response	Duration of Response- Rituximab in Years	Tositumomab Therapeutic Regimen Response	Duration of Response- Tositumomab in Years
012-036-001 41F L75B	PR	0.5	PR	0.8
012-036-012 50F L75B	CR	0.6	CR	1.9+
012-037-002 57M T75B	PR	1.2	CR	1.2
012-037-007 58F T75B	CR	1	PR	0.1+
012-037-009 52M L75B	PR	0.6	CR	0.8

2. In amendment 4, the analytic plan in the protocol was modified to an analysis of comparison of the duration of response to the tositumomab therapeutic regimen and to the most recent rituximab regimen

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Using the same algorithm as applied in study RIT-II-004, the following table provides a summary of the results for the comparison of response durations for the tositumomab therapeutic regimen and prior rituximab :

Response	Frequency	% of 43
Equivalent response duration	11	26 %
Longer duration with tositumomab	25	58 %
Longer duration with Rituximab	7	16 %

The sign-rank test was used in FDA's analysis because it takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is a statistical change. The proportion of patients for whom the tositumomab therapeutic regimen provided more durable responses was significantly larger (sign-rank test)

The analysis of proportions was performed as follows:

Let p_1 = proportion of responses with equivalent duration to the tositumomab therapeutic regimen and to rituximab

p_2 = proportion of responses with longer duration to the tositumomab therapeutic regimen

p_3 = proportion of responses with longer duration to rituximab

Of interest is a test of the null hypothesis $H_0 : p_2 = p_3$ conditioned on equivalent response, i.e., ignoring equivalent response, and n becomes 32, and test is . $H_0 : p_2 = p_3 = 0.5$ versus $H_1 : p_2 \neq p_3$.

p-value for testing this H_0 was significantly different (two sided, Fisher's exact) in favor of the tositumomab therapeutic regimen

Table 8:

ITT population (n=43)				
		Response to Tositumomab		
		Response	No Resp	Total
Response to Rituximab	Response	11	7	18
	No Resp	16	9	25
	Total	27	16	43

p-value (McNemar) = 0.0719

The following table summarizes the data on 40 patients (instead of intent to treat analysis), who received Bexxar and were stratified as per their prior response to Rituximab.

Table 9: Efficacy Outcomes Patients (CP-97-012)

	Objective Responses to the BEXXAR Therapeutic Regimen in patients refractory to Rituximab		Objective Responses to the BEXXAR Therapeutic Regimen in all Patients	
	Response Rate (%) (95% CI ^a) (n=35)	Median duration of response (Mos) (Range)	Response Rate (%) (95% CI ^a) (n=40)	Median Duration of Response (Mos) (Range)
Overall Response	63% (45% - 79%)	25 (4+ - 35+)	68% (51% - 81%)	16 (1+ - 35+)
Complete response ^c	29% (15% - 46%)	NR ^b (4 - 35+)	33% (19% - 49%)	NR (4 - 35+)

^a C.I. = Confidence Interval
^b NR = Not reached
^c Complete response rate = Pathologic and clinical complete responses

3.3.3 Clinical Microbiology

Not Applicable

3.3.4 Efficacy Conclusions

The overall response rate of 68% and complete response rate of 33% in Study CP97-012, the study that assesses the activity of the tositumomab therapeutic regimen in patients whose disease is refractory to, or only transiently responsive to, Rituximab, supported by the activity in other studies in patients with chemotherapy-refractory disease, are adequate and are reasonably likely to predict clinical benefit for the treatment of patients with follicular NHL that has relapsed following chemotherapy and is refractory to Rituxan. It should be noted that complete responses are uncommon in this disease.

The small size of the study imposes a drawback, but the Oncology Advisory Committee also felt that the responses seen with Bexxar are likely to predict true clinical benefit. The findings of this single study, when viewed with the corroborative evidence of efficacy from four other trials justifies such conclusion.

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3.4 Integrated Review of Safety

3.4.1 Approach to Review of Safety

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

In describing hematologic toxicity of cytopenias, missing data was imputed as showing grade III/IV toxicity thereby depicting the worst case scenario.

3.4.2 Safety Findings

3.4.2.1 Exposure

Bexxar therapeutic regimen is given as a one time administration.

3.4.2.2 Deaths

One hundred and 128 of the 230 patients died during the course of follow-up. Of these, 94 patients died from progression of disease. The remaining 34 patients died of other causes. The following table describes these causes of death along with the interval in days between study entry and the death.

Table 10:

PATID	DAY OF Death	CAUSE OF DEATH
000-002-019 58F T65C	2792	MYELOYDYSPLASIA
000-002-031 41M T75C	2824	ACUTE MYELOGENOUS LEUKEMIA
000-002-050 49F L75C	1159	MYELOYDYSPLASIA

000-002-055 68M L75C	470	BAD INFECTION, STROKE, LOW BLOOD COUNTS (NO BONE MARROW LEFT)
000-002-056 66F T75C	1177	PROGRESSIVE LYMPHOMA WITH ASSOCIATED MYELODYSPLASTIC SYNDROME AND PANCYTOPENIA
001-003-004 46F T75C	304	METASTATIC COLON CANCER
001-004-004 40F L75C	856	ASPERGILLUS PNEUMONIA, BONE MARROW FAILURE, MATCHED UNRELATED BMT, REFRACTORY...
001-004-007 47M T75C	395	COMPLICATIONS OF HIGH-DOSE THERAPY & STEM CELL TRANSPLANT, FUNGAL INFECTION &...
001-006-001 51M L75C	980	COMPLICATIONS OF ALLO BMT FOR SECOND DEGREE MDS
001-006-004 69F T75C	746	MDS WITH TRANSFORMATION TO AML
001-008-002 30F L00C	4	UPPER GASTROINTESTINAL TRACT HEMORRHAGE, DISSEMINATED INTRAVASCULAR COAGULATION
001-009-002 56F L75C	967	ACUTE MYELOID LEUKEMIA
002-011-016 50F L75C	2175	SEPSIS & PROGRESSION OF OVARIAN CARCINOMA
002-011-917 50F L75C	586	PROGRESSION OF NHL WITH MDS & CML
002-030-002 69F L75L	54	RESPIRATORY FAILURE SECONDARY TO GRAM NEGATIVE SEPSIS
002-030-019 52M L65B	248	MDS LEADING TO MATCHES UNRELATED DONOR BMT RESULTED IN DEATH SECOND. TO BMT
002-030-023 54M L65B	374	FUNGAL PNEUMONIA WITH SEPSIS WHICH LEAD TO RESPIROTARY FAILURE AND DEATH
002-030-024 57M L65B	769	HEPATIC FAILURE (UNRELATED TO RIT) POSSIBLY RELATED TO ACETAMINOPHEN INGESTION
002-030-906 57M T75B	524	METASTATIC GASTRIC ADENOCARCINOMA
004-013-013 55F L75L	1163	CARDIOVASCULAR ACCIDENT
004-015-006 71F T75L	136	PATIENT DEVELOPED OTHER MEDICAL CONDITIONS DURING HOSPITALIZATION. CT SCAN W...
004-016-007 61M T75L	1390	PROGRESSION OF LYMPHOMA AND PROGRESSION OF MYELODYSPLASTIC SYNDROME
004-018-001 39F T00C	14	PATIENT DEVELOPED ENCEPHALOPATHY, EXCLUDING HER FROM HAVING FURTHER TREATMENT
004-020-002 50M T75C	430	IDIOPATHIC INTERSTITIAL PNEUMONITIS
004-020-006 60M L75L	433	PROGRESSION OF LYMPHOMA; CARDIAC ARREST ACUTE RENAL FAILURE
004-020-008 71M L65L	1182	MDS
004-029-001 72M T65L	111	SEPSIS RELATED TO FURTHER CHEMOTHERAPY GIVEN FOR PROGRESSION OF LYMPHOMA
012-035-002 63M L75L	896	ACUTE LEUKEMIA
012-035-014 72M L75B	222	COMPLICATIONS RELATED TO GALLBLADDER SURGERY

012-035-016 69F T75B	529	ASPIRATION PNEUMONIA
012-036-001 41F L75B	900	IMMUNOCOMPROMISED STATUS POST MARROW TRANSPLANT
012-036-002 37M L75B	409	INTERSTITIAL PNEUMONITIS
012-036-009 67F T75B	235	SEPSIS, SECONDARY TO LYMPHOMA
012-037-005 63M T75B	35	RESPIRATORY FAILURE DUE TO ASPIRATION PNEUMONIA

3.4.2.3 Other Serious Adverse Events

Hematologic Events: Hematologic toxicity was the most frequently observed adverse event in clinical trials with the BEXXAR therapeutic regimen (Table 6). Sixty-three (27%) of 230 patients received one or more hematologic supportive care measures following the therapeutic dose: 12% received G-CSF; 7% received erythropoietin; 15% received platelet transfusions; and 16% received packed red blood cell transfusions. Twenty-eight (12%) patients experienced hemorrhagic events; the majority were mild to moderate.

Infectious Events: One hundred and four of the 230 (45%) patients experienced one or more adverse events possibly related to infection. The majority were viral (e.g. rhinitis, pharyngitis, flu symptoms, or herpes) or other minor infections. Nineteen of 230 (8%) patients experienced infections that were considered serious because the patient was hospitalized to manage the infection. Documented infections included pneumonia, bacteremia, septicemia, bronchitis, and skin infections.

Hypersensitivity Reactions: Fourteen patients (6%) experienced one or more of the following adverse events: allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus, and serum sickness.

Gastrointestinal toxicity: Eighty-seven patients (38%) experienced one or more gastrointestinal adverse events, including nausea, emesis, abdominal pain, and diarrhea. These events were temporally related to the infusion of the antibody. Nausea, vomiting, and abdominal pain were

often reported within days of infusion, whereas diarrhea was generally reported days to weeks after infusion.

Infusional Toxicity: A constellation of symptoms, including fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea, have been reported during or within 48 hours of infusion. Ninety-two patients (40%) reported fever, rigors/chills, or sweating. Although all patients in the clinical studies received pretreatment with acetaminophen and an antihistamine, the value of premedication in preventing infusion-related toxicity was not evaluated in any of the clinical studies. Infusional toxicities were managed by slowing and/or temporarily interrupting the infusion. Symptomatic management was required in more severe cases. Adjustment of the rate of infusion to control adverse reactions occurred in 16 patients; seven patients required adjustments for only the dosimetric infusion, two required adjustments for only the therapeutic infusion, and seven required adjustments for both the dosimetric and the therapeutic infusions. Adjustments included reduction in the rate of infusion by 50%, temporary interruption of the infusion, and in 2 patients, infusion was permanently discontinued.

Delayed Adverse Reactions

Delayed adverse reactions, including hypothyroidism, HAMA, and myelodysplasia/leukemia, were assessed in 230 patients included in clinical studies and 765 patients included in expanded access programs. The entry characteristics of patients included from the expanded access programs were similar to the characteristics of patients enrolled in the clinical studies, except that the median number of prior chemotherapy regimens was fewer (2 vs. 3) and the proportion with low-grade histology was higher (77% vs. 70%) in patients from the expanded access programs.

