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APPLICATION NUMBER:

125011

STATISTICAL REVIEW(S)

Statistical Review

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Type: BLA

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Product/Application: BEXXAR™ therapeutic regimen (I 131 tositumomab) for patients with chemotherapy-refractory low-grade and transformed low-grade NHL

Sponsor: Corixa

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Note: This report is analysis of the data submitted on April 3, 2003 and focuses on CBER defined agreed upon dataset. It is primarily based on package insert issues and supplements statistical report issued on December 16, 2002. The primary focus of this report is 230 safety/efficacy patient population identified by both CBER and Corixa.

Datasets used and notation:

This was a rolling BLA and several datasets were submitted as a part of rolling BLA. The datasets submitted on April 4, 2003 were used for analysis in this report.

INDICATIONS AND USAGE

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.

Clinical Studies

Five clinical studies (RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012), 6 single-patient studies, and an Expanded Access Study (CP-98-020) provide data in support of this application.

The patient population is described in Table 1 below:

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Table 1: 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

^e 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.

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)

CP-97-012 Rituxan-failure patients

CP-98-020 Expanded Access Study

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/safety 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

Table 2

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%)

% grade 3/4 at baseline is not available/not determined

Confirmed vs. Unconfirmed Administered Activity

Response Rates:

Overall 182 of the 250 (73%) patients in the Integrated Efficacy Population had their administered activity confirmed. The confirmed response rate and confirmed complete response rate for the five clinical studies by confirmation of administered activity are presented in Table below. Both the response rate (p=0.454, Cochran-Mantel-Haenszel test with study as stratification variable) and complete response rate (p=0.937, Cochran-Mantel-Haenszel test with study as stratification variable) were similar between patients with confirmed administered activity and patients with unconfirmed administered activity.

Table 3
Overall Response and Complete Response Rates by Study
Confirmed vs. Unconfirmed Administered Activity

Study	Overall Response Rate Administered Activity		Complete Response Rate Administered Activity	
	Confirmed	Unconfirmed	Confirmed	Unconfirmed
	RIT-I-000	67% (2/3)	64% (25/39)	33% (1/3)
RIT-II-001	49% (18/37)	50% (5/10)	32% (12/37)	0% (0/10)
RIT-II-002	55% (28/51)	80% (8/10)	31% (16/51)	60% (6/10)
RIT-II-004	47% (24/51)	44% (4/9)	20% (10/51)	22% (2/9)
CP-97-012	68% (27/40)	NA	33% (13/40)	NA
Total	54% (99/182)	62% (42/68)	29% (52/182)	34% (23/68)

p-value (using Cochran-Mantel-Haenszel test with study as stratification variable)

p=0.454

p=0.937

NA =Not applicable as no patients had unconfirmed administered activity in Study CP-97-012.

**Confirmed vs. Unconfirmed Administered Activity
Hematologic Toxicities:**

Table 3 (continued)
Standard Grade III/IV Hematologic Toxicities by Administered Activity
Confirmed vs. Unconfirmed Administered Activity

Toxicity	ISS-E N=230 Administered Activity		EAP n = 765 Administered Activity		ISS n=995 Administered Activity	
	Confirmed	Unconfirmed	Confirmed	Unconfirmed	Confirmed	Unconfirmed
N	180	50	277	488	457	538
Platelet	42%	42%	40%	33%	41%	33%
Duration(Days)	30	35	29	30	29	30
ANC	52%	46%	41%	36%	45%	37%
Duration(Days)	30	29	29	31	29	31
Hemoglobin	14%	18%	13%	9%	14%	10%
Duration(Days)	21	16	22	16	22	16

Table 3 (continued)
Worst Case Grade III/IV Hematologic Toxicities by Administered Activity
Confirmed vs. Unconfirmed Administered Activity

Toxicity	ISS-E N=230 Administered Activity		EAP n = 765 Administered Activity		ISS n=995 Administered Activity	
	Confirmed	Unconfirmed	Confirmed	Unconfirmed	Confirmed	Unconfirmed
N	180	50	277	488	457	538
Platelet	54%	52%	48%	50%	50%	50%
Duration(Days)	32	40	29	39	30	39
ANC	65%	56%	52%	55%	57%	55%
Duration(Days)	30	31	29	37	30	36
Hemoglobin	29%	28%	26%	30%	27%	29%
Duration(Days)	23	20	29	NR	29	101

There are no significant differences in the response rates or Grade III/IV hematologic toxicity profile between Confirmed vs. Unconfirmed Administered Activity

CLINICAL STUDIES

The efficacy of the BEXXAR therapeutic regimen was evaluated in 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 4 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 26 months for all patients and for the Rituximab-refractory subset.

Table 4
Efficacy Outcomes Patients

	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 details are given below:

Response Rates and Duration of Response for the Study CP-97-012

	Treated MIRROR Assessed (n=40)	Rituxan refractory (n=35) (88%)	Durable Responders (n=17) (43%)
Overall response rate (Number of responders) 95% CI	68% (27) 51 - 81 %	63% (22) 45 - 79 %	17 (100%) 80 - 100 %
Median Duration (Months) (K-M Curves) 95% CI on Median IQ Range in Months Range in Months	16.1 10.0, NR 10.0, NR 1.4+, 35.2+	25.3 10.5, NR 10.5, NR 3.8+, 35.2+	28.3 11.0, NR 14.7, NR 10.5, 35.2+
CR % (N) 95% CI	28% (11) 15 - 44 %	23% (8) 10 - 40 %	53% (9) 28 - 77 %
CCR % (N) 95% CI	5% (2) 1 - 17 %	6% (2) 1 - 19 %	12% (2) 1 - 36 %
CR+CCR % (N) 95% CI	33% (13) 19 - 49 %	29% (10) 15 - 46 %	65% (11) 38 - 86 %
PR % (N) 95% CI	35% (14) 21- 52 %	34% (12) 19 - 52 %	35% (6) 14 - 62 %
Median Duration (Months) CR+CCR (K-M Curves) 95% CI on Median IQ Range in Months Range in Months	NR NR 11.0, NR 14.7, NR 4.1+, 35.2+	NR NR 4.1, NR 28.3, NR 4.1, 35.2+	NR NR 14.7, NR 28.3, NR 11.0, 35.2+

Durable responses (defined as responses with a time to progression of greater than 1 year) were observed in 17 of 40 patients (43%).

CI = Confidence Interval

NR = Not Reached

Supportive Studies:

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 details are given below:

Objective Response Rates ORR = CR+CCR+PR:

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	< 65	>=65	< 65	>=65	< 75	>=75	< 75	>=75
CP-97-012 Rituxan Response ≤ 12 months	27/40 68%	16	23/29 79%	4/11 36%	16	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	---
Overall	128/230 56%	13	103/169 61%	25/61 41%	16	10	123/220 56%	5/10 50%	14	9

Significant difference detected in comparing ORR for CP-97-012 Age < 65 versus age >=65 (p=0.02), for RIT-II-002 (p=0.02), and for overall ORR (p=0.0103). The log-rank p-value for the duration of response for Age < 65 versus age >=65 is 0.0476 (overall n=230)..

Summary of Safety (n=230)

Prolonged and Severe Cytopenias

The most common adverse reactions associated with the BEXXAR therapeutic regimen were severe or life-threatening cytopenias (NCI CTC grade 3 or 4) with 71% of the 230 patients enrolled in clinical studies experiencing grade 3 or 4 cytopenias. These consisted primarily of grade 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The time to nadir was 4 to 7 weeks and the duration of cytopenias was approximately 30 days. Thrombocytopenia, neutropenia, and anemia persisted for more than 90 days following administration of the BEXXAR therapeutic regimen in 16 (7%), 15 (7%), and 12 (5%) patients respectively (this includes patients with transient recovery followed by recurrent cytopenia). Due to the variable nature in the onset of cytopenias, complete blood counts should be obtained weekly for 10-12 weeks. The sequelae of severe cytopenias were commonly observed in the clinical studies and included infections (45% of patients), hemorrhage (12%), a requirement for growth factors (12% G- or GM-CSF; 7% Epoetin alfa) and blood product support (15% platelet transfusions; 16% red blood cell transfusions). Prolonged cytopenias may also influence subsequent treatment decisions.

The safety of the BEXXAR therapeutic regimen has not been established in patients with > 25% lymphoma marrow involvement, platelet count <100,000 cells/mm³ or neutrophil count <1,500 cells/mm³.

Hypersensitivity Reactions Including Anaphylaxis:

Hypersensitivity reactions, including anaphylaxis, were reported during and following administration of the BEXXAR therapeutic regimen

ADVERSE REACTIONS

The most serious adverse reactions observed in the clinical trials were severe and prolonged cytopenias and the sequelae of cytopenias which included infections (sepsis), and hemorrhage in thrombocytopenic patients, allergic reactions (bronchospasm and angioedema), secondary leukemia and myelodysplasia.

The most common adverse reactions occurring in the clinical trials included neutropenia, thrombocytopenia, and anemia that are both prolonged and severe. Less common but severe adverse reactions included pneumonia, pleural effusion and dehydration.

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. Patients had a median follow-up of 35 months and 79% of the patients were followed for over 12 months. Patients had a median of 3 prior chemotherapy regimens, a median age of 55 years, 60% male, 27% had transformation to a higher grade histology, 29% were intermediate grade and 2% high grade histology (IWF) and 68% had Ann Arbor stage IV disease. Patients enrolled in these studies were not permitted to have prior hematopoietic stem cell transplantation or irradiation to more than 25% of the red marrow. In the expanded access program, which included 765 patients, data regarding clinical serious adverse events and HAMA and TSH levels were used to supplement the characterization of delayed adverse events, Hypothyroidism, Secondary Leukemia and Myelodysplastic Syndrome, Immunogenicity.)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

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 Epoetin alfa; 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. (Appendix A)

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. Sixty-seven patients (29%) reported fever, rigors/chills, or sweating within 14 days following the dosimetric dose. 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 (7%); 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.

Table 5 lists adverse events that occurred in $\geq 5\%$ of patients. Table 6 provides a more detailed description of the hematologic toxicity. The details are given in Appendix A.

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

Body System Preferred Term	All Grades	Grade 3/4
Total	(96%)	(48%)
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 5 (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	Excludes laboratory derived hematologic adverse events (See Table 6).	
^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.	

The details are given in Appendix A

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Table 6
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)	690
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.	

The details are given in Appendix A

Secondary Malignancies:

Myelodysplastic syndrome (MDS) and/or acute leukemia were reported in 8% (19/230) of patients enrolled in the clinical studies and 2% (13/765) of patients included in expanded access programs, with median follow-up of 35 and 20 months, respectively. Among the 32 reported new cases, the median time to development of MDS/leukemia was 27 months following treatment; however, the cumulative rate continues to increase. The pretreatment characteristics (e.g., median age, number of prior chemotherapy regimens) were similar in patients developing MDS/secondary leukemias as compared with those who did not. Additional malignancies were also reported in 52 of the 995 patients enrolled in clinical studies or included in the expanded access program. Approximately half of these were non-melanomatous skin cancers. The remainder which occurred in 2 or more patients included breast cancer, lung cancer, bladder cancer, head and neck cancer, colon cancer and melanoma, in order of decreasing incidence. The relative risk of developing secondary malignancies in patients receiving the BEXXAR therapeutic regimen over the background rate in this population cannot be determined, due to the absence of controlled studies.

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.

The details are as follows:

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HAMA

At Baseline (Revise the opening statement based on info below)

For ISS Population n = 995

N	HAMA- 978	HAMA+ 11	Missing evaluation or no baseline values 6
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For Efficacy Studies n = 230

N	HAMA- 220	HAMA+ 4	Missing evaluation or no baseline values 6
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For Expanded Access Population n = 765

N	HAMA- 758	HAMA+ 7	Missing evaluation or no baseline values 0
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	No Patients HAMA- at baseline	At least one post-treatment value obtained	Median follow-up Months for HAMA evaluation	HAMA+ post treatment	Median time to HAMA development Months	HAMA+ by 6 months
ISS Population (n=995)	978	785 (80%)	6 months	76 (10%)	5	45 (59%)
Efficacy Studies (n=230)	220	219 (99.5%)	6 months	23 (11%)	6	11 (48%)
Expanded Access Population (n = 765)	758	566 (74%)	6 months	53 (9%)	4	34 (64%)

The details are given in Appendix B

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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, in the absence of competing risks, 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, in the absence of competing risks, were 1.4% and 4.8% at 2 years and 4 years, respectively, in the expanded access population.

The details are as follows:

	New cases of MDS/AML	Median follow-up	Time to MDS
Efficacy Studies (n=229)	19 (8.3%)	35 months	30 months
ISS Population (n=994)	32 (3.2%)	21 months	27 months
Expanded Access (n=765)	13 (1.7%)	20 months	23 months

Note: One patient (000-002-055 68M L75C) developed MDS/AML 24 days before the therapy started and is not included in the above numbers.

Note: Do not include annualized incidence rate in PI.

Efficacy Studies (n=229)

1 year cumulative incidence (MDS/AML) = 1.0 %
2 year cumulative incidence (MDS/AML) = 4.2 %
4 year cumulative incidence (MDS/AML) = 10.7 %

Expanded Access (n=765)

1 year cumulative incidence (MDS/AML) = 0.8 %
2 year cumulative incidence (MDS/AML) = 1.3 %
4 year cumulative incidence (MDS/AML) = 4.8 %

ISS Population (n=994)

1 year cumulative incidence (MDS/AML) = 0.8 %
2 year cumulative incidence (MDS/AML) = 2.1 %
4 year cumulative incidence (MDS/AML) = 7.3 %

The details are given in Appendix C

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: (TSH)

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.

The details are as follows and also given in Appendix D.

At Baseline (Revise the opening statement based on info below)

For ISS Population n = 995

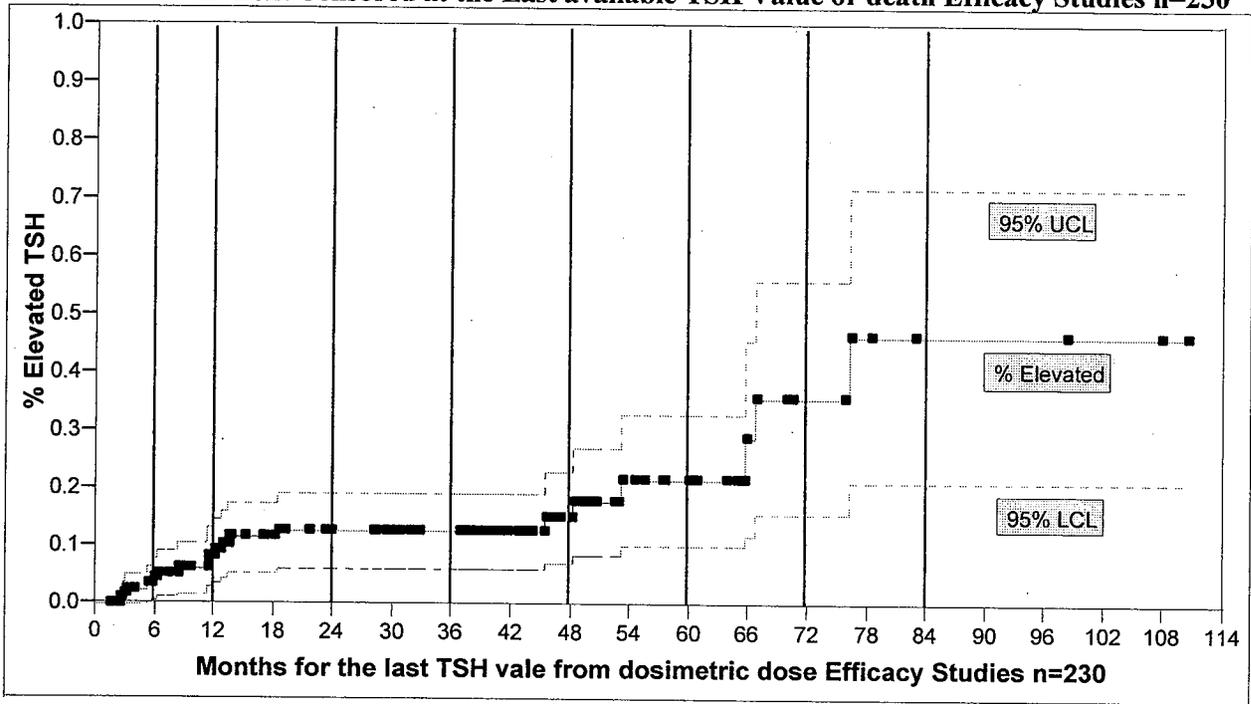
	No elevated TSH value	Elevated TSH value	Missing evaluation or on thyroid medication
N	873	74	48

For Efficacy Studies n = 230

	No elevated TSH value	Elevated TSH value	Missing evaluation or on thyroid medication
N	203	18	9

	No Patients euthyroid at entry	At least one post-treatment value obtained
ISS Population (n=995)	873	583
Efficacy Studies (n=230)	203	137

Percent Elevated TSH Censored at the Last available TSH Value or death Efficacy Studies n=230



Time to event: KMMONTH Censored by KMCENS

Months	0	3	6	12	24	36	48	60	72	84	96	114
Elevated		2	5	9	13	13	14	16	18	19	19	19
#Censored		12	27	40	57	69	92	105	112	115	115	118
# at Risk	137	123	105	88	67	55	31	16	7	3	3	0

6 months cumulative incidence (elevated TSH) = 4.2 %
12 months cumulative incidence (elevated TSH) = 8.1 %
2 year cumulative incidence (elevated TSH) = 12.6 %
4 year cumulative incidence (elevated TSH) = 15.0 %

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.

The data reflect the percentage of patients whose test results were considered positive for HAMA based on the ImmuSTRIP® ELISA for HAMA test kit, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of HAMA in patients treated with BEXXAR with the incidence of antibodies to other products may be misleading.

The details are given in Appendix B

Geriatric:

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.

Survival Analysis

Survival Time from Dose (SURDOSE)

Sponsor's Algorithm:

If the death day is not missing, then SURDOSE = Death Day + 1

If the death day is missing then SURDOSE = follow-up day + 1 (Censored)

For the patients who have been lost to follow-up, or if the death day is missing then survival time has been censored at the last follow-up day + 1.

The median **follow-up** from the first dosimetric dose for the 230 patients was 35 months and ranged from 0.2 to 114.1 months.

Follow-up time in months

Study	N	Median	Range	Q1	Q3
CP-97-012 Rituxan Response <= 12 months	40	35.0	1.2 - 52.2	13.8	42.6
CP-97-012 Rituxan Response <= 6 months	35	25.9	1.2 - 40.0	11.4	30.6
RIT-I-000	22	45.5	2.4 - 114.2	14.6	94.4
RIT-II-001	47	34.0	0.2 - 82.9	13.9	72.2
RIT-II-002	61	35.3	1.8 - 71.5	14.5	49.9
RIT-II-004	60	30.2	0.5 - 71.4	10.3	51.9
CP-97-098	765	19.8	0.1 - 49.9	10.8	30.2

Termination Reason (TRMRSN) (n=230)

Reason	1	3	4	7	8	9	10	99	Missing	Total
Number	2	1	1	3	2	178	4	2	37	230

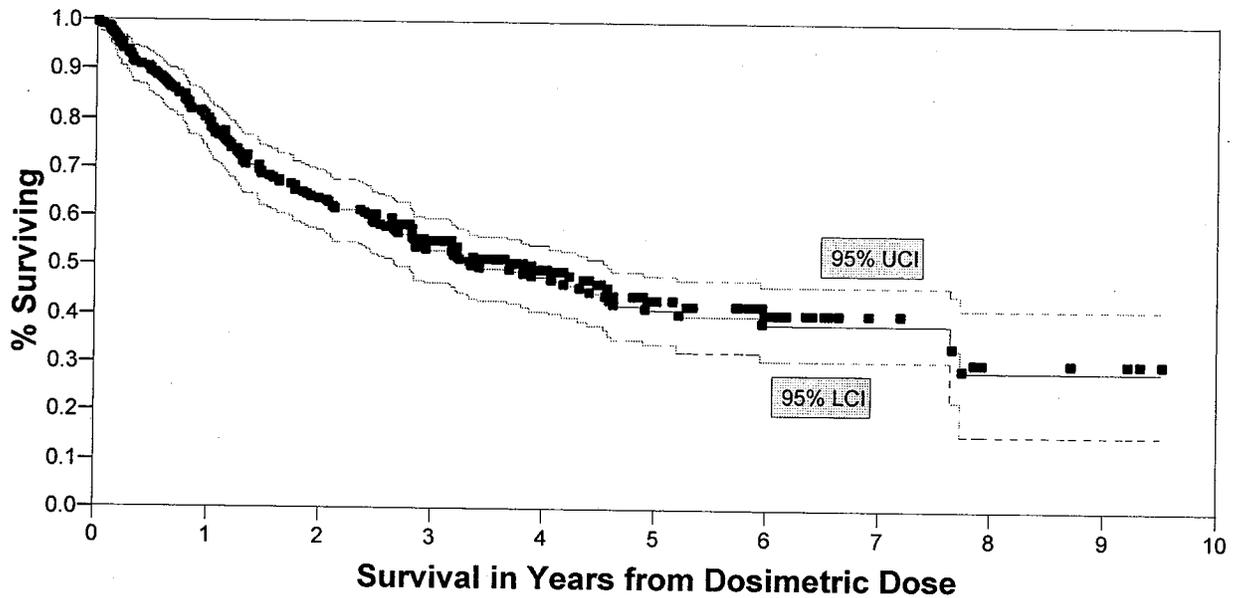
Termination Reason: 0=unknown, 1 = adverse event, 2 = protocol violation, 3 = non-compliance, 4 = lost to follow up, 5 = patient wish, 6 = protocol-restricted medication, 7=alternative therapy, 8 = medical condition, 9 = Progression, 10 = death, 99 = other

Cause of Death (DTHCAU) (n=230)

Cause	0	1	2	3	Total deaths
Number	0	94	0	34	128 (56%)

Cause of Death: 0 = unknown, 1 = Progression, 2 = Complications related to drug, 3 = Other

Survival in Years for safety/efficacy population (n=230)



Median Survival Time = 3.4 years, 95% CI (2.7, 4.6), Q1 = 1.2, Q3 = Not Reached

No. of deaths = 128

No. Censored = 102

Months	0	3	6	9	12	18	24	30	36	48	60	114
# Deaths	0	14	24	34	48	72	83	94	106	116	124	128
# Censored	0	1	1	1	1	3	3	4	14	42	67	102
# at Risk	230	215	205	195	181	155	144	132	110	72	39	0

#s are cumulative

Appendix A

Incidence of Clinical Adverse Experiences Regardless of Relationship to Study Drug occurring in the Patients Treated with BEXXAR Therapeutic Regimen^a

Pooled AEs for efficacy patients (n=230)

AE Preferred Name	Number of Patients with AE Efficacy n=230	Number of AEs in Efficacy n=230
Infection (type not specified), Pharyngitis, Pneumonia, Bronchitis, Herpes zoster, Urinary tract infection, Sepsis, Sinusitis, Herpes simplex, Cellulitis, Fungal dermatitis, Periodontal abscess, Injection site reaction	104	159
Hemorrhagic events (hemorrhage, epistaxis, ecchymosis, Melena, Gastrointestinal hemorrhage, hemoptysis, Gum hemorrhage, Lung hemorrhage, cerebral hemorrhage)	28	32
Fever, sweating, chills & fever	92	152
Chills, sweating, chills & fever	53	80
UGI (Nausea, Vomiting, Nausea & Vomiting, Gastrointestinal disorder)	87	137
UGI (Nausea, Vomiting, Nausea & Vomiting, Intestinal obstruction)	87	136
LGI (Diarrhea, Abdominal pain, Abnormal stools, Gastroenteritis, Intestinal Perforation, Ulcerative colitis, Colitis)	55	78
Urinary (Urinary tract infection)	8	9
Other Urinary (Urination impaired, Urinary tract disorder, Urinary retention, Dysuria, Oliguria, Nocturia, Urinary incontinence, Urinary urgency, Urinary frequency)	14	16
potential allergic reactions- Allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus & serum sickness.	14	14

Infusional Toxicity (n=230)

The number of patients with fever, chills, sweating, chills and fever	# of Events
Within first 2 days of dosimetric dose = 47 (20%)	65
Within first 7 days of dosimetric dose = 54 (23%)	86
Within first 14 days of dosimetric dose = 67 (29%)	134
Anytime in the observational period = 97 (42%)	212

Appendix A (cont'd)

**Incidence of Clinical Adverse Experiences Regardless of Relationship to Study Drug occurring in the Patients Treated with BEXXAR Therapeutic Regimen^a
Summary of all adverse events for 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 of Serious Events (194)
ASTHENIA	106	117	4	4	2	2
FEVER	85	132	4	4	9	9
NAUSEA	82	96	6	6	1	1
COUGH INCREASED	48	55	2	2	1	1
INFECTION	48	56	1	1		
PAIN	44	55	3	4	2	3
CHILLS	41	60	3	3	1	1
RASH	39	45	1	1		
HEADACHE	36	43				
THROMBOCYTOPENIA	36	40	32	35	5	5
ABDOMINAL PAIN	34	41	6	6	2	2
ANEMIA	34	38	14	14	4	4
VOMITING	34	38	3	3	2	2
ANOREXIA	33	36				
MYALGIA	30	31	1	1		
DIARRHEA	28	33				
PHARYNGITIS	27	28				
DYSPNEA	25	30	7	9	5	7
ARTHRALGIA	24	27	3	4	2	2
PRURITUS	24	34				
RHINITIS	24	30				
NEUTROPENIA	22	23	20	21	3	3
PERIPHERAL EDEMA	20	21				
MYELOPROLIFERATIVE DISORDER	19	19	19	19	19	19
BACK PAIN	18	20	2	2	1	1
SWEATING	18	19	1	1		
HYPOTENSION	16	18	2	2	4	4
HYPOTHYROIDISM	16	16				
CHEST PAIN	15	19				
NECK PAIN	14	15	2	2		
SKIN CARCINOMA	14	19	6	10	14	19
WEIGHT LOSS	14	14	1	1	1	1
CONSTIPATION	13	14	2	2	2	2
DYSPEPSIA	13	15	1	1		
PNEUMONIA	13	14	7	8	7	7
DIZZINESS	12	12				
SOMNOLENCE	12	12				

VASODILATATION	12	13				
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				

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Appendix A (cont'd)

Incidence of Clinical Adverse Experiences Regardless of Relationship to Study Drug occurring in the Patients Treated with BEXXAR Therapeutic Regimen^a Summary of all Hematologic Adverse Events and Toxicity for Efficacy Studies (n=230)

In order to achieve an accurate assessment of the depth and duration of the nadir and to confirm recovery from toxicity, FDA determined that subjects would need to be assessed at least weekly during 4 of the 5 weeks when the onset of the nadir was noted (weeks 5-9) and once at the recovery period (week 13). FDA reviewed the data from 995 patients, including 230 from studies RIT-II-000, 001, 002, 004 and CP 97-012 and 765 patients enrolled in the expanded access experience.

Based on the pattern of toxicity observed in individual patients and in a scatterplot of the study population, FDA considered that only those patients with a sufficient data obtained during the predicted likely period of hematologic toxicity could be adequately assessed. FDA defined sufficient data to assess for hematologic toxicity as having complete blood counts obtained in at least 4 of the 5 weeks (weeks 5-9) when the nadir might occur and at the time of the predicted recovery, which coincided with the end of the treatment period (week 13).

Algorithm

Source – HEMOUT and HEMAT datasets submitted on April 03, 2003

Time is in days.

Percentages are based on overall N.

Duration of toxicity is obtained by using CBER's definition, i.e., Time from last value above grade 3 to next value above grade 3 (additive if multiple occurrences of grade 3 toxicity), censored if not recovered. Median duration is based on Kaplan-Meier estimate with censored observations at last value.

Grade III/IV toxicity derived from hematologic parameters.

NCI CTC toxicity grades:

ANC (1000 cells/mm³): Grade II = 1.0 to <1.5, Grade III = 0.5 to <1.0, Grade IV = <0.5.

Platelets (1000 cells/mm³): Grade II = 50 to <75, Grade III = 25 to <50, Grade IV = <25.

Hemoglobin (g/dL): Grade II = 8.0 to <10.0, Grade III = 6.5 to <8.0, Grade IV = <6.5.

Worst-case Hematology

Patients who did not have Grade 3/4 hematologic toxicity but who had incomplete week 5–9 data (2 or more weeks of missing evaluations) were classified as Grade 3/4 regardless of their hematology values and regardless of their time on-study. (Ref: ISS-Lab data submitted April 03, 2003).

Briefly, the worst case results were performed as follows:

Worst case nadir for ANC, platelet, and hemoglobin: Patients with an undocumented grade III/IV were assigned a value of the lowest grade III possible and patients with an undocumented grade IV were assigned a value of 0 (the lowest possible value for ANC, platelet, and hemoglobin). For example for platelet count, patients with an undocumented grade III/IV were assigned a nadir of 25000/mm³ and patients with an undocumented grade IV were assigned a nadir of 0/mm³.

Worst-case duration of grade III/IV hematologic toxicity: Patients with an undocumented grade III/IV and less than Week 9 hematologic follow-up were assigned a duration of 1000+ days.

Maximum hematologic toxicity:

Grade III if less Grade III and missing 2 or more weeks of hem f/u between Week 5 and Week 9.

Grade IV if Grade III and missing 2 or more weeks of hem f/u between Week 5 and Week 9.

Otherwise Documented maximum hematologic toxicity (i.e., grade IVs stay as grade IVs and all others have adequate hematologic f/u).