Secondary Leukemia and Myelodysplastic Syndrome (MDS): There were 32 new cases of MDS/secondary leukemia reported among 994 (3.2%) patients included in clinical studies and expanded access programs, with a median follow-up of 21 months. The overall incidence of MDS/secondary leukemia among the 229 patients included in the clinical studies, was 8.3% (19/229), with a median follow-up of 35 months and a median time to development of MDS of 30 months. The cumulative incidences of MDS/secondary leukemia were 4.2% and 10.7% at 2 and 4 years, respectively. Among the 765 patients included in the expanded access programs, where the median duration of follow-up was shorter (20 months), the overall incidence of MDS/secondary leukemia was 1.7% (13/765) and the median time to development of MDS was 23 months. The cumulative incidences of MDS/secondary leukemia were 1.37% and 4.8% at 2 years and 4 years, respectively, in the expanded access population.

Secondary Malignancies: There were 52 reports of second malignancies, excluding secondary leukemias. The most common included non-melanomatous skin cancers, breast, lung, bladder, and head and neck cancers. Some of these events included recurrence of an earlier diagnosis of cancer.

Hypothyroidism: Twelve percent (27/230) of the patients included from the clinical studies had an elevated TSH level (8%) or no TSH level obtained (4%) prior to treatment. Of the 203 patients documented to be euthyroid at entry, 137 (67%) patients had at least one follow-up TSH value. The overall incidence of hypothyroidism, in the absence of competing risks, in the clinical study patients was 14% with cumulative incidences of 4.2% at 6 months and 8.1%, 12.6%, and 15.0% at 1, 2, and 4 years, respectively. New events have been observed up to 72 months post treatment. Twelve percent (117/990) of the patients included in clinical studies or the expanded access programs had an elevated TSH level (8%) or a history of hypothyroidism (4%) prior to treatment and 5 patients had no baseline information. Of the 873 who were euthyroid at entry, 583 (67%) had at least one post-treatment TSH value obtained. With a median observation period of 18 months, 54 patients (9%) became

hypothyroid as determined by elevated TSH. The cumulative incidence of hypothyroidism in the combined populations was 9.1% and 17.4% at 2 and 4 years, respectively.

Immunogenicity: Two percent (4/230) of the chemotherapy-relapsed or refractory patients included in the clinical studies had a positive serology for HAMA prior to treatment and six patients had no baseline assessment for HAMA. Of the 220 patients who were seronegative prior to treatment, 219 (99.5%) had at least one post-treatment HAMA value obtained. With a median observation period for HAMA seroconversion of 6 months, 23 patients (11%) seroconverted to HAMA positivity. The median time to development of HAMA was 6 months. In a study of 77 patients who were chemotherapy-naïve, the incidence of conversion to HAMA seropositivity was 70%, with a median time to development of HAMA of 27 days.

One percent (11/989) of the chemotherapy-relapsed or refractory patients included in the clinical studies or the expanded access program had a positive serology for HAMA prior to treatment and six patient had no baseline assessment for HAMA. Of the 978 patients who were seronegative for HAMA prior to treatment, 785 (80%) had at least one post-treatment HAMA value obtained. With a median observation period of 6 months, a total of 76 patients (10%) became seropositive for HAMA post-treatment. The median time of HAMA development was 148 days; with 45 (59%) patients seropositive for HAMA by 6 months. No patient became seropositive for HAMA more than 30 months after administration of the BEXXAR therapeutic regimen.

3.4.2.4 Dropouts and Other Significant Adverse Events

Of the 230 patients, 193 patients were considered to have been terminated from the clinical studies. One hundred and seventy eight patients were removed from the study for progressive disease. Of the remaining, 2 were removed because of infusion had to be stopped, 1 for non-compliance, 1 patient was lost to follow up, 3 patients sought alternative treatment, 2 patients for

medical conditions unrelated to lymphoma or therapy, 4 patients for death (at 35, 41, 470 and 524 days) and 2 patients for other reasons.

3.4.2.5 Other Search Strategies Applied to Clinical Safety Database

Not Applicable

3.4.2.6 Common Adverse Events

Table 5 lists adverse events that occurred in $\geq 5\%$ of patients. Table 11 provides a more detailed description of the hematologic toxicity.

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Table 11
Incidence of Adverse Experiences Regardless of Relationship to Study
Drug occurring in $\geq 5\%$ of the Patients Treated with BEXXAR Therapeutic
Regimen^a
(N = 230)

Body System Preferred Term	All Grades	Grade 3/4
Total	(97%)	(77%)
Non-Hematologic AEs		
Body as a Whole	81%	12%
Asthenia	46%	2%
Fever	37%	2%
Infection ^b	21%	<1%
Pain	19%	1%
Chills	18%	1%
Headache	16%	0%
Abdominal pain	15%	3%
Back pain	8%	1%
Chest pain	7%	0%
Neck pain	6%	1%
Cardiovascular System	26%	3%
Hypotension	7%	1%
Vasodilatation	5%	0%
Digestive System	56%	9%
Nausea	36%	3%
Vomiting	15%	1%
Anorexia	14%	0%
Diarrhea	12%	0%
Constipation	6%	1%
Dyspepsia	6%	<1%
Endocrine System	7%	0%
Hypothyroidism	7%	0%
Metabolic and Nutritional Disorders	21%	3%
Peripheral edema	9%	0%
Weight loss	6%	<1%
Musculoskeletal System	23%	3%
Myalgia	13%	<1%
Arthralgia	10%	1%
Nervous System	26%	3%
Dizziness	5%	0%
Somnolence	5%	0%

Table 11 (cont'd)
Incidence of Adverse Experiences Regardless of Relationship to Study Drug occurring in $\geq 5\%$ of the Patients Treated with BEXXAR Therapeutic Regimen^a
(N =230)

Respiratory System	44%	8%
Cough increased	21%	1%
Pharyngitis	12%	0%
Dyspnea	11%	3%
Rhinitis	10%	0%
Pneumonia	6%	0%
Skin and Appendages	44%	5%
Rash	17%	<1%
Pruritus	10%	0%
Sweating	8%	<1%

^a Adverse events for all patients prior to the day of dosimetric dose and for 13 weeks following the dosimetric dose and for all patients who continued on study for up to 2 years.

^b The COSTART term for infection includes a subset of infections (e.g., upper respiratory infection). Other terms are mapped to preferred terms (e.g., pneumonia and sepsis). For a more inclusive summary see ADVERSE REACTIONS, Infectious Events.

Table 12
Hematologic Toxicity^a (N=230)

Endpoint	Values
<u>Platelets</u>	
Median nadir (cells/mm ³)	43,000
Per patient incidence ^a platelets <50,000/mm ³	53% (n=123)
Median ^b duration of platelets <50,000/mm ³ (days)	32
Grade III/IV without recovery to Grade II, N (%)	16 (7%)
Per patient incidence ^c platelets <25,000/mm ³	21% (n=47)
<u>ANC</u>	
Median nadir (cells/mm ³)	0.69
Per patient incidence ^a ANC<1,000 cells/mm ³ (%)	63% (n=145)
Median ^b duration of ANC<1,000 cells/mm ³ (days)	31
Grade III/IV without recovery to Grade II, N (%)	15 (7%)
Per patient incidence ^c ANC< 500 cells/mm ³ , N (%)	25% (n=57)
<u>Hemoglobin</u>	
Median nadir (gm/dL)	10
Per patient incidence ^a < 8 gm/dL	29% (n=66)
Median ^b duration of hemoglobin < 8.0 gm/dL (days)	23
Grade III/IV without recovery to Grade II, N (%)	12 (5%)
Per patient incidence ^c hemoglobin <6.5 gm/dL, N (%)	5% (n=11)
^a Grade III/IV toxicity was assumed if patient was missing 2 or more weeks of hematology data between Week 5 and Week 9. ^b duration of grade III/IV of 1000+ days (censored) was assumed for those patients with undocumented grade III/IV and no hematologic data on or after Week 9. ^c Grade IV toxicity was assumed if patient had documented Grade III toxicity and was missing 2 or more weeks of hematology data between Week 5 and Week 9.	

3.4.2.7 Less Common Adverse Events

Of the 230 patients from the five clinical trials, 10 patients had no reported adverse events. The following table lists the less common adverse events, occurring in less than 5% of patients:

TABLE 13: Summary of all adverse events occurring in less than 5% of patients from Efficacy Studies (n=230)

Prefer Name of AE	No of Patients with all AEs (220)	No of all AEs (1635)	No of Patients with gr 3-4 AEs (110)	No_ of Gr 3-4 events (271)	No of Patients with Serious Events (89)	No o Seriot Event (194)
TACHYCARDIA	11	11				
EPISTAXIS	10	11				
INSOMNIA	10	10				
LEUKOPENIA	10	11	8	9	3	3
MALAISE	10	10	1	1	1	1
BRONCHITIS	9	12	1	1	2	2
ECCHYMOSIS	9	10	1	1		
URTICARIA	9	13				
HERPES ZOSTER	8	8			1	1
SEPSIS	8	9	5	5	7	8
URINARY TRACT INFECTION	8	9	1	1	1	1
EDEMA	7	8	1	1	1	1
SKIN DISORDER	7	8				
ANXIETY	6	6				
CARDIOVASCULAR DISORDER	6	6				
DEHYDRATION	6	6	2	2	1	1
INJECTION SITE REACTION	6	6			1	1
LUNG DISORDER	6	6	1	1	1	1
PLEURAL EFFUSION	6	6	4	4	5	5
SINUSITIS	6	6				
SKIN ULCER	6	6	3	3	1	1
ACUTE MYELOBLASTIC LEUKEMIA	5	5	5	5	5	5
ASTHMA	5	6				
CONJUNCTIVITIS	5	5				
DEEP THROMBOPHLEBITIS	5	5	2	2	3	3
DYSPHAGIA	5	5	2	2	1	1
EAR DISORDER	5	5				
FACE EDEMA	5	5				
HYPERCALCEMIA	5	5	2	2	4	4
LYMPHADENOPATHY	5	6				
PALPITATION	5	5				
PELVIC PAIN	5	5				
PETECHIA	5	8				
STOMATITIS	5	5	1	1		
SYNCOPE	5	5	1	1	1	1

CELLULITIS	4	4			1	1
CONFUSION	4	4	3	3	1	1
FLATULENCE	4	4				
HERPES SIMPLEX	4	4				
PANCYTOPENIA	4	4	4	4	2	2
PARESTHESIA	4	4				
PATHOLOGICAL FRACTURE	4	4	2	2	1	1
RECTAL DISORDER	4	4			1	1
URINARY FREQUENCY	4	4				
ARTHRITIS	3	3	1	1	1	1
BLADDER CARCINOMA	3	3	1	1	3	3
DEPRESSION	3	3				
DYSURIA	3	3				
FLU SYNDROME	3	3				
GASTRITIS	3	3				
GASTROINTESTINAL CARCINOMA	3	3	3	3	3	3
HYPOCHROMIC ANEMIA	3	5	2	3	1	3
INJECTION SITE HYPERSENSITIVITY	3	3				
LYMPHOMA LIKE REACTION	3	3	2	2	2	2
MELENA	3	3			1	1
MOUTH ULCERATION	3	3				
MYASTHENIA	3	3				
PERIPHERAL NEURITIS	3	3				
POSTURAL HYPOTENSION	3	3			2	2
ULCERATIVE STOMATITIS	3	3				
ABDOMEN ENLARGED	2	2			1	1
ABNORMAL GAIT	2	2				
ACCIDENTAL INJURY	2	2				
ACNE	2	2				
ALLERGIC REACTION	2	2				
AMBLYOPIA	2	3				
AMNESIA	2	3				
ASCITES	2	2	1	1	1	1
ATAXIA	2	2	1	1	1	1
BREAST PAIN	2	2				
CARCINOMA OF MOUTH	2	2	1	1	2	2
DRY EYES	2	3	1	1		
DRY MOUTH	2	2				
FUNGAL DERMATITIS	2	2				
GASTROINTESTINAL DISORDER	2	2				
GASTROINTESTINAL HEMORRHAGE	2	2	2	2	1	1
HEMOPTYSIS	2	2			1	1
HERNIA	2	2	1	1	1	1