Table : Missing Data Ignored and Worst Case Analysis for Hematology Endpoints (N=230)

Endpoint	Missing Data Ignored Analyses	“Worst Case” Analyses	Missing Data Ignored Analyses by Age Category		“Worst Case” Analyses by Age Category	
			< 65	>= 65	< 65	>= 65
Age						
Platelets N	230	230	169	61	169	61
Median nadir (1000/mm ³)	57	43	54	69	40	56
Per patient incidence platelets <50,000/mm ³	96 (42%)	123 (53%)	78 (46%)	18 (30%)	97 (57%)	26 (43%)
Median duration of platelets <50,000/mm ³ (days)	30	32	30	40	31	56
Grade 3/4 without recovery ^a to Grade II, N (%)	7 (3%)	16 (7%)	4 (2%)	3 (3%)	11 (7%)	5 (8%)
Per patient incidence platelets gr IV <25,000/mm ³	42 (18%)	47 (20%)				
ANC						
Median nadir (1000 cells/mm ³)	1.0	0.69	0.85	1.21	0.66	0.91
Per patient incidence ANC<1,000 cells/mm ³ , N (%)	116 (50%)	145 (63%)	91 (54%)	25 (41%)	111 (66%)	34 (56%)
Median ^c duration of ANC<1,000 cells/mm ³ (days)	29	31	29	39	30	45
Grade 3/4 without recovery ^a to Grade II, N (%)	4 (2%)	15 (7%)	3 (2%)	1 (2%)	10 (6%)	5 (8%)
Per patient incidence gr IV ANC<500 cells/mm ³ , N (%)	49 (21%)	57 (25%)				
Hemoglobin						
Median Nadir	11	10	10	11	10	10
Per patient incidence Hemoglobin (g/dL) < 8.0 Grade III/IV	35 (15%)	66 (29%)	27 (16%)	8 (13%)	48 (28%)	18 (30%)
Median duration of Hemoglobin (g/dL) < 8.0 Grade III/IV (days)	19	23	20	16	22	39
Grade 3/4 without recovery ^a to Grade II, N (%)	1 (.4%)	12 (5%)	1 (1%)	0 (0%)	8 (5%)	4 (7%)
Per patient incidence gr IV hemoglobin <6.5 gm/dL, N (%)	8 (3%)	11 (5%)				

^a Recovery can occur at any timepoint after the Grade 3/4 toxicity.

The worst-case hematologic grade III/IV assumes a grade III/IV if a patients was missing 2 or more weeks of hem data between Week 5 and Week 9. A worst-case 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.. A worst-case nadir (1000/mm³) was assumed to be 0.

Appendix B
HAMA Evaluation for Efficacy Studies (n=230)

HAMA Values (Site or Central Evaluation)

For the **site or central assay**, the data were pooled and patients were classified as HAMA positive if they were positive either the site or central assay. The concordance between the site central HAMA assays was 96% with 421 of 440 blood samples assayed by both the site and central HAMA assays in agreement. Data were pooled for a site or central HAMA analysis, and patients were classified as HAMA positive if they were positive either the site or central assay.

There were 978 patients (out of 995 patients in the Safety database) who had a negative baseline HAMA, 11 had a positive baseline HAMA and 6 had missing value. Out of 978 with negative baseline HAMA, 785 patients had had at least one follow-up assessment (evaluatable for HAMA population). A total of 76 of the 785 patients (10%) with a negative baseline HAMA and follow-up HAMA converted to HAMA positivity. For these 76 patients, the median time to HAMA positivity converting to HAMA positivity was 76 days (95% CI: 96-188 days, Range: 5–3400 days, IQ range 91 to 239 days). Forty-five of 76 (59%) patients converting to HAMA positivity on or prior to Month 6 (183 days).

The event (HAMA positive) was assumed to have occurred the first time a patient was HAMA positive for these 76 patients. The remaining 709 patients are assumed to be HAMA negative at their last day of HAMA evaluation during the HAMA follow-up, and are censored at individual patient’s last available day of HAMA measurements.

Laboratory HAMA follow-up

Time Interval	Site or Central HAMA Assay	
	Number of Patients with a HAMA Value in Time Interval	Number Initially Elevated^a in Time Interval
>0 – 3 months	125	20
>3 – 6 months	250	25
>6 – 12 months	179	22
>12 – 24 months	106	6
>24 months	125	3
Overall		76

^a Patients with conversion to HAMA positivity in time interval, no HAMA positivity in previous time intervals, and a negative HAMA at baseline. Thus 76 patients with a negative baseline HAMA converted to HAMA positivity based on Site or Central HAMA Assay. (SOURCE: dataset, LAB, HAMAOUT submitted April 03, 2003. Protocol specified Laboratory HAMA schedules were baseline, week 7 (except CP-98-020 study), week 13, month 6 and semi-annual for two years following the dosimetric dose. The variable APOSDAY when AEVAL=1 (baseline) and APOSDAYC=0 (censor) and APOSDAY identify the times for any HAMA central or site patients, for central assay use the variable CPOSDAY when CEVAL=1 and CPOSDAYC=0.)

HAMA

At Baseline (Revise the opening statement based on info below)

For ISS Population n = 995

N	HAMA- 978	HAMA+ 11	Missing evaluation or no baseline values 6
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For Efficacy Studies n = 230

N	HAMA- 220	HAMA+ 4	Missing evaluation or no baseline values 6
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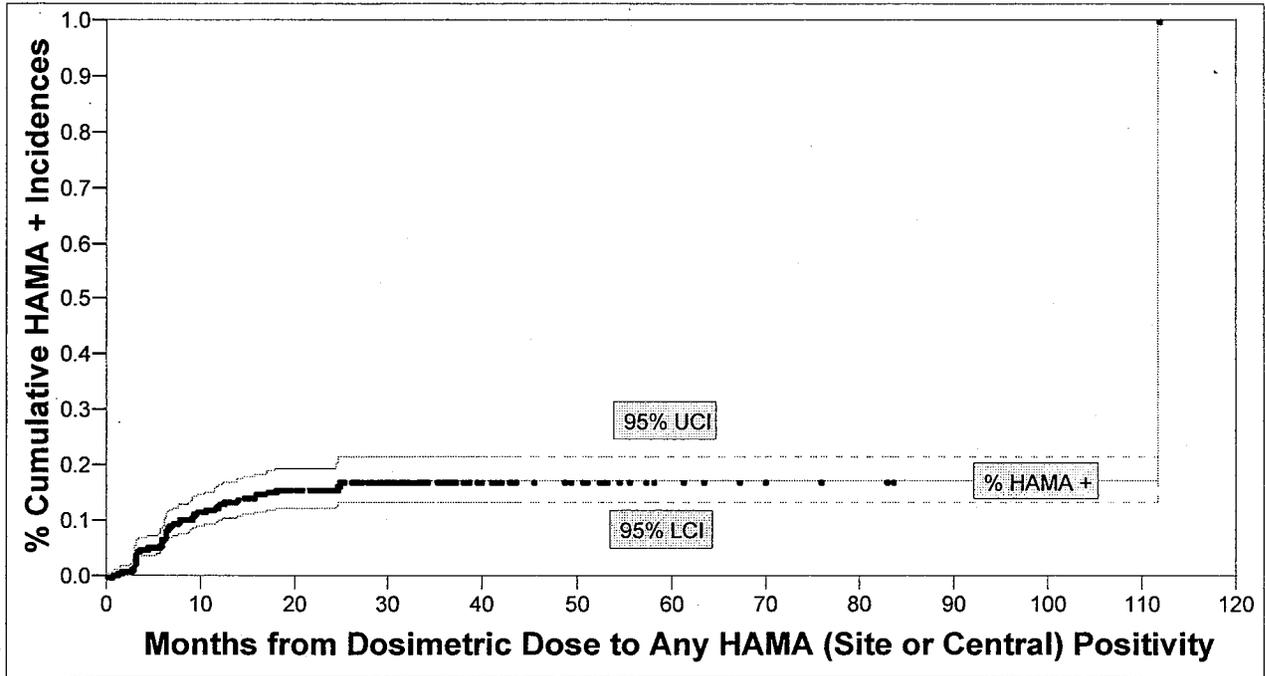
For Expanded Access Population n = 765

N	HAMA- 758	HAMA+ 7	Missing evaluation or no baseline values 0
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	No Patients HAMA- at baseline	At least one post-treatment value obtained	Median follow-up Months for HAMA evaluation	Median HAMA+ post treatment development Months	Median time to HAMA development Months	HAMA+ by 6 months
ISS Population (n=995) (59%)	978	785 (80%)	6 months	76 (10%)	5	45
Efficacy Studies (n=230) (48%)	220	219 (99.5%)	6 months	23 (11%)	6	11
Expanded Access Population (n = 765) (64%)	758	566 (74%)	6 months	53 (9%)	4	34

The cumulative incidence for conversion to HAMA positivity is presented in the figure below.

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) – All Safety Patients (n = 785 evaluable (at least one HAMA follow-up) patients out of 995 patients in the Safety Population)



Time to event:: APOSMON, Censored by : APOSDAYC

NOTE: The HAMA increase to 1 at month 111 is based on a single longest lasting patient who had a HAMA reaction in month 111, so the curve jumped to 1.

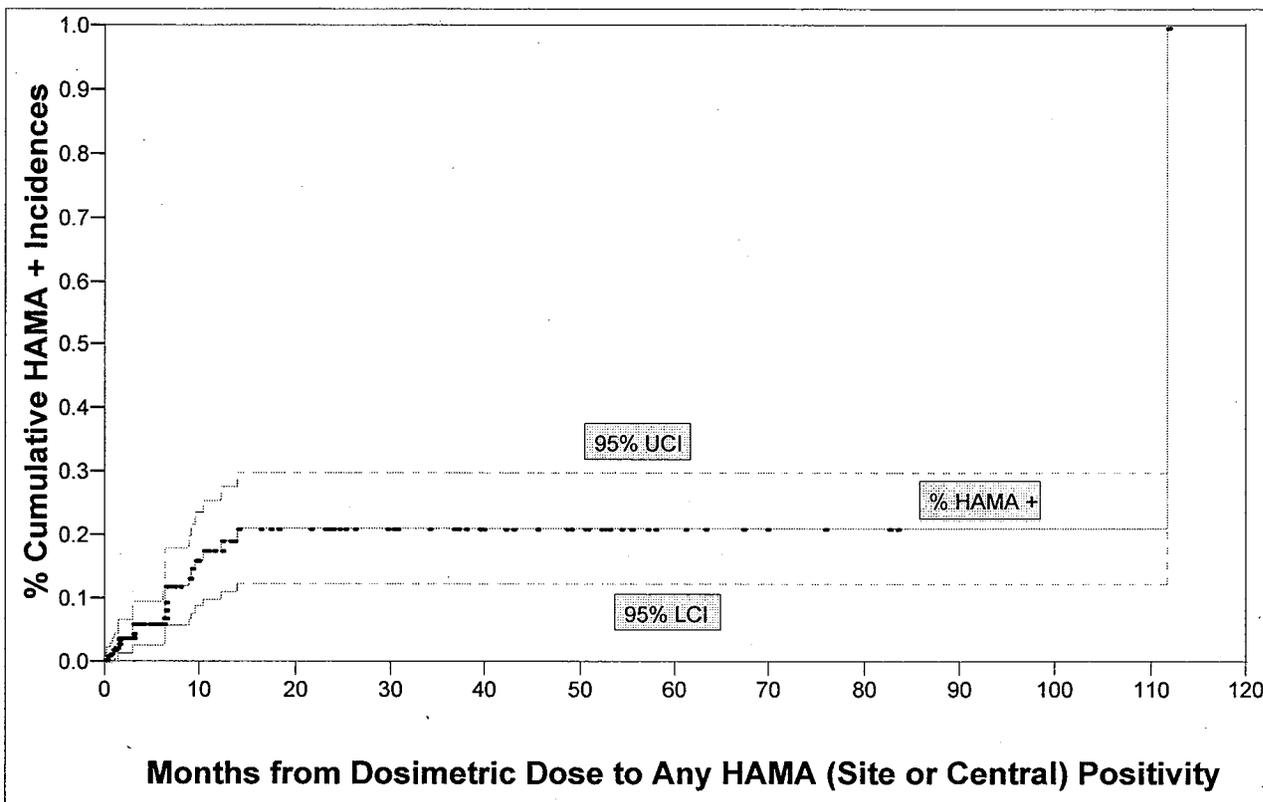
Months	0	3	6	9	12	18	24	30	36	112
# HAMA+	0	20	45	59	67	73	73	75	75	76
# Censored	0	105	329	449	487	527	588	627	656	709
# at Risk	785	660	411	277	231	185	124	83	51	0

#s are cumulative

One patient (000-002-022) converted to HAMA positive on Study Month 111.8 (Study Day 3400). Previous HAMA negative was on Study Day 901 and the patient was re-treated with iodine I 131 tositumomab on Study Day 863.

For these 76 patients, the median time to HAMA positivity converting to HAMA positivity was 76 days (95% CI: 96-188 days, Range: 5-3400 days, IQ range 91 to 239 days). Forty-five of 76 (59%) patients converting to HAMA positivity on or prior to Month 6 (183 days).

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) – All Efficacy Patients (n = 219 evaluable (at least one HAMA follow-up) patients out of 230 patients in the Efficacy Population)



Time to event:: APOSMON, Censored by : APOSDAYC

NOTE: The HAMA increase to 1 at month 111 is based on a single longest lasting patient who had a HAMA reaction in month 111, so the curve jumped to 1.

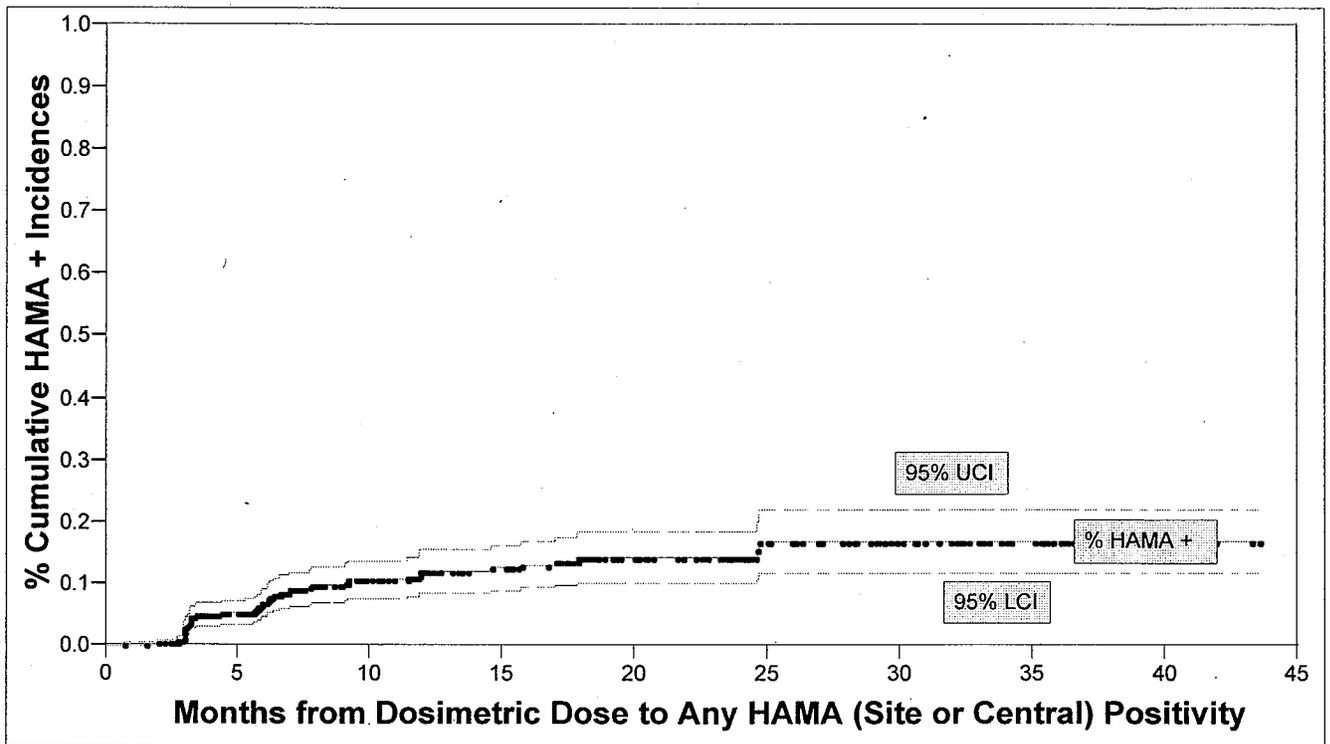
Months	0	3	6	9	12	18	24	30	36	112
# HAMA+	0	8	11	17	20	22	22	22	22	23
# Censored	0	56	118	143	146	152	157	161	164	196
# at Risk	219	155	90	59	53	45	40	36	33	0

#s are cumulative

One patient (000-002-022) converted to HAMA positive on Study Month 111.8 (Study Day 3400). Previous HAMA negative was on Study Day 901 and the patient was re-treated with iodine I 131 tositumomab on Study Day 863.