HYDRONEPHROSIS	2	2	2	2		
HYPERTONIA	2	4				
HYPOKALEMIA	2	2	1	1		
INCREASED APPETITE	2	2				
INJECTION SITE PAIN	2	2				
KIDNEY FAILURE	2	2			2	2
KIDNEY FUNCTION ABNORMAL	2	2				
MACULOPAPULAR RASH	2	2				
MIGRAINE	2	2				
NECK RIGIDITY	2	2				
NOCTURIA	2	2				
ORAL MONILIASIS	2	2	1	1		
SERUM SICKNESS	2	2	1	1	1	1
THINKING ABNORMAL	2	2	1	1		
THROMBOSIS	2	2	1	1	1	1
TREMOR	2	2				
URINARY URGENCY	2	2				
VESICULOBULLOUS RASH	2	2				
WEIGHT GAIN	2	2				
ABNORMAL STOOLS	1	1				
ABNORMAL VISION	1	1				
AGITATION	1	1				
ANAPHYLACTOID REACTION	1	1				
AORTIC STENOSIS	1	1				
ARRHYTHMIA	1	1	1	1	1	1
ARTHROSIS	1	1				
ASPIRATION PNEUMONIA	1	1	1	1	1	1
ATELECTASIS	1	1				
ATRIAL FLUTTER	1	1			1	1
BONE DISORDER	1	1	1	1	1	1
BONE PAIN	1	1	1	1		
BREAST CARCINOMA	1	1			1	1
CARCINOMA	1	1			1	1
CARCINOMA OF LUNG	1	1	1	1	1	1
CARDIOMEGALY	1	1			1	1
CEREBRAL HEMORRHAGE	1	1	1	1	1	1
CHEST PAIN SUBSTERNAL	1	1				
CHILLS AND FEVER	1	1				
CHOLECYSTITIS	1	1	1	1	1	1
CHRONIC LEUKEMIA	1	1	1	1	1	1
COLITIS	1	1				
CYST	1	1				
DEPERSONALIZATION	1	1				

DIPLOPIA	1	1				
EAR PAIN	1	1				
ENCEPHALOPATHY	1	1	1	1	1	1
ERUCTATION	1	1				
ERYTHEMA NODOSUM	1	1	1	1	1	1
FOLATE DEFICIENCY ANEMIA	1	1				
FOOT DROP	1	1				
GASTROENTERITIS	1	1	1	1		
GENERALIZED EDEMA	1	1	1	1		
GENITAL EDEMA	1	1				
GINGIVITIS	1	1				
GLOSSITIS	1	1				
GUM HEMORRHAGE	1	1				
HAIR DISORDER	1	1				
HEMOLYTIC ANEMIA	1	1	1	1		
HEMORRHAGE	1	1				
HEPATITIS	1	1	1	1		
HYPERURICEMIA	1	1	1	1	1	1
HYPERVENTILATION	1	1				
HYPOGLYCEMIA	1	1				
HYPOKINESIA	1	1				
HYPONATREMIA	1	1				
HYPOVOLEMIA	1	1	1	1		
HYPOXIA	1	1	1	1	1	1
INJECTION SITE EDEMA	1	1				
INTESTINAL OBSTRUCTION	1	1	1	1	1	1
JAUNDICE	1	1				
LACRIMATION DISORDER	1	1				
LARYNGISMUS	1	1				
LEUKEMIA	1	1	1	1	1	1
LIVER FUNCTION TESTS ABNORMAL	1	1	1	1		
LUNG HEMORRHAGE	1	1	1	1	1	1
LYMPHEDEMA	1	1				
MUSCLE ATROPHY	1	1				
NAUSEA AND VOMITING	1	1				
NERVOUSNESS	1	1				
NEURALGIA	1	1				
NEUROPATHY	1	1	1	1	1	1
OLIGURIA	1	1	1	1	1	1
PARALYSIS	1	1	1	1		
PAROSMIA	1	1				
PERIODONTAL ABSCESS	1	1				
PERIPHERAL VASCULAR DISORDER	1	1				

PNEUMOTHORAX	1	1				
PULMONARY EMBOLUS	1	1	1	1	1	1
PUSTULAR RASH	1	1				
SHOCK	1	1	1	1	1	1
SKIN BENIGN NEOPLASM	1	1				
SKIN DISCOLORATION	1	1				
SKIN MELANOMA	1	1	1	1	1	1
SKIN NODULE	1	1				
SUBDURAL HEMATOMA	1	1	1	1	1	1
TASTE LOSS	1	1				
TASTE PERVERSION	1	1				
TENDON DISORDER	1	1				
TENESMUS	1	1				
TENOSYNOVITIS	1	1				
THROMBOPHLEBITIS	1	1				
TINNITUS	1	1				
ULCERATIVE COLITIS	1	1	1	1	1	1
URINARY INCONTINENCE	1	1				
URINARY RETENTION	1	1				
URINARY TRACT DISORDER	1	1	1	1	1	1
URINATION IMPAIRED	1	1				
VESTIBULAR DISORDER	1	1				
VOICE ALTERATION	1	1				

3.4.2.8 Laboratory Findings

Bexxar therapeutic regimen leads to significant cytopenias. It also can lead to development of HAMA and elevated TSH. Please see section 3.4.2.3

3.4.2.9 Vital Signs

A constellation of symptoms, including fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea, have been reported during or within 48 hours of infusion. Ninety-two patients (40%) reported fever, rigors/chills, or sweating. Although all patients in the clinical studies received pretreatment with acetaminophen and an antihistamine, the

value of premedication in preventing infusion-related toxicity was not evaluated in any of the clinical studies. Infusional toxicities were managed by slowing and/or temporarily interrupting the infusion. Symptomatic management was required in more severe cases. Adjustment of the rate of infusion to control adverse reactions occurred in 16 patients; seven patients required adjustments for only the dosimetric infusion, two required adjustments for only the therapeutic infusion, and seven required adjustments for both the dosimetric and the therapeutic infusions. Adjustments included reduction in the rate of infusion by 50%, temporary interruption of the infusion, and in 2 patients, infusion was permanently discontinued.

Fourteen patients (6%) experienced one or more of the following adverse events: allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus, and serum sickness.

3.4.2.10 ECGs

Not Applicable

3.4.2.11 Special Safety Studies

Not applicable

3.4.2.12 Withdrawal Phenomena/Abuse Potential

Not Applicable

3.4.2.13 Human Reproduction and Pregnancy Data

Not available

3.4.2.14 Overdose Experience

The maximum dose of the BEXXAR therapeutic regimen that was administered in clinical trials was 88 cGy. Three patients were treated with a total body dose of 85 cGy of Iodine I 131 Tositumomab in a dose

escalation study. Two of the 3 patients developed Grade IV toxicity of 5 weeks duration with subsequent recovery. In addition, accidental overdose of BEXXAR occurred in one patient at total body doses of 88 cGy. The patient developed Grade III hematologic toxicity of 18 days duration. Patients who receive an accidental overdose of Iodine I 131 Tositumomab should be monitored closely for cytopenias and radiation-related toxicity. The effectiveness of hematopoietic stem cell transplantation as a supportive care measure for marrow injury has not been studied; however, the timing of such support should take into account the pharmacokinetics of the BEXXAR therapeutic regimen and decay rate of the Iodine-131 in order to minimize the possibility of irradiation of infused hematopoietic stem cells.

3.4.2.15 Post-Marketing Experience in U.S. and Foreign Markets

Not applicable

**APPEARS THIS WAY
ON ORIGINAL**

3.4.3 Adequacy of Safety Exposure and Safety Assessments

The safety exposure and safety assessments carried out by the sponsor were adequate to delineate the toxicity profile of Bexxar.

3.4.4 Safety Conclusions

The most significant early toxicity of Bexxar therapeutic regimen cytopenas and their consequences. It also produces hypersensitivity and infusional toxicity. Because of the radioiodine it also produces hypothyroidism. Because of the murine protein content it induces development of HAMA. It may also contribute to development of myelodysplastic syndrome/acute leukemia, although the degree of this contribution is difficult to ascertain. The safety profile is comparable to the other currently available radiolabeled product for low grade lymphoma, Zevalin. As part of post-marketing commitment, the sponsor has agreed to perform a study comparing the overall safety with Zevalin.

**APPEARS THIS WAY
ON ORIGINAL**

3.5 Other Clinical Issues

None

3.5.1 Dosing, Regimen and Administration Issues

The Bexxar therapeutic regimen comprises of administering patient specific therapeutic dosing based on data collected from the dosimetric dose given 7 to 14 days before. Regarding nuclear medicine specific issues, please see the following review from Dr. George Mills.

Because of the uniqueness and complexity of this dosing concept, the sponsor has agreed to set up training and certification program as well as quality assurance program for physicians administering Bexxar.

Biodistribution and Dosimetry

In the review of Corixa's submission of the biodistribution imaging, normal organ dosimetry and tumor dosimetry, CBER has performed the following:

- A review of the imaging findings from the biodistribution imaging studies with I-131 tositumomab
- Analyzed and recalculated the submitted normal organ dosimetry for I-131 tositumomab
- Analyzed and recalculated the submitted normal organ dosimetry I-131 tositumomab
- Analyzed and recalculated the submitted tumor dosimetry

Biodistribution Imaging Findings

ELECTRONIC SUBMISSION

The whole body biodistribution images were electronically archived and submitted without data compression or data loss. The images have been presented in an electronic dataset within a searchable, interactive database. The supporting datasets have been submitted in SAS transport files.

BIODISTRIBUTION IMAGING – NORMAL ORGANS

In the biodistribution imaging, the normal organs are visualized by having uptake of I-131 tositumomab in the organ greater than the adjacent whole body background activity.

The review findings of the biodistribution imaging for the visualized organs are as follows:

Liver and Spleen

The imaging of the liver demonstrates an intense and somewhat grainy uptake pattern seen commonly with I-131 diagnostic imaging. The spleen is seen variably in imaging studies with similar, but occasionally less intense uptake of radiotracer.

Bone Marrow

The bone marrow compartment is variably seen in the expected distribution of the red marrow in adults. In some subjects, the bone marrow imaging demonstrated patchy areas of increased localization, suggesting possible imaging of NHL bone marrow involvement.