For these 23 patients, the median time to HAMA positivity converting to HAMA positivity was 189 days (95% CI: 48-198 days, Range: 5-3400 days, IQ range 46 to 279 days). Eleven of 23 (48%) patients converting to HAMA positivity on or prior to Month 6 (183 days).

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) – All Expanded Access Patients (n = 566 evaluable (at least one HAMA follow-up) patients out of 765 patients in the Expanded Access Population)



Time to event:: APOSMON, Censored by : APOSDAYC

Months	0	3	6	9	12	18	24	30	36	44
# HAMA+	0	12	34	42	47	51	51	53	53	53
# Censored	0	49	211	306	341	375	431	466	492	513
# at Risk	566	505	321	218	178	140	84	47	21	0
#s are cumulative										

For these 53 patients, the median time to HAMA positivity converting to HAMA positivity was 134 days (95% CI: 97-181 days, Range: 21-752 days, IQ range 92 to 214 days). Thirty-four of 53 (64%) patients converting to HAMA positivity on or prior to Month 6 (183 days).

Appendix B (Cont'd)
HAMA Evaluation for Study - RIT-II-003

HAMA incidence in a chemotherapy-naïve population

The rates of HAMA were higher in RIT-II-003, "Phase II Trial of Bexxar therapeutic regimen for Previously Untreated, Advanced-Stage, Low-Grade Non-Hodgkin's Lymphoma". This single arm, single center (University of Michigan Medical Center) study was intended to assess the activity (response rates, complete response rates, response duration) and safety of Bexxar therapeutic regimen in patients who had received no prior therapy for treatment of lymphoma. The dose and schedule of Bexxar therapeutic regimen was the same as for that described in RIT-II-004. There were 77 subjects who received at least one dose (dosimetric dose) of tositumomab. In this study, the estimated cumulative incidence of HAMA following treatment is 56% at one year and 63% at two years following treatment.

Total of 77 patients

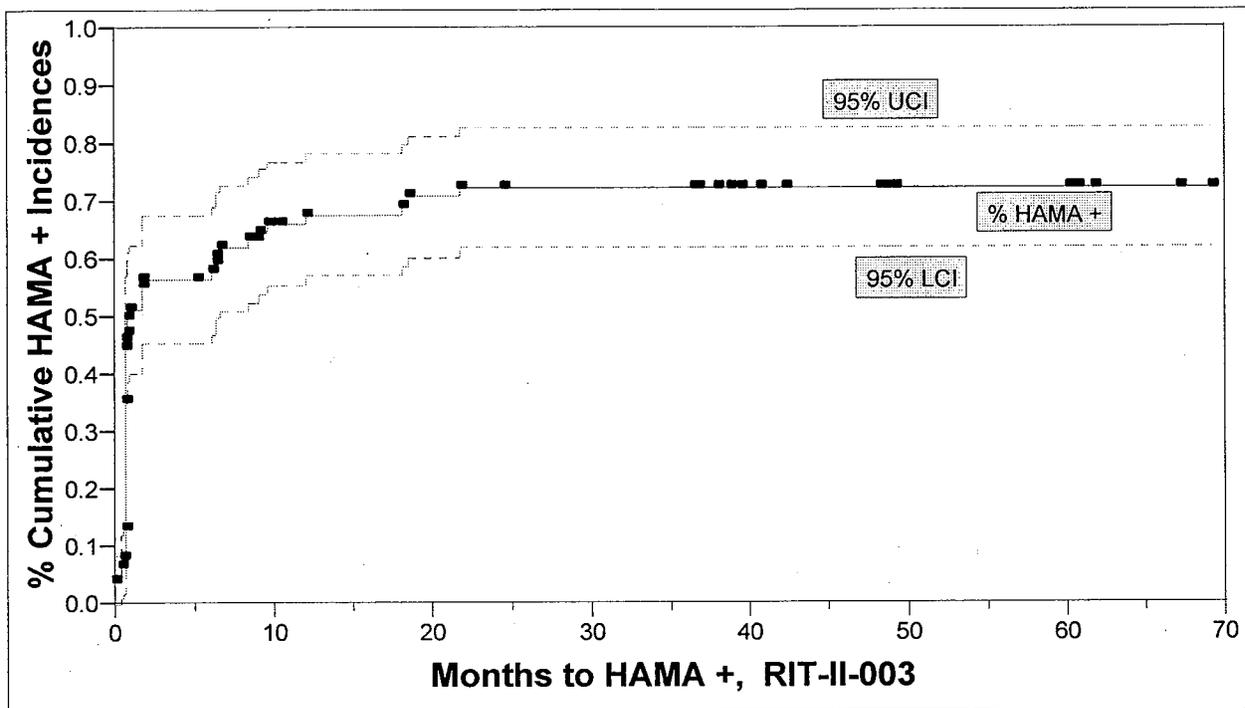
At baseline 73 negative
3 positive
1 Died

Evaluable 73 patients
Not evaluable 4 patients

Results

54 Positive (70%) ITT analysis
23 Negative
Median Time to HAMA positivity = 27 days
95% CI : 23 to 202 days
Q1 = 22 days
Q3 = NR
N Failed = 54
N Censored = 22
Min = 0 years
Max = 2106+ Days (5.8+ years)

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) – RIT-II-003 Patients (n = 76 evaluable (at least one HAMA follow-up) patients out of 77 patients in the RIT-II-003 Population)



Months	0	1	2	3	6	12	18	24	30	70
# HAMA+	0	39	43	43	43	50	51	54	54	54
# Censored	0	0	0	0	1	4	4	4	5	22
# at Risk	76	37	33	33	32	22	21	18	17	0

#s are cumulative

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Appendix C
MDS/AML Evaluation for Efficacy Studies (n=230)

Myelodysplasia (MDS)

The major long-term safety concern associated with radioimmunotherapy is myelodysplasia (MDS) and associated acute leukemia. Patients treated with iodine I 131 tositumomab were followed for the development of MDS/AML from study entry or until death or until the data cutoff. Information was collected semiannually.

The 995 patients had a median follow-up of 1.8 years (IQ range: 0.95 to 2.93 years; range 0.01 to 9.51 years). Thirty-three (33) patients had pre-existing MDS or developed MDS and/or acute leukemia with a crude incidence of MDS/AML of 3.3% (95% CI: 2.3%–4.6%). The total follow-up time for MDS was 2008.9 years and an annualized MDS incidence was 1.6%/year (95% CI: 1.2%/yr–2.3%/yr). The total follow-up time for MDS for the efficacy group was 684.8 years and an annualized MDS incidence was 2.9%/year.

INCIDENCE RATE OF MYELODYSPLASIA/ACUTE LEUKEMIA (MDS or AML)

Study	N	Median follow-up Time (Years) Range	# MDS/AML	MDS/AML Rate (95% CI)	Median Time to MDS/AML(Yrs) ^a Range	IQ Range (Years) ^a for MDS/AML	Mean (Yrs) ^a 95% CI	Annualized Rate (%/yr) (95% CI)
RIT-I-000	22	3.8 (0.2, 9.5)	5	22.7 % (7.8, 45.3%)	3.1 (-0.1, 7.7)	1.3 -7.4	4.1 0.1-8.1	4.9%/yr 2.0-11.8
RIT-II-001	47	2.8 (0.0, 6.9)	5	10.6 % (3.5, 23.1%)	1.8 (0.9, 4.4)	1.3 -3.4	2.2 0.6-3.9	3.0 1.3-7.3
RIT-II-002	61	2.9 (0.2, 6.0)	4	6.6 % (1.8, 15.9%)	1.2 (0.4, 4.7)	0.6 -3.8	1.9 0.0-4.9	2.3 0.9-6.2
RIT-II-004	60	2.5 (0.0, 5.9)	4	6.7% (1.8, 16.2%)	2.7 (1.8, 3.4)	1.9 -3.3	2.7 1.5-3.8	2.7 1.0-7.1
CP-97-012	40	2.9 (0.1, 4.4)	2	5.0 % (0.6,16.9%)	2.7 (2.1, 3.3)	2.1 -3.3	2.6 0-10.7	2.1 0.5-8.3
Efficacy Studies	230	2.9 (0.0, 9.5)	20	8.7 %	2.5 (1.7, 3.3)	1.7 –3.4	2.8 1.8-3.7	2.9
CP-98-020	765	1.6 (0.0, 4.4)	13	1.7 % (0.9, 2.9%)	1.9 (0.4, 2.9)	0.5 -2.7	1.7 1.1-2.3	1.0 0.6-1.7
Overall	995	1.8 (0.0, 9.5)	33	3.3 % (2.3, 4.6%)	2.1 (-0.1, 7.7)	1.0 -3.0	2.3 1.7-3.0	1.6 1.2-2.3

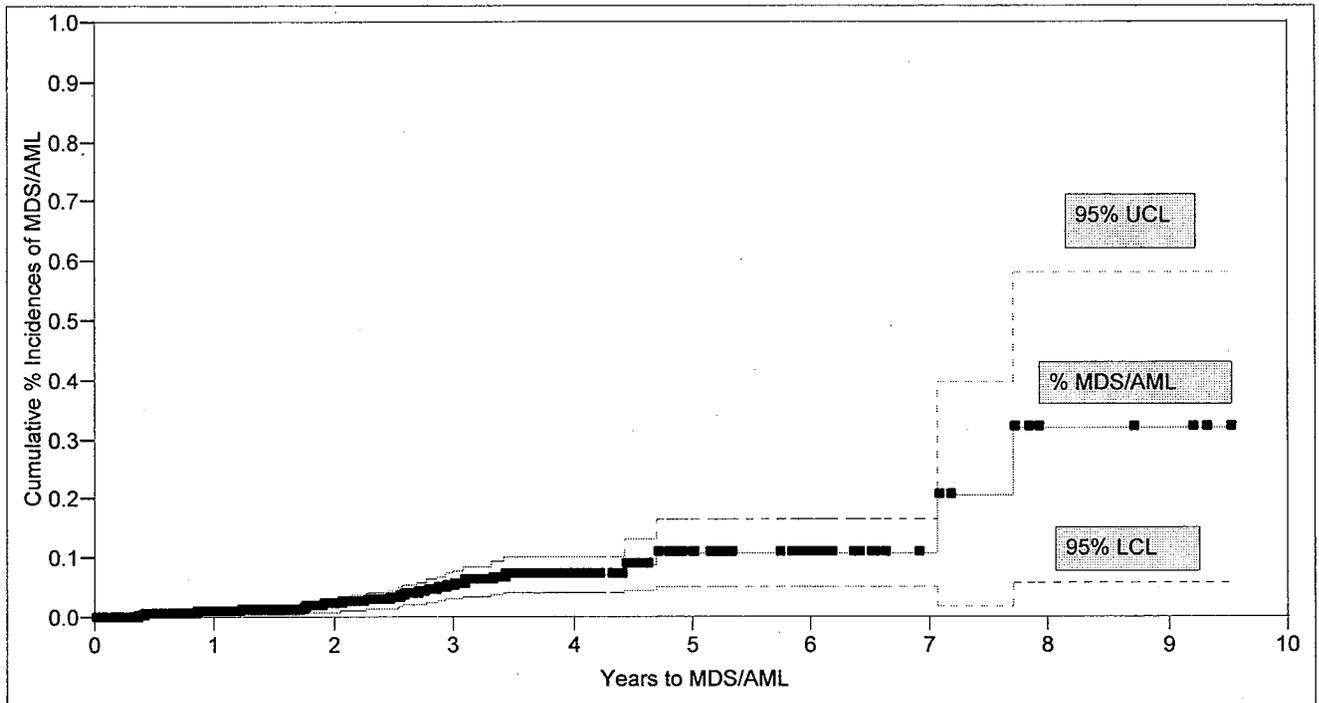
^a For patients who developed MDS and/or acute leukemia

Note: One patient (000-002-055 68M L75C) developed MDS/AML 24 days before the therapy started. and is included in the analysis.

	New cases of MDS/AML	Median follow-up	Time to MDS
Efficacy Studies (n=229)	19 (8.3%)	35 months	30 months
ISS Population (n=994)	32 (3.2%)	21 months	27 months
Expanded Access (n=765)	13 (1.7%)	20 months	23 months

Note: One patient (000-002-055 68M L75C) developed MDS/AML 24 days before the therapy started. and is not included in the above numbers.

**Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Year
(ISS Population, n = 995)**



ISS Population (n=994)

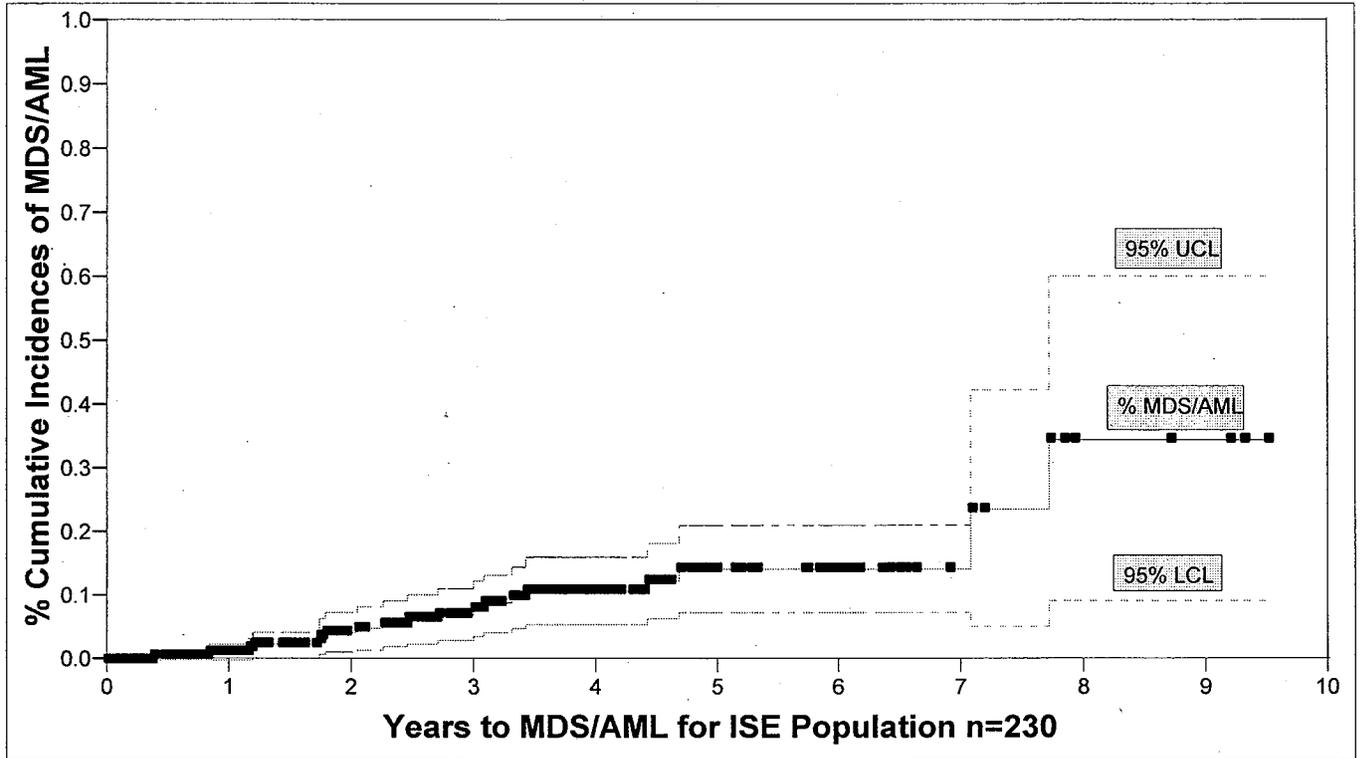
1 year cumulative incidence (MDS/AML) = 0.8 %
 2 year cumulative incidence (MDS/AML) = 2.1 %
 4 year cumulative incidence (MDS/AML) = 7.3 %

Years	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.5	9.5
# MDS/ AML	0	4	7	9	14	18	24	28	28	29	30	30	30	30	30	31	32	32
Censored	0	146	265	400	543	657	743	833	890	912	925	933	942	951	955	956	959	961
# at Risk	994	844	722	585	437	319	227	133	76	53	39	31	22	13	9	7	4	1

Note: One patient (000-002-055 68M L75C) developed MDS/AML 24 days before the therapy started, and is **not** included in this analysis..

#s are cumulative; Time to event: EVENTYEAR; Censored by : EVENTDYC

**Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Year
(ISE Population, n = 230)**



Efficacy Studies (n=229)

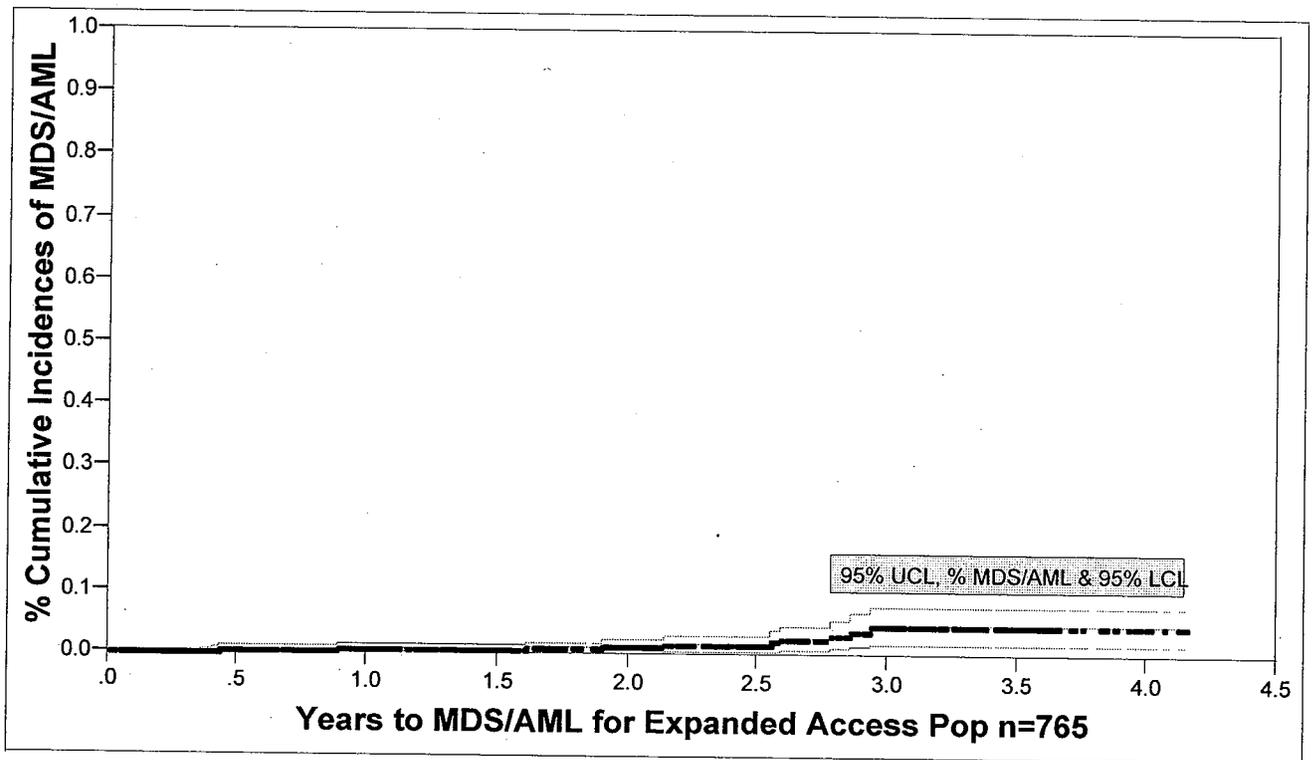
- 1 year cumulative incidence (MDS/AML) = 1.0 %**
- 2 year cumulative incidence (MDS/AML) = 4.2 %**
- 4 year cumulative incidence (MDS/AML) = 10.7 %**

Years	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.5	9.6	
# MDS/AML	0	1	2	4	7	10	11	15	15	16	17	17	17	17	17	17	18	19	19
Censored	0	25	48	71	81	91	110	128	144	160	173	181	190	199	203	204	206	210	
# at Risk	229	203	179	154	141	128	108	86	70	53	39	31	22	13	9	7	4	0	

Note: One patient (000-002-055 68M L75C) developed MDS/AML 24 days before the therapy started, and is not included in this analysis..

#s are cumulative; Time to event: EVENTYEAR; Censored by : EVENTDYC

**Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Year
(Expanded Access Population, n = 765)**



Expanded Access (n=765)

1 year cumulative incidence (MDS/AML) = 0.8 %
 2 year cumulative incidence (MDS/AML) = 1.3 %
 4 year cumulative incidence (MDS/AML) = 4.8 %

Years	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.2
# MDS/ AML	0	3	5	5	7	8	13	13	13	13
Censored	0	121	217	329	462	566	633	705	746	752
# at Risk	765	644	543	431	296	191	119	47	6	0

#s are cumulative; Time to event: EVENTYEAR; Censored by : EVENTDYC

Appendix D
Thyroid (TSH) Evaluation for Efficacy Studies (n=230)

The protocol-specified laboratory TSH schedule was Baseline, Month 6 and every 3 months up to year 2 (one year for RIT-II-001) for all the studies and additional week 7 and week 13 for the study RIT-I-000 and week 13 for the study RIT-II-002.

There were 947 patients (out of 995 patients in the Safety database) who had TSH measured at baseline. Seventy four (74) of 947 (8%) patients had an elevated TSH prior to the therapeutic dose, and an additional 43 patients had a history of thyroid medication. Thus 117 of 995 (12%) patients had a history of hypothyroidism prior to receiving their therapeutic dose. These patients were excluded from analyses of post-iodine I 131 tositumomab hypothyroidism. There were 528 patients who had normal TSH values at the baseline and did not have Thyroid medication prior to Iodine I 131 tositumomab treatment. The data are summarized below:

Elevated TSH Values at Baseline prior to therapeutic dose					
Any Thyroid Medication Pre-Iodine I 131 tositumomab		No (0)	Yes (1)	Missing	Total
	No (0)	842	60	44	946
	Yes (1)	31	14	4	49
	Total	873	74	48	995

There were 583 patients (out of 995 patients in the Safety database) who had a TSH value after treatment. There were 54 patients (9%) who had an elevated TSH (event) during the course of follow-up. For these 54 patients, the median time to TSH elevation 12.0 months (95% CI on median 6.3 to 14.5 months; range: 1.8 months to 76.3 months, IQ range 6.0 to 24.8 months).

Algorithm:

Once patients become hypothyroid, they continue to be hypothyroid. Therefore, the event was assumed to have occurred the first time a patient had elevated TSH for these 54 patients. The remaining 529 patients are assumed to have non-elevated TSH at their last day of TSH evaluation during the TSH follow-up, and are censored at individual patient's last evaluation day of TSH measurements.

Safety update (BLA Submission 125011.054, clinstat\iss\iss.pdf, April 3, 2003 Source: Dataset THYROUT). For all analyses a patient was classified as becoming hypothyroid if they developed an elevated TSH (with or without initiation of thyroid medication) or initiated thyroid medication (with or without an elevated TSH).

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Laboratory TSH Follow-up: Integrated Safety Population (N=995)

Time Interval	Number of Patients with a TSH Value within or after Interval ^a	Number Initially Elevated ^b in Time Interval
>0 – 3 months	583	3
>3 – 6 months	565	11
>6 – 12 months	487	14
>12 – 24 months	376	11
>24 months	200	9
>36 months	87	6
Overall	583	54

^a Excludes patients with elevated baseline TSH, missing baseline TSH or prior history of thyroid medication at study entry. There were 873 (out of 995) patients who did not have elevated TSH at the baseline or Pre-Iodine I 131 tositumomab treatment. Out of 873 patients, 290 patients had missing TSH after treatment and 583 patients had a TSH value after treatment (54 elevated and 529 not elevated).

^b Patients with an elevated TSH in time interval, no elevated TSH in previous intervals, and a low/normal TSH at baseline. Thus 54 of 583 (9%) TSH evaluable (i.e., patients with low/normal baseline TSH level, no history of prior thyroid medication, and with follow-up TSH data) patients developed an elevated TSH following therapy.

Analyses were conducted assessing the time to hypothyroidism based on elevated TSH value and/or initiation of thyroid supplementation.

Analyses are provided for three scenario as follows:

- (1) Percent Elevated TSH Censored at the Last available TSH Value or death. These estimates do not account for competing risks and overestimate the percent of patients who develop an elevated TSH.
- (2) Percent Elevated TSH Censored at the Last follow-up date (assuming no TSH elevated up to the date of last follow-up, even though patients were not evaluated for TSH) or death-- sponsor's approach. These estimates account for some competing risks.
- (3) Percent Elevated TSH or start of thyroid medication Censored at the Last follow-up date or death-- middle approach accounting for inclusion of available information. These estimates include some additional information about probable TSH.

At Baseline

For ISS Population n = 995

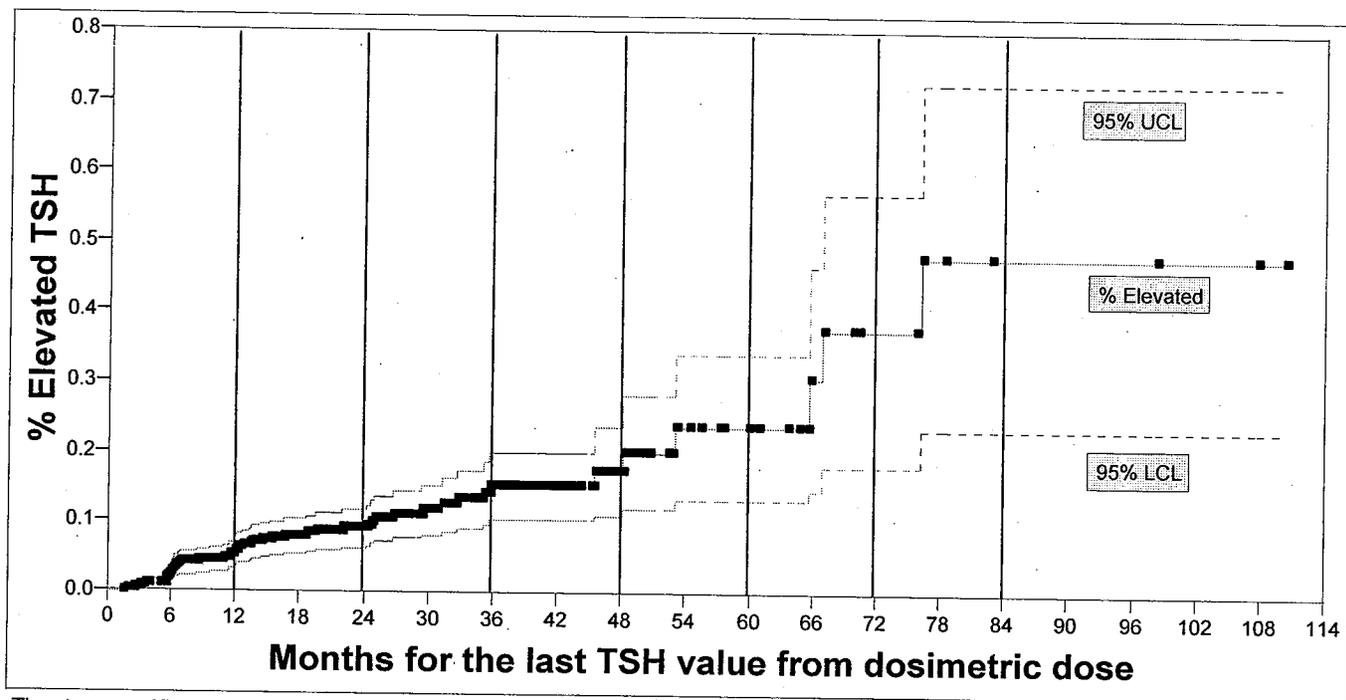
	No elevated TSH value	Elevated TSH value or	Missing evaluation or on thyroid medication
N	873	74	48

For Efficacy Studies n = 230

	No elevated TSH value	Elevated TSH value or	Missing evaluation or on thyroid medication
N	203	18	9

	No Patients euthyroid at entry	At least one post-treatment value obtained
ISS Population (n=995)	873	583
Efficacy Studies (n=230)	203	137

Percent Elevated TSH Censored at the Last available TSH Value or death ISS Population n=995