Testes

Imaging of the testes is remarkable for the intensity of the radiotracer localization (equivalent to the liver). No asymmetry of the testes or focal localization to suggest imaging of occult, focal NHL was identified.

Kidney, Urinary Bladder

The kidneys and urinary bladder are seen. The urinary bladder is variable in its configuration and partially filled with radiotracer, compatible with the urinary tract function as the clearance pathway of the I-131.

Large Bowel

Variable regions of the large bowel demonstrate localization of I-131 in subjects. Once seen, the localization appears unchanging in its anatomical distribution through later imaging time points. The imaging of the large bowel is compatible with I-131 tositumomab targeting normal sites of lymphoid aggregates in the bowel wall as well as sites of NHL. It must be noted, the imaging of the large bowel may represent the presence of an occult second clearance pathway in the bowel.

Small Bowel

Occasional regions of the small bowel appear to be imaged in some subjects.

Stomach

Diffuse, slight but definite localization in the stomach is seen in some subjects.

Heart, Large Vascular Structures

The cardiac chambers and major vascular structures demonstrate localization in the early imaging with the expected loss of imaging in later imaging. This imaging pattern is compatible with the infusion of I-131 tositumomab, and the expected clearance of the radiolabeled antibody from the vascular space.

Lung Fields

The lung fields demonstrate a modest diffuse to somewhat irregular localization of the radiolabeled antibody as compared to the whole body background activity.

Thyroid

Intense uptake of I-131 is demonstrated in the thyroid gland of many subjects.

BIODISTRIBUTION IMAGING – TUMOR SITES

Occasionally tumor sites are seen poorly-defined localization of I-131 tositumomab.

CBER REVIEW COMMENTS

Consistent with the diagnostic imaging characteristics of I-131 but compromised by the variable imaging quality submitted by the sponsor, the I-131 tositumomab whole body biodistribution imaging provided marginal quality whole body and organ imaging at the imaging time points.

If adequate, and well controlled imaging techniques are applied to the biodistribution imaging with I-131 tositumomab, the whole body imaging should be able to provide supportive information for the safe administration of I-131 tositumomab to confirm the presence of the expected pattern of I-131 tositumomab in the normal organs. An alteration in the biodistribution of I-131 tositumomab would suggest the presence of one or more of the following conditions:

- Immune response, HAMA.
- Organ dysfunction, e.g., urinary tract obstruction.
- Improper preparation of the I-131 tositumomab imaging agent.

Imaging of tumor sites was unable to confirm localization of I-131 tositumomab. Thus, the review of the whole body biodistribution images appears to be unable to establish routinely the “normal structures at risk” due to the radiation absorbed dose exposures from adjacent tumor sites. In addition, the review of the whole body biodistribution imaging does not appear to allow the following:

- Quantitation of the radiation dose for those tumor sites, which are adjacent to “normal structures at risk.”
- Quantitation of the radiation absorbed dose to normal organs and tumor sites.

Normal Organ Dosimetry

Organ Dosimetry

Prior to the therapy administration of I-131 tositumomab therapy, the clinical sites performed biodistribution imaging studies with a diagnostic dose of I-131 tositumomab for each subject. The routine whole body biodistribution studies resulted in whole body images for at least 3 time points (imaging days). Based on the whole body imaging study, the clinical sites determined the therapy dose for the subject.

For the BLA submission, organ dosimetry was performed after 126 infusions in subjects receiving a predose of at least 475 mg of antibody based on regions-of-interest (ROI) counts from the kidneys, liver, lungs, spleen obtained daily after the dosimetric dose. Counts from blood samples, urinary bladder and remainder of the body were additional source organs.

Due to the inadequate and incomplete assignment of regions of interest, a subset of ten subjects were selected to properly estimate radiation-absorbed doses to organs, based on ROIs assigned to all organs demonstrating increased radiotracer localization as compared to the whole body background activity for 6 to 8 time points (imaging days). These subjects were selected to assure that there were at least 5 patients with well-defined thyroid uptake, 5 patients with well-defined stomach uptake, and 5 patients with well-defined large bowel uptake, and approximately 50% male subjects.

Residence times were determined for kidneys, liver, lungs, spleen, bone marrow, heart, lower large intestine (LLI), upper large intestine (ULI), small intestine, stomach, thyroid, testes (for males), urinary bladder, and tumors. The remainder method was used for all other organs.

ORGANS TO BE EVALUATED BY TIME ACTIVITY CURVES

For the determination of dosimetry by the MIRDOSE software, all organs visualized are considered to have greater concentration of the radiolabeled antibody as compared to the whole body background activity. These visualized organs are evaluated by regions of interest (ROIs) with quantification of the radioactivity present in these organs at the multiple time points. The determination of the radioactivity localization in these organs by the ROIs for the multiple time points produces the time-activity curves. By integration of the time activity curves, the residence times are obtained, which are required for the MIRDOSE software to estimate the normal organ dosimetry.

SUBJECT POPULATION

Ten subjects selected for adequate imaging technique and demonstrated normal organ localization of the radiolabeled antibody.

REGIONS OF INTEREST

Corixa has evaluated the following listed organs/tissues and total body activity:

1. Total Body
2. Blood
3. Heart
4. Kidneys
5. Lung
6. Liver
7. Small Intestine
8. Large Intestine
9. Spleen
10. Testes
11. Thyroid
12. Humeral head (Bone Marrow)

ROUTE OF EXCRETION

Urine was collected following 49 dosimetric doses.

Samples were collected and counted for the following intervals: 0–12 hours, 12–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, and 96–120 hours.

In the first 120 hours following the dosimetric dose, the whole body clearance of the iodine 131 was $67\% \pm 13\%$ of the injected dose. The percent of the injected dose collected in the urine was $65\% \pm 13\%$.

The percent of total body excretion that was captured in the urine over the 5-day time period was $98\% \pm 15\%$.

CBER Review Comment:

CBER's review of the whole body biodistribution images demonstrates localization of the radiotracer in the bowel in several subjects. The possible contribution of activity in the bowel lumen from a second route of clearance in the bowel can not be ruled out.

Tumor Dosimetry

Tumor doses are summarized based on data from 29 patients.

Tumor selection was limited due to the following:

- 1) no quantification of a tumor site because the tumor was not visualized
- 2) the tumor could not be clearly delineated from adjacent radiotracer activity

The tumor dosimetry data were calculated based on ROIs drawn over the tumors. Corrections for attenuation and background were performed as for normal organ dosimetry.

Tumor volumes were calculated by outlining individual tumors slice-by-slice on CTs.

For tumors with masses between 10 and 100 g, tumor dosimetry was performed using the table of absorbed fractions for spheres. For tumors greater than 100 g, a splenic mass adjusted model was used. The tumor dose represents the nonpenetrating and penetrating doses from iodine 131 within the tumor plus the expected penetrating dose from the total body.

**APPEARS THIS WAY
ON ORIGINAL**

Dosimetry Analysis

This review has been based on the information submitted by Corixa in the Bexxar BLA: CD entitled "Resubmission: Response to Complete Review Letter, Part II. Items: 1, 8, 10, 11, and 20. Dated September 7, 2001, Disk 1 of 1.

Study Design

This section assesses the study design for adequate data collection for the dosimetry analysis. It will begin with summary tables of the time-activity data collected for dosimetry, and will acknowledge a standard checklist for adequate data collection for the dosimetry analysis.

TABLE DA1: DATA COLLECTION SUMMARY.

Organ Data Collected	Data Source	n	Reported Number of Time points (Range)	CBER Evaluation
Bone Marrow*	Gamma Camera/Blood	10	6-8	Good
Heart	Gamma Camera	10	6-8	Good
Kidneys	Gamma Camera	10	6-8	Good
Liver	Gamma Camera	10	6-8	Good
Lungs	Gamma Camera	10	6-8	Good
LLI	Based on ULI ROI	10	na	Good
SI	ICRP-30 GI model	10	na	Good
Spleen	Gamma Camera	10	6-8	Good
Stomach	Gamma Camera	10	6-8	Good
Testes	Gamma Camera	6	6-8	Good
Thyroid	Gamma Camera	10	6-8	Good
Tumors	Gamma Camera	29	6-8	Good
ULI	Gamma Camera	10	6-8	Good
Urinary Bladder [‡]	Gamma Camera	10	6-8	Good
Whole Body	Gamma Camera	10	6-8	Good

* Corixa Performed analysis using both blood based and ROI based methods. ROI based results were presented in the main table.

‡ Based on Whole Body Images.

Were an adequate number of subjects utilized? Yes

Complete dosimetry was determined for 10 patients.

Were the number and spacing of the data collection time points adequate? Yes

The data collected does adequately describe the time activity curves for the listed organs/tissues. Image data were collected for between 6 and 8 time points. To fully describe the time activity curves for all organs/tissues that demonstrate uptake of activity, dosimetry studies require that adequate data be collected, at the appropriate times,

Was whole body activity measured over the course of the study? Yes

Did activity quantification methods seem reasonable and adequate? Yes

Were all organs showing significant uptake measured and reported? Yes

Were excretion data from all significant routes of excretion collected? Yes

CBER Review Comment

Study Design is considered appropriate and sufficient.

**APPEARS THIS WAY
ON ORIGINAL**

Image Quantification Validation on 2 patients

This section describes the image quantification methods (transformation of counts to activity in regions of interest) used by Corixa, and compares results obtained by CBER for two patients, to the results obtained by Corixa on the same patients. This analysis is not intended to confirm the results for all organs/tissues, but rather to confirm the general reliability of the Corixa methodology and results by selecting a representative group of organs and comparing the results.

DESCRIPTION OF THE IMAGE QUANTIFICATION METHODS USED BY CORIXA

Whole body and spot images were collected at 6 to 8 different time points. The eight time points at which data were collected were approximately 1.5, 18, 40, 66, 113, 136, and 161 hours. When time points were excluded, those typically excluded were the 5 and 136 hour time points.

The conversion of counts to activity was performed by Corixa based on a series of phantom studies with I-131. This method modeled the efficiency of the camera as a function of depth. Effective thicknesses in the patients at each region of interest were determined using modified transmission scan data using a Co-57 source. This methodology converts counts to activity, and accounts for attenuation in the patient at each ROI. ROIs were drawn for Bone Marrow (humeral head), Heart, Kidneys (one), Liver, Lungs, Spleen, Stomach, Testes, Thyroid, Tumors, ULI, and Whole Body. This method should result in reasonable activity quantification. Given that no activity standard was used, this methodology requires that consistent camera settings be used. Spot images were used for all of the listed regions of interest except whole body, where whole body scans were used.

CBER METHODOLOGY FOR IMAGE QUANTIFICATION

Corixa supplied whole body and spot images for 10 patients in the BLA submission. Of the 10, 2 patients were selected at random for the validation (Patient 003-012-003 and Patient 003-012-056) Regions of interest (ROIs) were selected and drawn around the selected group of organs/tissues [whole body, lungs, liver, spleen, kidneys, and heart] in both the whole body and spot images. Activity in each organ/tissue, at each time point, was determined by taking the geometric mean of the anterior and posterior counts in each ROI and dividing by the number of geometric mean whole body counts in the first image. Geometric mean whole body counts in the first spot image were estimated based on the available image area.