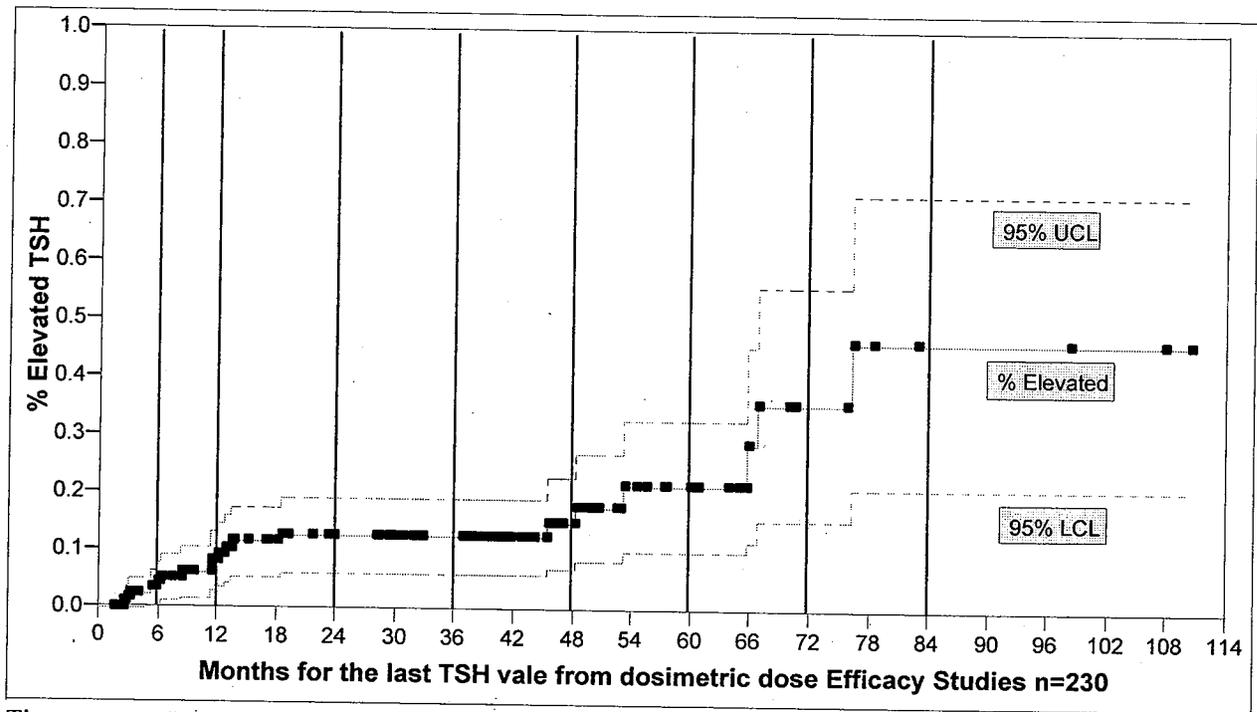


Months	0	3	6	12	24	36	48	60	72	84	96	114
Elevated	0	3	14	28	39	48	49	51	53	54	54	54
#Censored	0	15	82	179	344	448	503	516	523	526	526	529
# at Risk	583	568	487	376	200	87	31	16	7	3	3	0

2 year cumulative incidence (elevated TSH) = 9.1 % (95% CI: 6.2% - 11.8%)

4 year cumulative incidence (elevated TSH) = 17.4 % (95% CI: 10.8% - 23.4%)

Percent Elevated TSH Censored at the Last available TSH Value or death Efficacy Studies n=230



Time to event: KMMONTH Censored by KMCENS

Months	0	3	6	12	24	36	48	60	72	84	96	114
Elevated		2	5	9	13	13	14	16	18	19	19	19
#Censored		12	27	40	57	69	92	105	112	115	115	118
# at Risk	137	123	105	88	67	55	31	16	7	3	3	0

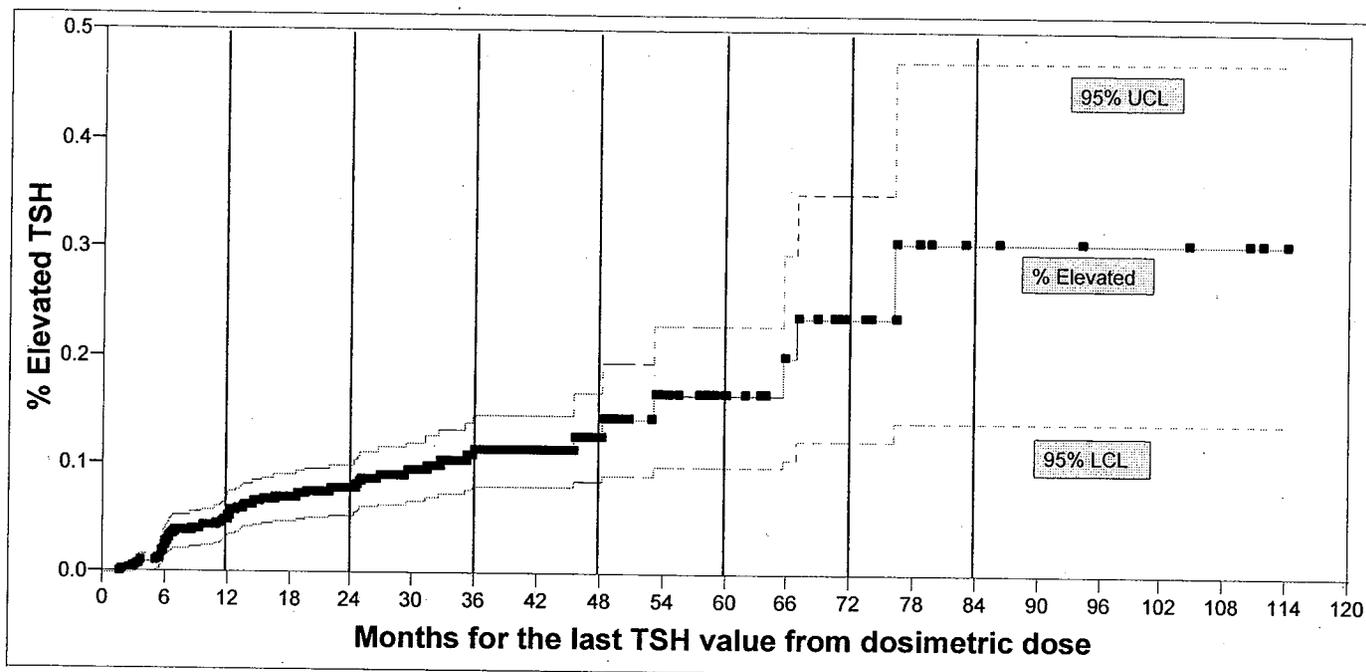
6 months cumulative incidence (elevated TSH) = 4.2 %

12 months cumulative incidence (elevated TSH) = 8.1 %

2 year cumulative incidence (elevated TSH) = 12.6 %

4 year cumulative incidence (elevated TSH) = 15.0 %

Percent Elevated TSH Censored at the Last follow-up date (assuming no TSH elevated up to the date of last follow-up, even though patients were not evaluated for TSH) or death— sponsor's approach - ISS Population n=995



Months	0	3	6	12	24	36	48	60	72	84	96	115
Elevated	0	3	14	28	39	48	49	51	53	54	54	54
#Censored	0	8	39	92	241	374	480	504	515	523	525	529
# at Risk	583	572	530	463	303	161	54	28	15	6	4	0
# censored due to death	0	7	31	66	97	101	104	107	108	109	109	109

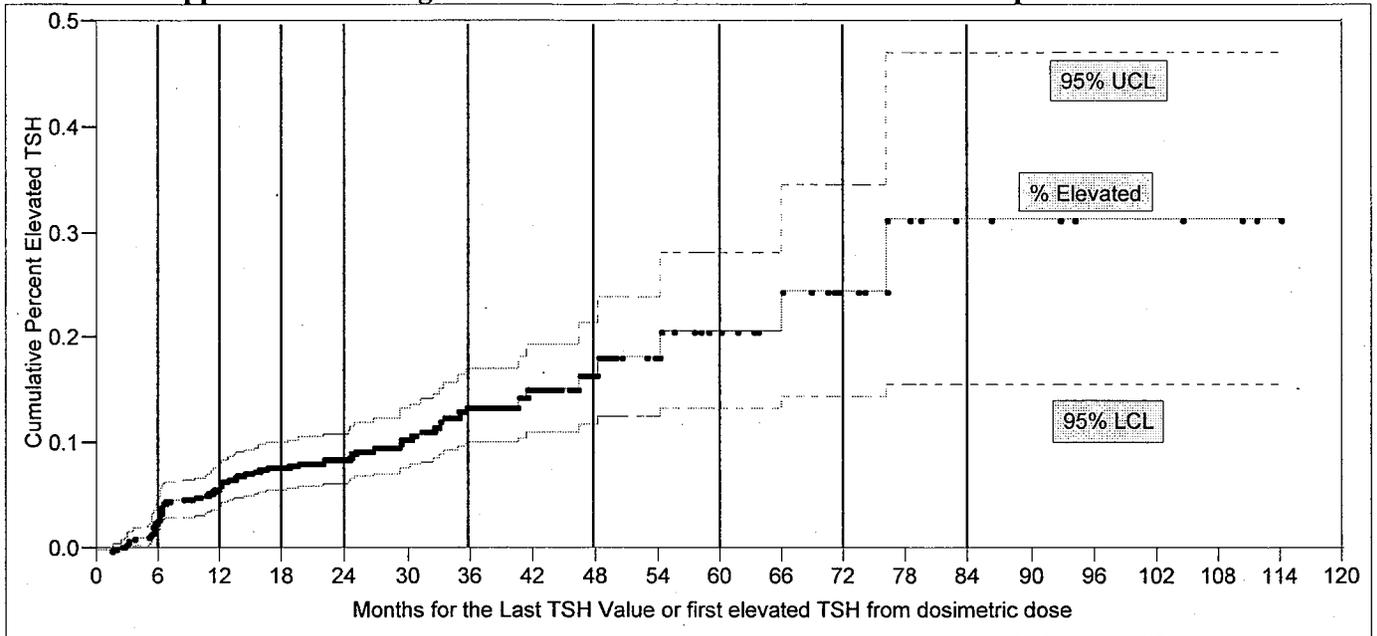
2 year cumulative incidence (elevated TSH) = 7.7 % (95% CI: 5.2% - 9.5%)

4 year cumulative incidence (elevated TSH) = 12.6 % (95% CI: 8.1% - 15.0%)

Elevated = TSH elevation

#s are cumulative (# dead are included in censor)

Percent Elevated TSH or start of thyroid medication Censored at the Last follow-up date or death - middle approach accounting for inclusion of available information. ISS Population n=995



Time to event: Months Last TSH or first elevated; Censored by: Censor Day at Last TSH value and/or initiation of thyroid supplementation.

Months	0	3	6	12	24	36	48	60	72	84	96	115
Elevated	0	3	17	34	46	59	62	64	65	66	66	66
#Censored	0	3	6	42	196	350	457	481	491	498	501	505
# at Risk	571	565	548	495	329	162	52	26	15	7	4	0
# censored due to death	0	2	3	19	57	85	94	97	98	98	99	99

(12 TSH values had missing censor day)

Elevated = TSH elevation and/or initiation of thyroid supplementation

#s are cumulative (# dead are included in censor)

2 year cumulative incidence (elevated TSH or started thyroid medication) = 8.6%

4 year cumulative incidence (elevated TSH or started thyroid medication) = 16.6%

Censor By Elevated TSH

Censor Values	Elevated TSH Value= NO	Elevated TSH Value=YES	Total
0=Elevated TSH or Thyroid Medication	12	54	66
1 = Not Elevated	406	0	406
2 = Censored due to Death	99	0	99
Total	517	54	571

Appendix E
Growth Factors – Safety/Efficacy Population (n=230)

Platelet Transfusions

Study	Number of Patients receiving transfusion	Number of transfusions
RIT-I-000	2	9
RIT-II-001	12	43
RIT-II-002	9	27
RIT-II-004	9	14
CP-97-012	3	3
Total	35 (15%)	

RBC Transfusions

Study	Number of Patients receiving transfusion	Number of transfusions
RIT-I-000	2	6
RIT-II-001	10	34
RIT-II-002	10	38
RIT-II-004	8	19
CP-97-012	6	12
Total	36 (16%)	

Platelet Transfusions or RBC Transfusions n = 49 (21%)

G-CSF/GM-CSF

Study	Number of Patients receiving G-CSF/GM-CSF	Total No. of Days of G-CSF/GM-CSF
RIT-I-000	2	71
RIT-II-001	6	85
RIT-II-002	7	103
RIT-II-004	10	279
CP-97-012	3	148
Total	28 (12%)	

Median Days of G-CSF/GM-CSF = 16
 95% CI = 9 - 30 days, Q1 : Q3 = 9 : 34 days
 Min = 1 day, Max = 134 days

Erythropoietin (EPO)

Study	Number of Patients receiving EPO	Total No. of Days of EPO
RIT-I-000		
RIT-II-001	2	66
RIT-II-002	5	160
RIT-II-004	3	191
CP-97-012	6	464
Total	16 (7%)	

Median Days of EPO = 52
 95% CI = 9 - 123 days
 Q1 : Q3 = 32 : 123 days
 Min = 1 day
 Max = 258 days

G-CSF/GM-CSF or Erythropoietin (EPO) n = 35 (15%)

Statistical Review

Date: December 16, 2002

Type: BLA

FDA/STN Number: 125011

Product/Application: BEXXAR™ therapeutic regimen (I 131 tositumomab) for patients with chemotherapy-refractory low-grade and transformed low-grade NHL

Sponsor: Corixa

From: Satish C. Misra, Ph. D., HFM-219



Through: Ghanshyam Gupta, Ph. D., Branch Chief, Biostatistics, HFM-219



To: File: Terrye Zaremba / HFM-594
George Mills / HFM-570
Steve Litwin / HFM-570
Pat Keegan / HFM-573
Karen Weiss / HFM-570
Leon Epps / HFM-594
Susan Ellenberg / HFM-210
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Chron/HFM-215

Karen Jones - original - DCC

Note: This report is an integrated report and replaces all other prior reports issued on this BLA.

Proposed Indication

Treatment of Patients with Relapsed or Refractory, Low-Grade, Follicular, or Transformed Low-Grade Non-Hodgkin's Lymphoma (NHL) including Patients with Rituximab-Refractory Follicular NHL

Efficacy Summary

- Primary efficacy trial in 61 chemo-refractory patients demonstrated significantly higher proportion of patients with longer duration of response following the TTR as compared to last chemotherapy

- ORR 46%

- CR/CCR 20%

- Median response duration 11.7 months

- Primary efficacy trial in 30 Rituximab refractory patients with follicular NHL demonstrated

- ORR » 60%

- CR/CCR »30%

- Median response duration 2 yrs

Supportive studies showed

- ORR from 48% - 63%

- Median durations of response from 1.0-1.3 years

- CR/CCR from 27% - 33%

Safety Summary

Hematologic toxicity

- 60-71% incidence of any grade 3-4 hematologic toxicity, median duration 30 days

- Profound and prolonged B-cell lymphopenia

- 43% incidence of infectious events

- 12% incidence hemorrhagic events

- Symptom complex of infusional toxicities, comprised of fever, chills, nausea, asthenia, rash in » 50% of patients

- Clinical and serologic immune responses

- 20% cumulative incidence of HAMA at 18 months in heavily pretreated patients

- 70% cumulative incidence of HAMA in chemotherapy -naïve patients at 18 mos

- Clinical sequelae (anaphylactoid reactions and serum sickness infrequently observed)

- Hypothyroidism-

- an observed 30% cumulative rate of TSH elevation at 5 years

- an observed 45% cumulative rate of TSH elevation at 7 years

- Leukemias and myelodysplasia observed with increasing cumulative incidence (23% in study with longest follow-up)

- Across all studies, incidence is 3% with median time to MDS/AML of 2.1 yrs

Clinical Studies

Five clinical studies (RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012), 6 single-patient studies, and an Expanded Access Study (CP-98-020) provide data in support of this application. The primary efficacy data supporting the indication are from the pivotal study (RIT-II-004) and another controlled study, Study RIT-II-002. Studies RIT-I-000, RIT-II-001 and CP-97-012 provide data supportive of the proposed indication. Another study, RIT-II-003, provides supplemental data in previously untreated patients.

The pivotal study (RIT-II-004) was a phase III, single-arm, open-label, controlled, multicenter, open-label study evaluated the efficacy of Bexxar therapeutic regimen in 60 patients with chemotherapy-refractory low-grade and transformed low-grade NHL. Patients were considered to have chemotherapy-refractory disease if they had been treated with at least two different qualifying chemotherapy regimens and had not responded to or had progressed within 6 months after completion of their last qualifying chemotherapy regimen. The qualifying chemotherapy regimens were prospectively defined in the protocol. The patients had not previously undergone bone marrow or stem cell transplantation, had $\leq 25\%$ intratrabecular bone marrow space involvement with lymphoma, and had a platelet count $\geq 100,000$ cells/mm³. Prior to study entry, patients had received a median of four prior chemotherapy regimens (range: 2–13) and 27% of patients had received prior radiotherapy. Of the 60 patients, 98% had stage III or IV disease at study entry, 44% had elevated lactate dehydrogenase (LDH), 38% had transformed low-grade NHL, and 56% had bone marrow involvement. The patients received a single dosimetric and therapeutic dose Bexxar therapeutic regimen.

To provide an adequate control for this trial, an external control (termed “patient-as-own-control”) was incorporated into the design. This approach used the duration of response following the last qualifying chemotherapy regimen as a [aired control.

The following were the aims and objectives of the study.

- (1) The primary efficacy endpoint of the study was the comparison, as assessed by the Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel, of the number of patients having a longer duration of response (i.e., more than 30 days) on their last qualifying chemotherapy (LQC) regimen to the number of patients having a longer duration of response on Bexxar therapeutic regimen.
- (2) To compare the response rate, duration of response, and time to treatment failure after Iodine-131 Antibody therapy to the patient’s last qualifying chemotherapy outcome.
- (3) To establish response rates, duration of response, time to progression, time to treatment failure, and survival after treatment with Iodine-131 Antibody in patients chemotherapy-refractory low-grade or transformed low-grade NHL.
- (4) To assess the safety of Iodine-131 Anti-B1 Antibody and assess the quality of life of treated patients.

The **integrated safety population** includes only those relapsed and refractory patients prescribed to receive non-myeloablative, total body doses of either 65 or 75 cGy of Bexxar therapeutic regimen. Patients were generally heavily pretreated, had experienced multiple relapses (median of 3 prior regimens; range: 1–13 regimens), and typically had other poor prognostic characteristics such as age over 60, advanced-stage disease, elevated LDH and transformed low-grade NHL. shows the number of patients receiving study drug, as well as the number of patients from each study included in the integrated safety population . There were 193 all relapsed/refractory low-grade or transformed low-grade NHL

patients who had received study drug and were prescribed (intent-to-treat analysis) an Bexxar therapeutic regimen dose of 65 or 75 cGy total body dose. Patients enrolled in Studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, CP-97-014c, CP-97-016c, CP-98-023c, and CP-98-024c. There were 40 patients who received study drug in Study CP-97-012 Rituxan-Failure Study, and 387 patients in the study CP-97-020 (Expanded Access Study) -- All low-grade or transformed low-grade NHL patients who received study drug in Study CP-98-020 and either withdrew from study for any cause or were on-study with at least 13 weeks of follow-up.

Datasets used and notation:

This was a rolling BLA and several datasets were submitted as a part of rolling BLA. The following datasets were used to analyze the efficacy and safety.

Efficacy:

Data (respout) used are in submission number 023 (September 7, 2001) for studies 000, 001, 003, and single patient studies; in submission number 024 (September 7, 2001) for studies 002 and CP-97-012; in submission 028 (December 11, 2001) for studies 004 and ongoing responders in 000, 001, 002 and 004.

Study 002 data includes 42 patients from Arm A (hot antibody, Iodine I-131 tositumomab) 36 form 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)). The analysis include characteristics before cross-over.

There were six (6) single patient studies (CP-97-014C, CP-97-016C, CP-98-023C, CP-98-024C, CP-98-029C, CP-00-039C).

Study CP-97-012 is Rituxan-Failure study with 36 out of 40 patients (90%) either did not respond to Rituxan therapy or the duration of response was less than 6 months.

Total number of patients in all the efficacy studies combined is 385.

All other studies in the indicated patient population (RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, CP-97-014c, CP-97-016c, CP-98-023c, and CP-98-024c), n = 193, All relapsed/refractory low-grade or transformed low-grade NHL patients who had received study drug and were prescribed (intent-to-treat analysis) an Bexxar therapeutic regimen dose of 65 or 75 cGy total body dose.

Efficacy Evaluations:

MIRROR panel-assessment were available for the studies 004, single patient studies, CP-97-012 and ongoing responders.

Investigator-assessed responses for the study 003. (no MIRROR Panel assessments were performed for this study). Patients were previously untreated and there was no last qualifying data for the study.

Investigator-assessed best response for the last qualifying chemotherapy represents the combination of confirmed and unconfirmed responses.

Investigator-assessed responses for the studies 000 and 001 except for the 7 patients in 000 and 6 patients in 007 who had MIRROR panel-assessments of their ongoing response (submission 028).

Expanded Access Program Study CP-98-020 was not designed to support efficacy claims (submission no. 023) - All low-grade or transformed low-grade NHL patients (n=387).

Investigator-assessed best response for the last qualifying chemotherapy for 004 trial – CR=1, CCR=1, PR=15.

Location of datasets:

Safety & efficacy: This report analyzes the datasets 125011.028 submitted on December 11, 2001, and March 04, 2002 and 125011.045 - cr/datasets submitted October 4, 2002

Chemo and Rituxan Refractory Patients

Patients were classified as chemotherapy refractory if they did not respond to their last chemotherapy or responded but had a duration of response of 6 months or less (dataset PTOUT, filter LQRESP>0 and LQDUR<183). Patient were classified as Rituxan refractory if they did not respond to their last Rituxan therapy or responded but had a duration of response of 6 months or less (dataset CHEMO for study CP-97-012, variable MDRESP and the variable MDDUR, and filter LQ=2 and (MDRESP>0 and MDDUR<=6)).

**Chemotherapy and Rituxan Refractory Numbers
Overall Patient Population**

Study	Patient Number	Chemo Refractory	Prior Rituxan	Rituxan Refractory
RIT-I-000	59	45 (76%)	0	0
RIT-II-001	47	40 (85%)	0	0
RIT-II-002	78	54 ^a (69%)	0	0
RIT-II-003	76	0	0	0
RIT-II-004	60	59 (98%)	0	0
Single Pt	6	6 (100%)	0	0
CP-97-012	40	22 ^b (55%)	40	36 (90%)
CP-98-020	464	NA	229	NA
TOTAL	830	226	269	36

^a Excludes two patients with unknown outcome or duration to last chemotherapy.
^b Excludes one patient with unknown outcome or duration to last chemotherapy.

**Chemotherapy and Rituxan Refractory Numbers
Integrated Safety Population (N=620)**

Study	Patient Number	Chemo Refractory	Prior Rituxan	Rituxan Refractory
RIT-I-000	22	18	0	0
RIT-II-001	47	40	0	0
RIT-II-002 ^a	61	42 ^b	0	0
RIT-II-003	0	0	0	0
RIT-II-004	59	58	0	0
Single Pt	4	4	0	0
CP-97-012	40	22 ^c	40	36
CP-98-020	387	NA	178	NA
TOTAL	620	184	218	36

^a Arm A and Crossover (excluded 17 patients who never received Bexxar therapeutic regimen.

^b Excludes two patients with unknown outcome or duration to last chemotherapy.

^c Excludes one patient with unknown outcome or duration to last chemotherapy.

The response and duration of response to prior therapies were not collected in the Expanded Access Study CP-98-020. Thus no refractory information can be obtained for this population. Patients from this study who previously received Rituxan can be identified using the variable RITUXAN (1=yes, 2=no) in the dataset DXHIST. Per protocol patients had to have received at least on prior chemotherapy regimen. Data on the number of chemotherapy regimens each patient received prior to Bexxar therapeutic regimen are in the dataset PTOUT in the variable CHEMOCNT.

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Overview of Clinical Studies

The primary efficacy data supporting the proposed indication for the treatment of chemotherapy-refractory patients with low grade and follicular NHL, with or without transformation are derived from Study RIT-II-004. The primary efficacy data supporting the indication for the treatment of Rituxan-refractory patients with low grade and follicular NHL, with or without transformation, are derived from Study CP-97-012. Three additional studies (RIT-I-000, RIT-II-001, and RIT-II-002) provide supportive anti-tumor activity data for the proposed indications.

Safety information relevant to single agent use of Iodine I-131 tositumomab in this patient population were obtained from the five efficacy/activity studies, the interim results of an additional study (RIT-II-003) conducted as an exploratory, Phase 2 study of initial treatment in patients with low grade, follicular NHL. Additional, limited safety data are provided from the expanded access experience under Protocol CP-98-020 and supplement by data provided to the sponsor from six sponsor-investigator INDs for the treatment of individual patients.

**Table 1: Number of Patients in Clinical Studies
CBER Derived Data**

Study	Number of Patients Enrolled	Number of Patients in Safety (ISS) Population (see notes)	Data Cutoff Date For Safety	Number of Patients in Efficacy (ISE) Population (ITT Analysis)	Number of Patients in Durable Response Population Durpop
RIT-I-000	59	22	31 Jan 02	59	16
RIT-II-001	47	47	31 Jan 02	47	10
RIT-II-002 Arm A	42	42	31 Jan 02	42	12
RIT-II-002 Arm B	36	0	31 Jan 02	0	0
RIT-II-002 Arm X	19	19	31 Jan 02	19	8
RIT-II-003	77	0		0	0
RIT-II-004	61	59	31 Jan 02	61	15
CP-97-012	43	40	08 Feb 02	43	17
CP-98-020	464	387	31 Aug 01	0	0
Single Patient	6	4	31 Jan 02	0	0
Total	854	620		271	78
ISS – A (Eff)		229			
ISS – B(Exp. Access)		391			

Notes:

- (1) Number of patients enrolled or receiving Bexxar therapeutic regimen as of August 31 2000
- (2) **Study - RIT-I-000:** 37 patients received total body doses other than 65 or 75 cGy
- (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.
- (4) **Study - RIT-II-004:** 1 patient received dose = 0 cGy. 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)
- (6) **Study CP-98-020 Expanded Access Study --** 77 patients on study had less than 13 weeks of follow up as of 31 August 2001 -- data cut-off date.
- (7) **Single Patient Studies:** 2 patients received total body doses other than 65 or 75 cGy
- (8) **ISS – A** is sum of patients in RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-003, RIT-II-004, & CP-97-012.
- (9) **ISS – B** is sum of patients in CP-98-020 & Single Patient Studies.
- (10) **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.
- (11) **ISE- Durpop** is patients in the ISE population who did not have durable response.
- (12) **Tran Pop** = Transformed low-grade patient population- includes all integrated efficacy population patients with transformed low-grade NHL

CBER's Efficacy Analysis :

Individual Clinical study results

Study RIT-II-004:

Title: Multicenter, Pivotal Phase 3 Study of Bexxar therapeutic regimen (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that Have Transformed to Higher Grade Histologies.

Design: A multicenter, historically-controlled, single-arm trial in patients with chemotherapy-refractory low grade or follicular NHL, with or without transformation.

Study opened- November 22, 1996

Study closed to accrual - March 6, 1998

Data cut-off- January 28, 2002

Specific Aims and Objectives (original protocol)

1. To establish the response rate, response duration, time to progression, time to treatment failure and survival after treatment with iodine I-131 tositumomab Radioimmunotherapy (RIT) in patients with chemotherapy-refractory low-grade or transformed non-Hodgkin's lymphoma
2. To compare these endpoints to the patient's previous chemotherapy outcome
3. To assess the safety of iodine I-131 tositumomab RIT
4. To assess the quality of life of treated patients using the EORTC QLA-C30(+3) validated questionnaire.

Final Analytic Plan

The primary endpoint of the study was a comparison of the number of patients having a longer duration of response (i.e., >30 days longer) after Bexxar therapeutic regimen therapy (Bexxar therapeutic regimen) compared to the number of patients having a longer duration of response after their LQC regimen. For the purposes of the primary efficacy endpoint, efficacy outcomes after the LQC and Bexxar therapeutic regimen therapies (Bexxar therapeutic regimen) were assessed by the MIRROR Panel. Secondary efficacy endpoints were response rate, complete response rate, and time to progression or death.

The original sample size of 60 patients is adequate to detect a a difference of 25% in the proportion of patients experiencing a longer duration of response (greater than 30 days) when treated with Bexxar therapeutic regimen therapy compared to the proportion of patients experiencing a longer duration of response (greater than 30 days) to the LQC.

There are two dichotomous treatment outcomes that are assessed in this analysis

- Durations equivalent- defined as ≤ 30 days difference in response durations to Bexxar therapeutic regimen and to prior chemotherapy for an individual patients

- Durations non-equivalent- defined as > 30 days difference in the durations of response to Bexxar therapeutic regimen and to prior chemotherapy.

Only the non-equivalent cases contribute to the test statistic in this approach. The null hypothesis is that the durations of response are the following the most recent chemotherapy regimen and following Iodine-131 Anti-B1 Antibody therapy.

MIRROR Panel

The MIRROR Panel was composed of two radiologists and two oncologists. All were board certified in their respective disciplines. The panel reviewed both patient radiographs and patient medical notes, while masked to the investigators' assessments of response. Efficacy endpoints include response rate, complete response rate, duration of response and time to progression based on the MIRROR Panel independent review assessment. The independent review process was coordinated by an independent CRO. The representative from the CRO facilitated the review process and ensured appropriate masking of the data and completion of the CRFs.

The independent review of data was expanded from the assessment of the primary endpoint to include the assessments of secondary endpoints in study RIT-II-004 ("Expanded MIRROR Panel").

Study Population:

The study population consists of low grade and follicular NHL; approximately 1/3 of the patients have disease, which has transformed to a higher histologic subtype. The population has been heavily pretreated with chemotherapy (median number of prior regimens -4) but not radiotherapy. None of the patients have undergone dose-intensive chemotherapy with prior stem cell support. The majority had advance disease (stage III and IV) and 11% have bulky lesions. The characteristics of the population at study entry are summarized in the following table.