VALIDATION AND EVALUATION OF IMAGE QUANTIFICATION RESULTS

CBER results matched those reported by Corixa to within the limits expected, given the data, and the approximate nature of CBER methodology, which did not account for attenuation or over/underlying activity. Whole body numbers were almost identical, and other organs matched well enough to conclude that the quantification methods performed by Corixa were appropriate and likely conservative. Ratios of CBER to Corixa image quantification results for Patient 003-012-003 where CBER used the spot images are shown in Table 2. Ratios of CBER to Corixa image quantification results for Patient 003-056-003 where CBER used the whole body images are shown in Table 3. There were some discrepancies in some of CBER results for the whole body images, but these were very likely due to the remarkably poor whole body images at the later time points.

Table DA2: Ratio of CBER (using spot images) to Corixa ROI activity determination.

Patient 003-012-003

	1.17	17.08	40.17	65.13	140.83
Heart Wall	0.53	0.47	0.52	0.65	0.63
Kidneys	0.55	0.43	0.45	0.34	0.17
Liver	0.70	0.79	0.85	0.94	1.22
Spleen	0.72	0.65	0.69	0.75	0.78
Whole Body	1.00	1.03	1.03	1.02	1.09

Table DA3: Ratio of CBER (using whole body images) to Corixa ROI activity determination.

Patient 003-056-003

	1.22	18.47	43.12	66.83	113.98	145.12
Liver	0.78	0.93	0.90	0.88	1.01	0.92
Kidneys	0.38	0.42	0.44	0.46	0.47	0.62
Spleen	0.45	0.44	0.48	0.55	0.49	0.63
Whole Body	1.00	1.07	1.02	0.92	1.08	1.13

The small image size of the spot and whole body images, and the low quality of the whole body images made region determination somewhat difficult for smaller and low activity uptake regions.

It is difficult to assess if the regions used by Corixa for some organs/tissues, such as GI organs, testes and marrow, would result in accurate dosimetry as the structures were difficult to visualize on the images. However, it was apparent that in the cases where the structures were difficult to visualize, that Corixa would typically use a generous and likely conservative region of interest. Thus it is likely that for the larger and high activity uptake regions that the resulting dosimetry estimates are fairly accurate, and for the small and/or lower activity uptake regions the resulting dosimetry estimates are at least conservative, if somewhat less accurate.

**APPEARS THIS WAY
ON ORIGINAL**

Kinetic Modeling

This sub-section describes and evaluates the methods Corixa used to determine residence times from whatever time activity data was collected using imaging, excreta sampling, and blood sampling.

MATHEMATICAL MODEL USED TO ESTIMATE ORGAN RESIDENCE TIMES

Organ residence times for most organs/tissues quantified were found by fitting the quantified data from imaging with sums of exponentials and integrating the resulting functions. For LLI, residence time was based on ULI region results. SI residence time was estimated using the ICRP-30 GI tract model and the activity seen in stomach. For stomach and thyroid, due to the erratic nature of the data collected, a trapezoidal methodology was used, assuming physical decay only beyond the final data point.

Urine residence times were found using whole body data assuming urinary excretion data only. A previous study compared whole body retention and urinary excretion to validate this method. A 4.8-hour voiding bladder model was then applied to the integration process.

Red marrow residence times were determined using two methodologies. The first method used a humeral head ROI to estimate marrow activity. This was done by assuming that the activity found in this region represented a fixed amount of the total red marrow (9.95 g). The second method used the blood data and the methodology described by Squoros [J Nuclear Medicine 1993;34:689-694]. This involves curve fitting the blood data using sums of exponentials and assuming that marrow activity is proportional to blood activity. The Squoros methodology is only appropriate when there is no specific uptake of activity in marrow elements. The ROI method was selected as more appropriate, and the results from this method were used to generate the final dosimetry.

Remainders of body residence times were determined by subtracting organ residence times from whole body residence times.

Were appropriate assumptions made about activity beyond the last time point imaged? Yes

After the last time point imaged, the time-activity curve was assumed to continue to follow mathematical fit (sums of exponentials) that was determined using the data collected, except for stomach and thyroid, where activity was assumed to be lost by physical decay only after the last observed data point.

Does the model conserve activity? Yes

The assumption of all activity not in whole body traveling through an excretion pathway and the determination of remainder of body residence times by subtracting organ

residence times from whole body residence times insures that the model accounts for 100% of the injected activity at all times (that is, it conserves activity).

VALIDATION AND EVALUATION OF KINETIC MODELING

CBER reproduced through independent analysis all residence times for 5 of the 10 patients using the kinetic data as supplied by Corixa. On average, residence times found by CBER matched almost exactly with those found by Corixa.

There were a few exceptions, notably heart wall and SI. The most significant example was the residence time for heart wall for patient 003-012-003 found by Corixa. It appeared to be different by approximately a factor of 2. However, this will have little impact on the final dosimetry for heart wall however, as all other residence times found by CBER for heart wall matched those found by Corixa to within about 3%.

CBER also found different results from Corixa for SI residence times. Corixa found these by assuming the activity in the stomach continued on to the SI following the kinetics of the ICRP-30 GI tract model. Corixa assumed that the fraction of the total activity traveling from Stomach to GI was equal to the ratio of the stomach and whole body residence times. This method appears inconsistent to CBER since transit through the stomach is much faster than whole body retention.

CBER assumed that the maximum activity seen in stomach was passed through to SI using ICRP-30 kinetics. Both of these methods have problems however. Since the SI region was not quantifiable, and activity uptake in GI was not apparent in the two patients evaluated, it is difficult to assess the methodology selected by Corixa or CBER. Especially given the fact that lymphoid aggregates in GI might have uptake of the activity. However, if this were the case, it was not apparent from either the spot or whole body images. In addition, the uptake in stomach could have been from free iodine, and would not be as likely to pass completely into SI.

Given that GI uptake was not apparent in the two image sets studied, CBER would be inclined to treat the SI, ULI, and LLI as remainder organs, which would result in much lower doses than those found by Corixa. However, it should be noted that GI uptake might have occurred in other patients than the 2 examined here. Thus CBER choose the more conservative assumption similar to the one chosen by Corixa, using the ICRP-30 model

If the uptake actually was in lymphoid aggregates in the GI tract, a better method for SI might be to assume similar uptake in SI as in ULI which would result in higher absorbed dose estimates. This would result in final dosimetry estimates for SI that would be very similar to those found for ULI and LLI.

Cber Review Comments

With the possible exception of SI, the kinetic modeling was appropriate and correct.

Physics (S-value) Modeling

This section describes and evaluates the methodology used by Corixa to obtain S-values. Most S-values used by Corixa are those using the Cristy-Eckerman Mathematical phantom as implemented in MIRDOse 3.1. There were some exceptions to this as follows:

GI tract organ S-values for the assumption of activity in wall

MIRDOse 3.1 assumes that for GI organs, activity is contained in the contents of the GI tract. There is no built in methodology for putting activity in the GI walls using MIRDOse 3.1. Corixa corrected the GI tract S-values by removing the non-penetrating component due to activity in the contents, and then adding a non-penetrating component assuming that the activity was located in the walls. For example, for LLI:

$$S_{\text{corrected}}(\text{LLI wall} \leftarrow \text{LLI contents}) = S_{\text{MIRDOse}}(\text{LLI wall} \leftarrow \text{LLI contents}) - \frac{\Delta_{\text{np}}}{2m_{\text{contents}}} + \frac{\Delta_{\text{np}}}{m_{\text{wall}}}$$

This method is appropriate and correct.

Spleen S-values

Spleen S-values from MIRDOse were modified to account for large mass differences from reference man values found in some patients using a well-known technique that accounts for photon and non-penetrating differences. This method is appropriate and correct.

Tumor S-values

Tumor S-values were based on published photon absorbed fractions for spheres, and the assumption of 100% absorption of electron emissions. This method is appropriate and correct for the range of tumor sizes in this study. Values found by Corixa match those found by using nodule module in MIRDOse almost exactly.

CBER Review Comments

Methods for S-value determination were appropriate and correct.

Normal Organ Dosimetry Methods and Results

This section describes and evaluates the methodology used by Corixa to obtain radiation absorbed doses using the residence times as described in the kinetic modeling section. This section shall also compare the absorbed dose results obtained by Corixa to the

absorbed dose results obtained by CBER. The results obtained by CBER in this subsection are based on the time-activity data exactly as provided by Corixa.

Description of Dosimetry Methods

Normal organ dosimetry estimates were determined by Corixa using the residence times as found and explained in the kinetic modeling section and the MIRDOSE 3.1 software.

For GI organs, dosimetry was calculated under 3 different scenarios:

- 1) assuming 100% of the activity was in contents,
- 2) assuming activity was distributed 50% in contents 50% in walls, and
- 3) assuming activity was distributed 100% in walls.

SOURCE OF S-VALUES: MIRDOSE 3.1

Was the remainder of body correction appropriately applied? Yes

VALIDATION RESULTS: CORIXA VS. CBER. Based on kinetic data as supplied by Corixa.

Table 4A shows the results obtained by Corixa and CBER, and the ratio of these results in cGy/mCi. Table 4B shows the same results in mGy/MBq. Table 5A shows the dose estimates in cGy/mCi determined by Corixa in the GI organs under the 3 different distribution (wall vs. contents) assumptions. Table 5B shows the same results in mGy/MBq.

TABLE DA4A: COMPARISON OF CORIXA RESULTS AND CBER RESULTS, BOTH BASED ON TIME-ACTIVITY DATA AS SUPPLIED BY CORIXA IN RADS/MCI.

	Source of Data for Dosimetry	cGy/mCi Corixa	cGy/mCi CBER	Ratio of Corixa to CBER
Adrenals	Whole Body ROI	1.1	1.0	1.09
Brain	Whole Body ROI	0.5	0.4	1.10

Breasts	Whole Body ROI	0.6	0.5	1.07
Gallbladder Wall	Whole Body ROI	1.1	1.0	1.08
LLI Wall †	Based on ULI ROI	4.6	4.8	0.97
Small Intestine †	ICRP Model	0.8	0.8	1.04
Stomach †	Organ ROI	1.7	1.7	1.02
ULI Wall †	Organ ROI	4.8	4.9	0.98
Heart Wall	Organ ROI	4.4	4.6	0.94
Kidneys	Organ ROI	7.3	7.0	1.05
Liver	Organ ROI	3.0	2.7	1.11
Lungs	Organ ROI	2.9	3.0	0.95
Muscle	Whole Body ROI	0.6	0.6	1.07
Ovaries	Whole Body ROI	0.9	0.9	1.03
Pancreas	Whole Body ROI	1.1	1.1	1.06
Red Marrow*	Organ ROI	2.6	2.2	1.19
Bone Surfaces	Whole Body ROI	1.7	1.4	1.16
Skin	Whole Body ROI	0.5	0.4	1.08
Spleen	Organ ROI	4.3	5.4	0.80
Testes	Organ ROI	3.0	2.5	1.21
Thymus	Whole Body ROI	0.8	0.8	1.04
Thyroid	Organ ROI	11.7	18.5	0.63
Urine Bladder Wall	Whole Body ROI**	2.7	2.6	1.00
Uterus	Whole Body ROI	0.7	0.7	1.00
Total Body	Whole Body ROI	0.9	0.8	1.08

* Humerus ROI results

** All excretion assumed to be urinary.

† Assumes 100% in contents.

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TABLE DA4B: COMPARISON OF CORIXA RESULTS AND CBER RESULTS, BOTH BASED ON TIME-ACTIVITY DATA AS SUPPLIED BY CORIXA IN MGY/MBQ.

	Source of Data for Dosimetry	mGy/MBq Corixa	mGy/MBq CBER	Ratio of Corixa to CBER
Adrenals	Whole Body ROI	0.3	0.3	1.09
Brain	Whole Body ROI	0.1	0.1	1.10
Breasts	Whole Body ROI	0.2	0.1	1.07
Gallbladder Wall	Whole Body ROI	0.3	0.3	1.08
LLI Wall †	Based on ULI ROI	1.2	1.3	0.97
Small Intestine†	ICRP Model	0.2	0.2	1.04
Stomach†	Organ ROI	0.5	0.5	1.02
ULI Wall †	Organ ROI	1.3	1.3	0.98
Heart Wall	Organ ROI	1.2	1.3	0.94
Kidneys	Organ ROI	2.0	1.9	1.05
Liver	Organ ROI	0.8	0.7	1.11
Lungs	Organ ROI	0.8	0.8	0.95
Muscle	Whole Body ROI	0.2	0.2	1.07
Ovaries	Whole Body ROI	0.2	0.2	1.03
Pancreas	Whole Body ROI	0.3	0.3	1.06
Red Marrow*	Organ ROI	0.7	0.6	1.19
Bone Surfaces	Whole Body ROI	0.5	0.4	1.16
Skin	Whole Body ROI	0.1	0.1	1.08
Spleen	Organ ROI	1.2	1.5	0.80
Testes	Organ ROI	0.8	0.7	1.21
Thymus	Whole Body ROI	0.2	0.2	1.04
Thyroid	Organ ROI	3.2	5.0	0.63
Urine Bladder Wall	Whole Body ROI**	0.7	0.7	1.00
Uterus	Whole Body ROI	0.2	0.2	1.00
Total Body	Whole Body ROI	0.2	0.2	1.08

* Humerus ROI results

** All excretion assumed to be urinary.

† Assumes 100% in contents.

TABLE DA5A: GI WALL DOSE ESTIMATES IN CGY/MCI UNDER DIFFERING ACTIVITY DISTRIBUTION ASSUMPTIONS.

	100% Contents	50% Wall, 50% Contents	100% Wall
Stomach Wall	1.7	3.0	4.2
LLI Wall	4.6	6.8	8.5
ULI Wall	4.8	6.9	8.6

TABLE DA5B: GI WALL DOSE ESTIMATES IN MGY/MBQ UNDER DIFFERING ACTIVITY DISTRIBUTION ASSUMPTIONS.

	100% Contents	50% Wall, 50% Contents	100% Wall
Stomach Wall	0.5	0.8	1.1
LLI Wall	1.2	1.8	2.3
ULI Wall	1.3	1.9	2.3

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CBER Review Comments

The dosimetry methods for normal organs used by Corixa were appropriate and correct. The final results matched those found by CBER (based on kinetic data as supplied by Corixa within about 10%) in all cases except red marrow, bone surfaces, testes, thyroid, and spleen.

The differences in red marrow and bone surface dosimetry (about 20%) are consistent with the smaller sample size used by CBER, which by pure chance contained the patients showing lower red marrow uptake. Comparing patient by patient for the red marrow and bone surface dosimetry, Corixa and CBER results match almost exactly.

The differences in testes dosimetry (about 20%) were consistent with the result of the smaller sample size used by CBER, which by chance contained the patients showing lower testes uptake. Comparing patient by patient for the testes dosimetry, Corixa and CBER results match almost exactly.

The differences in thyroid dosimetry (about 40%) were consistent with the result of the smaller sample size used by CBER, which by chance contained the patients showing lower thyroid uptake. Comparing patient by patient for the thyroid dosimetry, Corixa and CBER results match almost exactly.

CBER recalculated and confirmed the dosimetry results for GI organs under the 3 different distribution (wall vs. contents) assumptions (Table 5). Results were not an exact match, but were close enough to confirm that the methodology was likely correctly applied. Differences were likely due to the use of slightly different residence times and I-131 λ for the calculation. It is the tentative conclusion of CBER, based on the lack of observable uptake in intestine that the GI organ estimates given in Tables 4 and 5 likely represent overestimates.

The differences in spleen dosimetry (about 20%) were a result of the smaller sample size used by CBER, and the slightly different methodology for mass correction of the dose.

Tumor Dosimetry Verification

Tumor dosimetry was recalculated by CBER for 16 tumors, based on kinetic data, and tumor mass data supplied by Corixa. For absorbed fraction determination, the tumors were assumed to be spherical. Results are shown in Tables 6A and 6B. Average tumor dose found by CBER was within 10% of that found by Corixa. The absorbed dose found by CBER for 13 of the 16 tumors, was within about 15% of the absorbed dose estimated by Corixa. Differences were likely due to slightly different kinetic modeling and S-values.

TABLE DA6A: TUMOR DOSE ESTIMATES (CGY/MCI)

b(4)

Study	Patient	Mass grams	CBER cGy/mCi	Corixa cGy/mCi	Review/Corixa
RIT-II-001	001-003-004		5.5	5.3	1.04
RIT-II-001	001-003-004		21.2	21.0	1.01
RIT-II-003	003-012-003		4.0	4.4	0.92
RIT-II-003	003-012-003		4.3	4.9	0.88
RIT-II-003	003-012-009		10.1	8.7	1.16
RIT-II-003	003-012-009		8.8	11.4	0.77
RIT-II-003	003-012-010		2.0	2.9	0.69
RIT-II-003	003-012-010		6.1	6.9	0.90
RIT-II-003	003-012-038		6.8	7.8	0.88
RIT-II-003	003-012-051		10.3	11.5	0.90
RIT-II-003	003-012-053		5.0	5.4	0.92
RIT-II-003	003-012-056		12.1	13.6	0.89
RIT-II-003	003-012-057		10.4	11.6	0.90
RIT-II-003	003-012-057		5.3	5.9	0.91
RIT-II-003	003-012-065		7.7	8.7	0.88
RIT-II-003	003-012-065		40.6	41.2	0.98

TABLE DA6B: TUMOR DOSE ESTIMATES (MGY/MBQ)

b(4)

Study	Patient	Mass grams	CBER mGy/MBq	Corixa mGy/MBq	Review/Corixa
RIT-II-001	001-003-004		1.5	1.4	1.04
RIT-II-001	001-003-004		5.7	5.7	1.01
RIT-II-003	003-012-003		1.1	1.2	0.92
RIT-II-003	003-012-003		1.2	1.3	0.88
RIT-II-003	003-012-009		2.7	2.3	1.16
RIT-II-003	003-012-009		2.4	3.1	0.77
RIT-II-003	003-012-010		0.5	0.8	0.69
RIT-II-003	003-012-010		1.6	1.9	0.90
RIT-II-003	003-012-038		1.8	2.1	0.88
RIT-II-003	003-012-051		2.8	3.1	0.90
RIT-II-003	003-012-053		1.4	1.5	0.92
RIT-II-003	003-012-056		3.3	3.7	0.89
RIT-II-003	003-012-057		2.8	3.1	0.90
RIT-II-003	003-012-057		1.4	1.6	0.91

b(4)

RIT-II-003	003-012-065		2.1	2.4	0.88
RIT-II-003	003-012-065		11.0	11.1	0.98

Tumor radiation absorbed dose estimates found by both Corixa and CBER were obtained using absorbed fractions that were based on the average beta energy emission of I-131, and the assumption that the tumors could be modeled as spheres for radiation transport purposes. Both of these assumptions are very slightly conservative, that is they will result in an overestimate of the actual radiation absorbed dose to the tumors.

CBER Review Comment

The dosimetry methods for tumors used by Corixa were appropriate and correct. The final results matched those found by CBER (based on kinetic data as supplied by Corixa) (within about 15%) in almost all cases.

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Absorbed Dose to Surrounding Tissues From Activity in Tumors

This section reviews the use of some relatively simple geometric models and radiation transport simulations to estimate radiation absorbed dose to structures adjacent to tumors.

Given the possibility for large absorbed doses in tumors in RIT therapy, there exists a possibility of large absorbed doses to the tissue immediately surrounding the tumors. Three models were constructed with 3 tumor sizes each to investigate various situations including dose to generic tissue surrounding tumor, tumor around a small cylinder such as a nerve, and tumor against the pericardium or bowel wall.

Depth absorbed dose profiles for all models were calculated for I-131. This was performed by determining absorbed fractions using Monte Carlo simulation of the radiation transport the models. For each simulation between 100 thousand and 25 million particle histories were run. Full beta spectrum was generated for the simulations. For all simulations, sufficient numbers of histories were run such that the relative errors were less than 5%. The MCNP relative error criteria for generally reliable results is 10% or less. Listed below are methods and results for each of the models. These results are based on a paper submitted to the Journal of Nuclear Medicine for publication and is currently under review. [Sparks RB, Crowe EA, Wong FC, Toohey RE, Siegel JA. Radiation Dose Distributions in Normal Tissue Adjacent to Tumors Containing ^{131}I or ^{90}Y J Nuclear Medicine, Under Review].

Nerve Surrounded by Spherical Tumor

This simulation was designed to model the irradiation of a small nerve surrounded by tumor. The model consisted of a spherical source (representing tumor) encasing a small cylindrical nerve. Table 7 lists the depth absorbed dose profile into surrounding generic tissue using 10, 20 and 40-gram tumor models.

TABLE DA7: DEPTH DOSE PROFILE FOR ^{131}I : NERVE SURROUNDED BY SPHERICAL TUMOR.

Depth (cm)	% Source dose 10 gram Tumor	% Source dose 20 gram Tumor	% Source dose 40 gram Tumor
(Source)	100%	100%	100%
0.0085	50%	51%	52%
0.025	36%	37%	39%
0.042	31%	31%	35%

Generic Tissue Surrounding Spherical Tumor

This simulation was designed to model the irradiation of generic tissue surrounding a tumor. The model consisted of a spherical source (representing tumor) with surrounding concentric spherical shells. Table 8 lists the depth absorbed dose profile into surrounding generic tissue for 10, 20 and 40-gram tumor models.

TABLE DA8: DEPTH DOSE PROFILE FOR 131I: GENERIC TISSUE SURROUNDING SPHERICAL TUMOR

Depth (cm)	% Source dose 10 gram Tumor	% Source dose 20 gram Tumor	% Source dose 40 gram Tumor
-	100%	100%	100%
	43%	43%	44%
0.01	31%	31%	32%
0.02	21%	21%	22%
0.03	15%	16%	17%
0.04	11%	12%	13%
0.05	8%	9%	11%
0.06	7%	8%	9%
0.07	5%	6%	7%
0.08	5%	6%	7%
0.09	4%	5%	6%
0.1	4%	5%	6%
0.15	3%	4%	5%
0.25	2%	3%	4%
0.4	2%	3%	4%
0.6	2%	2%	3%

Hemispherical Tumor Adjacent to Bowel Wall or Pericardium

This simulation was designed to model the irradiation of tissue such as bowel wall or pericardium adjacent to a hemispherical tumor. The model consisted of a hemispherical source (representing tumor) adjacent to a series of cylindrical disks. Table 9 lists the depth absorbed dose profile into surrounding generic tissue for 10, 20 and 40-gram tumor models.

TABLE DA9: DEPTH DOSE PROFILE FOR ¹³¹I HEMISPHERICAL TUMOR ADJACENT TO BOWEL OR PERICARDIUM.

Depth (cm)	% Source dose 10 gram Tumor	% Source dose 20 gram Tumor	% Source dose 40 gram Tumor
-	100%	100%	100%
0.0025	46%	46%	47%
0.01	32%	33%	34%
0.02	22%	24%	24%
0.03	17%	18%	19%
0.04	13%	14%	15%
0.05	10%	11%	12%
0.06	8%	9%	10%
0.07	7%	8%	9%
0.08	6%	7%	8%
0.09	5%	6%	8%
0.1	5%	6%	7%
0.15	4%	5%	6%
0.25	3%	4%	6%
0.4	3%	4%	5%
0.6	2%	3%	4%

CBER Review Comment

Results for these estimates reported by Corixa are identical, which is as expected since Corixa consultant ~~_____~~, participated in the analysis. Corixa did not, however, report the dose depth estimates to the nerve surrounded by tumor case.

b(4)

Abnormal Situation Dosimetry

Dosimetry for Kidney Obstruction: Uptake and Indefinite Retention in the Kidneys

This section estimates the radiation-absorbed dose to the kidneys assuming indefinite retention of some level of percent-injected dose. The S-value for a single kidney was estimated using a 150-gram sphere with the MIRDOSE nodule module. Residence time was estimated assuming no biological removal of an instantaneous uptake of activity in a single kidney. The radiation-absorbed doses in a single kidney, for different levels of indefinite retention are shown in Table 10 below.

A similar analysis was discussed but not performed by Corixa.

TABLE DA10: I-131 DOSES IN OBSTRUCTED KIDNEY

% Injected Dose Retained	Single Kidney Absorbed Dose	
	cGy/mCi	mGy/MBq
1%	8	2
2%	16	4
3%	24	6
4%	32	9
5%	40	11

Dosimetry for Kidney Obstruction: Kidneys Fail to Process Activity

This section estimates the impact of renal obstruction for the first 24 hours, where the kidneys are assumed to stop functioning during this period, and then to resume normal function after this time. This will have the effect of increasing whole body residence time. It is assumed that all organ and remainder tissues residence times will increase roughly at the same percentage as whole body residence time increases, except for kidneys and urinary bladder residence times, which will decrease slightly, due to loss of about 8% of the activity by physical decay during the 24 hour period with no renal function, and no activity transfer to kidneys or bladder. For the average whole body half life of 90 hours, CBER found that the whole body residence time will show an increase of roughly 20%, which is in agreement with the number calculated by Corixa. CBER agrees with Corixa's assessment that a 20% increase in organ and remainder residence times will result in approximately a 20% increase in absorbed dose, except for kidneys and bladder wall, which will show a smaller increase in absorbed dose.

Dosimetry for Urinary Bladder Obstruction: 0-24 Hour Blockage

This section estimates the radiation-absorbed dose to the urinary bladder wall assuming a urinary bladder blockage lasting from 0 to 24 hours. This dose estimate assumes that the urinary bladder wall dose will be the most impacted by such a blockage, and that other organ, and remainder of body residence times will be impacted only slightly. Corixa performed this analysis with a series of assumed total body half lives. CBER verified this calculation based on the average whole body half-life of 90 hours in the 10 patients submitted. Results found by CBER and Corixa for a total body effective half-life of 90 hours are shown in Table 11 below. CBER and Corixa results are in excellent agreement.

TABLE DA11: URINARY BLADDER WALL ABSORBED DOSES WITH AND WITHOUT BLADDER OBSTRUCTION.

	CBER		Corixa		CBER/Corixa
	cGy/mCi	mGy/MBq	cGy/mCi	mGy/MBq	
Bladder Dose without Obstruction	2.6	0.7	2.8	0.8	0.93
Bladder Dose with 0 to 24 hour Obstruction	4.6	1.2	4.6	1.2	1.0

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Dosimetry Assuming Colloid Type Distribution

Dosimetry estimates for I-131 were determined using a colloid type distribution, based on the models described in ICRP-53 [ICRP 1988], by both CBER and Corixa.

The first model assumes "large" colloids (100-1000 nm diameter), with distributions of 70% in liver, and 10% each in spleen, red marrow, and remaining tissue.

The second model assumes "small" colloids (<100 nm diameter), with distributions of 70% in liver, and 10% in spleen, 15% in red marrow, and 5% remaining tissue.

In both models the colloid is assumed to break down with biological half lives of 3 hours and 5 days, for 80% and 20% of the total colloid, respectively. However, Corixa failed to account for the free iodide after the breakdown, and failed to account for the excretion of the activity in the bladder. These are clearly illustrated in ICRP-53 (Which was used by Corixa, but incorrectly called ICRP-50). This led to the rather large discrepancies seen below in Tables 12A and 12B. It should be noted that all estimates below assume complete blocking of the thyroid.

TABLE DA12A: DOSIMETRY ESTIMATES ASSUMING LARGE AND SMALL COLLOIDS (CGY/MCI).

	CBER (cGy/mCi)		Corixa (cGy/mCi)		Ratio CBER/Corixa	
	Large Colloids	Small Colloids	Large Colloids	Small Colloids	Large Colloids	Small Colloids
Adrenals	0.5	0.5	0.4	0.4	1.3	1.3
Brain	0.1	0.1	0.03	0.03	3.3	3.3
Breasts	0.2	0.2	0.08	0.07	2.5	2.9
Gallbladder Wall	0.7	0.7	0.6	0.6	1.2	1.2
LLI Wall	0.2	0.2	0.06	0.06	3.3	3.3
Small Intestine	0.3	0.3	0.1	0.1	3.0	3.0
Stomach	0.3	0.3	0.2	0.2	1.5	1.5
ULI Wall	0.3	0.3	0.2	0.2	1.5	1.5
Heart Wall	0.3	0.3	0.2	0.2	1.5	1.5
Kidneys	0.5	0.5	0.3	0.3	1.7	1.7
Liver	5.0	5.0	4.9	4.9	1.0	1.0
Lungs	0.3	0.3	0.2	0.2	1.5	1.5
Muscle	0.2	0.2	0.09	0.09	2.2	2.2
Ovaries	0.2	0.2	0.08	0.08	2.5	2.5
Pancreas	0.5	0.5	0.4	0.4	1.3	1.3
Red Marrow	0.7	0.9	0.6	0.8	1.2	1.1
Bone Surfaces	0.5	0.6	.4	.5	1.3	1.2
Skin	0.1	0.1	0.06	0.06	1.7	1.7
Spleen	6.5	6.5	6.4	6.4	1.0	1.0
Testes	0.2	0.1	0.03	0.02	6.7	5.0
Thymus	0.2	0.2	0.08	0.07	2.5	2.9
Thyroid	0.1	0.1	0.04	0.03	2.5	3.3
Urine Bladder Wall	1.9	1.9	0.05	0.04	38.0	47.5
Uterus	0.3	0.2	0.07	0.07	4.3	2.9

Total Body	0.4	0.4	0.3	0.3	1.3	1.3
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TABLE DA12B: DOSIMETRY ESTIMATES ASSUMING LARGE AND SMALL COLLOIDS (MGY/MBQ).

	CBER (mGy/MBq)		Corixa (mGy/MBq)		Ratio CBER/Corixa	
	Large Colloids	Small Colloids	Large Colloids	Small Colloids	Large Colloids	Small Colloids
Adrenals	0.14	0.14	0.11	0.11	1.3	1.3
Brain	0.03	0.03	0.01	0.01	3.3	3.3
Breasts	0.05	0.05	0.02	0.02	2.5	2.9
Gallbladder Wall	0.19	0.19	0.16	0.16	1.2	1.2
LLI Wall	0.05	0.05	0.02	0.02	3.3	3.3
Small Intestine	0.08	0.08	0.03	0.03	3.0	3.0
Stomach	0.08	0.08	0.05	0.05	1.5	1.5
ULI Wall	0.08	0.08	0.05	0.05	1.5	1.5
Heart Wall	0.08	0.08	0.05	0.05	1.5	1.5
Kidneys	0.14	0.14	0.08	0.08	1.7	1.7
Liver	1.35	1.35	1.32	1.32	1.0	1.0
Lungs	0.08	0.08	0.05	0.05	1.5	1.5
Muscle	0.05	0.05	0.02	0.02	2.2	2.2
Ovaries	0.05	0.05	0.02	0.02	2.5	2.5
Pancreas	0.14	0.14	0.11	0.11	1.3	1.3
Red Marrow	0.19	0.24	0.16	0.22	1.2	1.1
Bone Surfaces	0.14	0.16	0.11	0.14	1.3	1.2
Skin	0.03	0.03	0.02	0.02	1.7	1.7
Spleen	1.76	1.76	1.73	1.73	1.0	1.0
Testes	0.05	0.03	0.01	0.01	6.7	5.0
Thymus	0.05	0.05	0.02	0.02	2.5	2.9
Thyroid	0.03	0.03	0.01	0.01	2.5	3.3
Urine Bladder Wall	0.51	0.51	0.01	0.01	38.0	47.5
Uterus	0.08	0.05	0.02	0.02	4.3	2.9
Total Body	0.11	0.11	0.08	0.08	1.3	1.3

I-131 Dosimetry for Free Label

Dosimetry estimates for I-131 were determined by CBER for unbound Iodine, based on the model described in ICRP-53 [ICRP 1988]. Assumes 5% uptake by thyroid. Results are shown in Table 13.

Corixa did not perform this analysis.

Table DA13: Dosimetry Estimates Assuming Free Label

	cGy/mCi	mGy/MBq
Adrenals	0.1	0.03
Brain	0.1	0.03
Breasts	0.1	0.03
Gallbladder Wall	0.1	0.03
LLI Wall	0.2	0.05
Small Intestine	1.0	0.27
Stomach	1.6	0.43
ULI Wall	0.2	0.05
Heart Wall	0.1	0.03
Kidneys	0.2	0.05
Liver	0.1	0.03
Lungs	0.1	0.03
Muscle	0.1	0.03
Ovaries	0.2	0.05
Pancreas	0.2	0.05
Red Marrow	0.1	0.03
Bone Surfaces	0.2	0.05
Skin	0.1	0.03
Spleen	0.1	0.03
Testes	0.1	0.03
Thymus	0.2	0.05
Thyroid	252.0	68.11
Urine Bladder Wall	2.0	0.54
Uterus	0.2	0.05
Total Body	0.2	0.05

CBER Review Comments

Dosimetry for Kidney Obstruction: Uptake and Indefinite Retention in the Kidneys: Not reported by Corixa.

Dosimetry for Kidney Obstruction: Kidneys Fail to Process Activity:
Corixa methods are appropriate and correct. CBER results matched very closely.

Dosimetry for Urinary Bladder Obstruction:
0-24 Hour Blockage. Corixa methods are appropriate and correct. CBER results matched very closely.

Dosimetry Assuming Colloid Type Distribution.
Corixa failed to account for the free iodide after the breakdown, and failed to account for the excretion of the activity in the bladder. This led to the rather large discrepancies between CBER results and Corixa results.

I-131 Dosimetry for Free Label. Not reported by Corixa.

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Tolerance Doses per External Radiation Therapy

The following table lists the radiation-absorbed doses for external beam radiation therapy required to produce the listed effects in the listed organs. It must be emphasized that the primary source of these data is from external beam applications. The association and applicability of these values to unsealed source radiation therapy are unknown and not established.

TD 5/5 is the absorbed dose level required to produce the described injury within 5 years in 5% of those so exposed.

TD 50/5 is the absorbed dose level required to produce the described injury within 5 years in 50% of those so exposed.

The %-irradiated column describes the amount of the organ that was exposed to the radiation.

TABLE DA14: TOLERANCE DOSES*

Organ	Injury	TD 5/5 (cGy)	TD 50/5 (cGy)	% irradiated
Gastrointestinal Epithelial Cells	enteritis	500	1000	whole
Peripheral Nerve	neuropathy	1500	2000	whole
Heart	pericarditis and pancarditis	4500	5500	60%
Heart	pericarditis and pancarditis	7000	8000	25%
Intestine	ulcer, perforation, hemorrhage	4500	5500	400 square cm
Intestine	ulcer, perforation, hemorrhage	5000	6500	100 square cm
Large Arteries and Veins	sclerosis	>8000	>10000	10 square cm
Peripheral Nerves	neuritis	6000	10000	10 cm
Small Intestine	Obstruction, perforation, fistula	5000	6000	1/3
Small Intestine	Obstruction, perforation, fistula	none	none	2/3
Small Intestine	Obstruction, perforation, fistula	4000	5500	3/3

*Sources:

- 1) Vaeth JM, Meyer JL (eds) Radiation Tolerance of Normal Tissues. 23rd Annual San Francisco Cancer Symposium. 1988.
- 2) Bentel GC, Nelson CE, Noell KT. Treatment Planning and Dose Calculation in Radiation Oncology. 4th Edition. Pergamon Press, 1989.
- 3) Emani B, Lyman J, et al. Tolerance of Normal Tissue to Therapeutic Irradiation. Int J Rad Onc Biol Phys. Vol 21:1;109-122. 1991

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3.5.2 Use in Special Populations

Not Applicable

3.5.2.1 Demographic Worksheet

The following table provides the baseline characteristics. For individual study demographics, please refer to section 6.1

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BASELINE CHARACTERISTICS FOR PATIENT POPULATION IN COMBINED EFFICACY/SAFETY POPULATION (N=230)

Baseline Characteristic	Safety/Efficacy population n=230
Age (years)	
Median(range)	56 (23-82)
Q1; Q3	48, 65
Gender	
Males (%)	137 (60%)
Race	
Caucasian (%)	213 (93%)
Histologic diagnosis at entry	
Low grade	171 (74%)
Intermediate grade	57 (25%)
High grade	2 (1%)
Stage of disease at entry	
I	2 (1%)
II	21(9%)
III	50 (22%)
IV	157 (68%)
Missing	0
IPI category	
0	7 (3%)
1	40 (17%)
2	90 (39%)
3	62 (27%)
4	22 (10%)
5	2 (1%)
Missing	7 (3%)
Max. tumor diameter	
< 5 cm	56 (24%)
≥ 5, ≤10 cm	90 (39%)
> 10 cm	15 (7%)
# Prior chemo regimens	
Median (range)	3 (1-13)
25 th , 75 th quartiles	2, 4
# Prior RT regimens	
Median (range)	0 (0-7)
25 th , 75 th quartiles	0, 1
No Prior BMT	227 (99%)
Time from diagnosis to entry (Years)	
Median (range)	3.1 (0.5, 27.8)
25 th , 75 th quartiles	2.2, 6.8

TABLE 2 (CONT'D)

BASELINE CHARACTERISTICS FOR PATIENT POPULATION IN SEPARATE EFFICACY/SAFETY POPULATION

	# prior chemotherapy		Low Grade Histology	Low + Intermediate
	Median	Range		
ISS (n=995)	2	0-13	765 (77%)	776 (78%)
Efficacy (n=230)	3	1-13	161 (70%)	165 (72%)
ISS (n=764)	2	0-12	604 (79%)	611 (80%)

3.5.2.2 Special Considerations based on Race

None

3.5.2.3 Special Considerations based on Gender

3.5.2.4 Special Considerations based on Age for Adults

The following table compares the objective response rates according to age of the patient:

Table 14:

Study	ORR (%)	Median Duration Months	ORR (%) for Age		Median Duration for Age		ORR (%) for Age		Median Duration for Age	
			< 65	>=65	< 65	>=65	< 75	>=75	< 75	>=75
	All	All								
CP-97-012 Rituxan Response <= 12 months	27/40 68%	16	23/29 79%	4/11 36%	16 65	10	26/37 70%	1/3 33%	16	9

RIT-I-000	14/22 64%	18	13/20 65%	1/2 50%	18	13	14/22 64%	0	17	---
RIT-II-001	23/47 49%	14	19/39 49%	4/8 50%	14	NR	23/47 49%	0	14	---
RIT-II-002	36/61 59%	13	29/42 69%	7/19 37%	NR	6	33/58 57%	3/3 100%	NR	7
RIT-II-004	28/60 47%	12	19/39 49%	9/21 43%	10	12	27/56 48%	1/4 25%	11	---

In this analysis, significant difference detected in comparing Objective response rates (ORR) for CP-97-012 Age < 65 versus age ≥65 (p=0.02) and for RIT-II-002 (p=0.02). While this does not change the recommendation regarding its use in the elderly patients, the following wording was incorporated in the package insert under geriatric use section:

Clinical studies of the BEXXAR therapeutic regimen did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In clinical studies, 230 patients received the BEXXAR therapeutic regimen at the recommended dose. Of these, 27% (61 patients) were age 65 or older and 4% (10 patients) were age 75 or older. Across all studies, the overall response rate was lower in patients age 65 and over (41% vs. 61%) and the duration of responses were shorter (10 months vs. 16 months), however these findings are primarily derived from 2 of the 5 studies. While the incidence of severe hematologic toxicity was lower, the duration of severe hematologic toxicity was longer in those age 65 or older as compared to patients less than 65 years of age. Due to the limited experience greater sensitivity of some older individuals cannot be ruled out.

3.5.2.5 Special Considerations based on Age for Pediatrics

Not applicable. The product was not studied in pediatric population.

3.5.2.6 Other Special Considerations

Because of I-131 content of pregnant and lactating patients were excluded from the clinical trials. This product is labeled as Pregnancy category X and the label contains adequate warning for nursing mothers.

3.5.3 Outcome of Advisory Committee Meeting

The Oncology Advisory Committee met on December 17, 2002. The following summarizes the questions posed to them and their recommendations.

Questions to the Committee

- 1. Do the results (ORR 63%, median response duration 2.1 years) in 30 patients enrolled in this Phase 2 study (CP97-012), supported by the results observed in the other patients enrolled in this study and the activity in studies conducted in Rituxan-naïve patients with chemotherapy-refractory disease, constitute substantial evidence of clinical benefit?**

YES – 10 N - 3

The Committee felt that this implicitly-controlled trial was small, but there did appear to be evidence of clinical benefit and a response of long duration. Concerns were expressed about the quality of the data, including the number of protocol violations, and the observed myelodysplasia as an adverse event.

Chemotherapy-refractory low grade and follicular NHL, with or without transformation

2. Are the overall response rates and durations of responses observed across the 5 clinical trials conducted by the sponsor, in light of the toxicity profile observed, likely to predict clinical benefit in patients with chemotherapy-refractory, low grade and follicular NHL, with or without transformation?

YES – 13

N - 0

The Committee felt that, in these heavily pre-treated patients, this product produced a reasonable number of responses of good duration, and appeared as least as good as another line of cytotoxic treatment. Concerns about the hematologic toxicities and long term risks should be addressed in the informed consent forms, and make this treatment inappropriate for first-line therapy. There were also cautions that this is not a curative therapy and many patients will not respond.

Long-term responders

The sponsor has retrospectively defined and identified a subpopulation of patients with long-term responses. The sponsor defined these patients according to the following criteria

- Achieved a CR, CCR or PR to the TTR
- The time to progression (from study entry) was at least one year

These criteria were not prospectively discussed or agreed upon with FDA and the sponsor has provided no clear rationale or justification for these criteria based upon literature review or other sources. The 76 patients meeting these criteria constitute two-thirds of all patients who have responded to the TTR. The FDA has further segregated this subset into 68 patients who received the dose and schedule for which marketing approval is being sought and 8 patients who received a different dose and schedule. The efficacy results in these subsets are summarized in the following table:

Efficacy Outcome	Patients without long-term responses	Corixa Long-term Responder Dataset	Single Dose Long-term Responders Per FDA	Multiple Dose Long-term Responders Per FDA
Number of subjects	n=193	n=76	n=68	n=8
Response				
CR (%)	13 (7%)	30 (39%)	30 (44%)	
CCR (%)	2 (1%)	28 (37%)	24 (35%)	4 (50%)
PR (%)	49 (25%)	18 (24%)	14 (21%)	4 (50%)

3. Does the finding of a subpopulation of patients with long-term responses demonstrate that the TTR provides meaningful therapeutic benefit to patients over existing treatments (e.g., improved patient response over available therapy)?

No vote was taken on this question.

The Committee stressed that this treatment is a form of specifically-delivered radiotherapy, and although some clinical benefit can be seen, it is not clear that there is benefit over existing available therapy, as there were no studies of appropriate design for making these comparisons.

Additional studies

4. *Please comment on the types of information that should be obtained in additional studies to further characterize the safety and effectiveness of the tositumomab therapeutic regimen. Specifically, comment on the following:*
- The sponsor has proposed a trial of Rituximab vs. the TTR in patients with NHL who have received at least one and no more than two prior chemotherapy regimens. The primary objective of this trial is demonstration of a longer time to progression, alternative therapy, or death in TTR-treated patients. Survival is a secondary objective.
 - Please comment on the need to conduct studies to further assess delayed toxicities, including MDS/ secondary malignancies, hypothyroidism, and HAMA.

The Committee would like to see studies directly comparing this treatment to Zevalin, studies on the interactions with concomitant medications, and broader studies with longer more than 5 years, more careful follow-up. Quality of Life studies, including the impact of the treatment on the families and caregivers, were suggested. Eligibility criteria must consider the toxicity profile, e.g., asymptomatic patients with very localized disease should not be included, due to the risk of toxicity.

HAMA information should be clearly explained, as a positive HAMA status will alter future diagnostic studies using murine antibodies, and also alter the distribution of future treatment involving murine antibodies.

The opinion of the advisory committee was useful and contributed positively to the Agency's approval process and in arriving at agreed upon post-marketing commitments with the sponsor.

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