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Baseline Characteristics for Patient Population in Study RIT-II-004

Baseline Characteristic	III population n=61
Age (years)	
Median(range)	59 (38-82)
Q1; Q3	52; 68
Gender	
Males (%)	38 (62%)
Race	
Caucasian (%)	59 (97%)
Histologic diagnosis at entry	
W/o transformation	
Low grade	37 (61%)
Intermediate grade	1 (2%)
High grade	0
With transformation	
Low grade	0
Intermediate grade	23 (37%)
High grade	0
Stage of disease	
I	0
II	1 (2%)
III	13 (21%)
IV	47 (77%)
Missing	0
IPI category	
0	0
1	7 (12%)
2	22 (36%)
3	22 (36%)
4	7 (12%)
5	1 (2%)
Missing	2 (3%)
Max. tumor diameter	
< 5 cm	25 (41%)
≥ 5, ≤10 cm	29 (48%)
> 10 cm	7 (11%)
# Prior chemo regimens	
Median (range)	4 (2-13)
25 th , 75 th quartiles	3, 5
# Prior RT regimens	
Median (range)	0 (0-7)
25 th , 75 th quartiles	0, 1
No Prior BMT	61 (100%)
Time from diagnosis to entry (Years)	
Median (range)	4.4 (0.8, 27.8)
25 th , 75 th quartiles	2.6, 7.2

Primary Efficacy Outcome:

The response to treatment and response duration for the most recent qualifying chemotherapy regimen and for Bexxar therapeutic regimen was determined by the Expanded MIRROR panel for 60 patients; data were not reviewed for the patient who withdrew from study and received neither the dosimetric nor therapeutic dose. There were 7 patients who responded to the LQC for an ORR of 12% and a CR/CCR of 2%. There were 28 subjects who responded to Bexxar therapeutic regimen for an ORR of 47% and a CR/CCR of 20%. The response determinations by the MIRROR panel are summarized in the table below for Intent-to-treat (ITT) analysis.

Treatment Response by Expanded MIRROR Panel (RESPOUT dataset) According to Treatment for Patients enrolled in RIT-II-004 Last Qualifying Chemotherapy Not Confirmed Investigator Assessed Response (LQRESP), Last Qualifying Chemotherapy Confirmed MIRROR Assessed Response (MLQCRES) and Bexxar therapeutic regimen Confirmed MIRROR (Final) Assessed Response (AB1CRES)			
Response Category	LQRESP	MLQCRES	AB1CRES
Complete Response	1	1	7
Complete Clinical Response	1	0	5
Partial Response	15	6	16
Stable Disease	23	5	4
Progressive disease	21	49	29
Total Patients	61	61	61

One person who did not get any Bexxar therapeutic regimen has been assigned as non-responder (Progressive Disease) in the treatment group in this Intent-to-treat analysis. There were 29 patients whose disease did not respond to either therapy or for whom the duration of response to either therapy was roughly equivalent (< 30 days difference in the duration of response to either treatment). This group was classified as "Duration Equivalent".

MIRROR Assessed	Responded to Bexxar therapeutic regimen	No Response to Bexxar therapeutic regimen	
Responded to LQC	3	4	7
No Response to LQC	25	29	54
	28	33	61

p-value (Exact McNemar - two sided) = 0.0001

The remaining 32 patients achieved an objective tumor response (CR, CCR, or PR) following Bexxar therapeutic regimen, the last qualifying chemotherapy regimen, with a difference in the durations of response to Bexxar therapeutic regimen and to the last qualifying chemotherapy regimen of more than 30 days. Among these 32 patients, 27 patients experienced a longer duration of response to Bexxar therapeutic regimen (difference in the durations ≥ 30 days) as compared to the duration of response to last qualifying chemotherapy regimen. This group of 27 consisted of 25 patients who failed to respond to the

LQC but did respond to Bexxar therapeutic regimen and 2 patients who responded to both the LQC and to Bexxar therapeutic regimen but had a longer duration of response to Bexxar therapeutic regimen than to LQC (difference in response durations ≥ 30 days).

	Response to Bexxar therapeutic regimen	No Response to Bexxar therapeutic regimen	
Responded to LQC	(2 + 1)	4	7
No Response to LQC	25	29	54
	(27 + 1)	33	

The remaining 5 patients experienced a longer duration of response to the last qualifying chemotherapy regimen (difference in the durations ≥ 30 days) as compared to the duration of response to Bexxar therapeutic regimen. This group was comprised of 4 patients who responded to the LQC but not to Bexxar therapeutic regimen and one patient who responded to both the LQC and Bexxar therapeutic regimen, in whom the duration of response to LQC was longer than to Bexxar therapeutic regimen.

	Response to Bexxar therapeutic regimen	No Response to Bexxar therapeutic regimen	
Responded to LQC	(2 + 1)	4	7 (2 + 5)
No Response to LQC	25	29	54
	28	33	

Based on the Expanded MIRROR Panel assessment of response and response duration as described above, the following proportions were generated for use in the primary efficacy analysis:

29/61 (48%) patients had an equivalent duration of response

32/61 (52%) patients had a non-equivalent duration of response

- **27/32 (84%) patients had a longer duration of response to Bexxar therapeutic regimen**
- 5/32 (16%) patients had a longer duration of response to the last qualifying chemotherapy regimen

Primary Efficacy Analysis

The primary efficacy endpoint of the study was the comparison, as assessed by the Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel, of the number of patients having a longer duration of response (i.e., more than 30 days) on their last qualifying chemotherapy regimen to the number of patients having a longer duration of response on Bexxar therapeutic regimen.

FDA followed the protocol defined primary endpoint and compared the duration of response on I-131 Antibody therapy to prior chemotherapy. The duration of response is linked with the response. If there is no response (SD, PD) on both (Bexaar & Prior Chemo) then these patients were classified as equivalent regardless of how long their Stable Disease (in favor of either Iodine I-131 tositumomab (Bexxar therapeutic regimen)

or prior Chemo) was or if they had a response (CR, CCR or PR), but the difference in the duration of response between Bexaar and prior Chemo was less than 30 days. There were 28 patients in this group. The remaining 32 patients had a CR or CCR or PR on either therapy and the difference in the duration of response was more than 30 days. There were 27 patients from these 32 whose the duration of response was longer than 30 days on Bexxar therapeutic regimen as compared to Prior Chemo, and 5 from these 32 whose duration of response was longer than 30 days on prior chemo as compared to Bexxar therapeutic regimen.

Using this algorithm, the following table provides a summary of the results for the primary endpoint for confirmed responses:

Response	Frequency	% of 61
Equivalent duration	29	48 %
Longer response with Bexxar therapeutic regimen	27	44 %
Longer response with Chemo	5	8 %

The sign-rank test takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is no change. If there is a significant change, then the proportions can be compared.

p < 0.0001 using sign-rank test.

Analysis of Proportions

Let p_1 = proportions of equivalent responses

p_2 = proportions of longer response with Bexxar therapeutic regimen

p_3 = proportions of longer response with prior chemotherapy

Of interest is to test 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 $H_1 : p_2 \neq p_3$. The p-value for testing this H_0 is 0.0001 (Binomial test).

Note: FDA's analysis differs slightly from the analysis of the primary efficacy endpoint as performed by the sponsor.

While, FDA and the sponsor used different approaches to assess the primary endpoint, the results of both tests were similar; both demonstrating a highly significant increase in the durations of response after Bexxar therapeutic regimen. The sponsor applied the one-sided exact McNemar's test for comparing the number of patients with longer response on Bexxar therapeutic regimen compared to the number of patients with longer response on chemotherapy. This test only accounts for patients with nonequivalent durations of response. FDA applied the Wilcoxon signed rank test using all response duration data. As the Wilcoxon signed rank test includes the magnitude of the duration of response, it is more powerful in this study (as the higher response rate after Bexxar therapeutic regimen is also associated with a longer duration of response). The sponsor approach accounts for the paired censored data. As the censored values were almost exclusively with the longest durations of response, the censoring effect is minimal. Thus, while the statistical approaches used by FDA and the sponsor differed, the conclusions were similar.

Secondary Efficacy Outcomes

1. Comparison of other efficacy outcomes between Bexxar therapeutic regimen and LQC: The protocol identified several secondary endpoints, including comparisons between efficacy outcomes following Bexxar therapeutic regimen as compared to the most recent qualifying chemotherapy regimen. These outcomes included comparisons of overall response rates, complete response rates, durations of overall response and of complete responses. For each of these analyses, the differences were in favor of Bexxar therapeutic regimen and were significantly different.

MIRROR Panel–Assessed Secondary Efficacy Endpoint Data:
Study RIT-II-004 (N = 61)

Secondary Efficacy Endpoints	Last Qualifying Chemotherapy (N = 61)	Bexxar therapeutic regimen (N = 61)
Overall Response Rate	7/61 (11%)	28/61 (46%)
Median (95% CI) duration of response for responders (months)	4.1 (3.0–5.4)	11.7 (6.9–NR)
Complete response Rate	1/61 (2%)	12/61 (20%)
Median (95% CI) duration of response for complete responders (months)	4.8	NR (12.5–NR)

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Confirmed Response-MIRROR assessed

	Prior Chemo	Bexxar	Histology Grade Bexxar Response		
			Low	Transformed	
Intermediate					
N	61	61	37	23	1
PD-Progressive Disease (1)	49	29	12	17	
SD-Stable Disease (2)	5	4	2	1	1
PR-Partial Response (3)	6	16	14	2	
CCR-Complete Clinical Response (4)	0	5	5	0	
CR-Complete Response (5)	1	7	5	2	

No Response = PD + SD

Response = PR + CCR + CR

Exploratory Analyses -- Study RIT-II-004

Responses-LQC Investigator assessed versus LQC MIRROR assessed

Investigator Assessed	MIRROR Assessed Responded to LQC	MIRROR Assessed No Response to LQC	
Responded to LQC	4	13	17
No Response to LQC	3	41	44
	7	54	61

p-value (Exact McNemar - two sided) = 0.0123

Responses-LQC Investigator assessed versus I-131 MIRROR assessed -- Study RIT-II-004

MIRROR Investigator Assessed	Responded to Bexxar therapeutic regimen	No Response to Bexxar therapeutic regimen	
Responded to LQC	9	8	17
No Response to LQC	19	25	44
	28	33	61

p-value (Exact McNemar - two sided) = 0.0372

Using earlier defined algorithm, the following table provides a summary of the results for the primary endpoint for LQC investigator assessed responses versus Bexxar therapeutic regimen responses:

Response	Frequency	% of 61
Equivalent duration	26	43 %
Longer response with Bexxar therapeutic regimen	26	43 %
Longer response with Chemo	9	15 %

The sign-rank test takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is a statistically change. Then two proportions can be compared.

p < 0.0001 using sign-rank test in favor of Bexaar.

Analysis of Proportions

Let p_1 = proportions of equivalent responses

p_2 = proportions of longer response with Bexxar therapeutic regimen

p_3 = proportions of longer response with prior chemotherapy

Of interest is to test 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 $H_1 : p_2 \neq p_3$. The p-value for testing this H_0 is 0.006 (Binomial test) in favor of Bexxar therapeutic regimen

Exploratory Analyses

1. Subset analyses of the primary efficacy analysis in patients whose disease has undergone transformation and in patients whose disease has not undergone transformation to a higher histologic subtype of NHL.

Subset analyses were done comparing Last Qualifying Chemotherapy Response – Original & Expanded MIRROR Assessed to Bexxar therapeutic regimen Confirmed Response – expanded MIRROR Assessed to evaluate if the original and expanded MIRROR assessment made any difference to the efficacy of the primary endpoint for each of the following two subset populations.

2. Patients with low grade non-Hodgkin’s lymphoma (NHL) that has not undergone transformation (37 patients) – Not Transformed
3. Patients with intermediate grade, follicular NHL that has not undergone transformation (1 patient)
4. Patients with low grade non-Hodgkin’s lymphoma (NHL) that has undergone transformation (23 patients) – Transformed

Last Qualifying Chemotherapy Response Versus Bexxar therapeutic regimen Confirmed Response – expanded MIRROR Assessed

Using previously defined algorithm, the following table provides a summary of the results of the subset analysis for the primary endpoint (the patient with an intermediate grade histologic subtype of NHL was not classified as not transformed, this patient was a non-responder):

Response	Low Grade/follicular		Transformed	
	Frequency	% of 38	Frequency	% of 23
Equivalent response duration	12	32 %	17	74 %
Longer duration with Bexxar therapeutic regimen	22	58 %	5	22 %
Longer duration with Chemo	4	11 %	1	4 %
p-value (sign-rank test)	<0.0001		0.0625	

Conclusions: There is a significant difference in favor of Bexxar therapeutic regimen for patients with low grade, untransformed NHL ($p < 0.0001$), but not significantly different in patients with NHL with transformation, ($p=0.0625$, trend in favor of Bexxar therapeutic regimen). Bexxar therapeutic regimen activity is different in two sub-populations. The patients with NHL without transformation (all but one with low grade histologic subtype) benefit significantly more from Bexxar therapeutic regimen than transformed patients ($p=0.0071$, Fisher’s exact test).

5. Assessment of response to Bexxar therapeutic regimen in patient subsets (patients with and without evidence of histologic transformation to a more aggressive (higher grade) histologic subtype.

At the initiation of the study, the sponsor was urged to limit the patient population to a more homogeneous group. Specifically, the sponsor was asked to exclude subjects with evidence of histologic transformation since FDA felt this was a biologically different disease than low grade and follicular lymphoma. The sponsor declined, stating that evidence of histologic transformation was a prognostic factor but only one of many in this chemotherapy refractory population. As a result of these discussions, the protocol was to include a plan for analysis of the study results in patient subsets, i.e., those with and those without evidence of histologic transformation. As can be seen in the table below, the likelihood of achieving a response was much lower in the transformed subset.

Response Category	Response Rate in Subset without Transformation N=38	Response Rates in Subset with Transformation N=23
CR	13% (5/38)	13% (3/23)
CCR	11% (4/38)	0 (0/23)
PR	37% (14/38)	8% (2/23)
ORR	61% (23/38)	21% (5/23)
SD	8% (3/38)	4% (1/23)
PD	32% (12/38)	74% (17/23)

6. Analyses of response according to I-131 dose administered
The dose of 131-Iodine administered was derived for each subject. This exploratory analyses were conducted to assess for relationships between response to Bexxar therapeutic regimen treatment and the total dose of 131-I administered or the dose adjusted for body mass or surface area administered. The results are presented in the table below.

Confirmed Response according to Dose of Iodine-131			
Dose Basis	Non Response	Response	Total
Dose (mCi)			
Median	77.9	97.7	90.2
Range	(0-173.4)	(47.2-212)	(0-212)
Dose (mCi/m²)			
Median	43.9	49.7	46.4
Range	(0-83.8)	(33-100)	(0-100)
Dose (mCi/kg)			
Median	1.1	1.2	1.2
Range	(0-2)	(0.9-2.4)	(0-2.4)

7. During the course of the study, the source of the tositumomab antibody was changed from Lonza to Coulter. The antibodies from the different manufacturing sites were biochemically comparable and yielded a similar pharmacokinetic profile. A comparison of the response rates by antibody-source showed a slightly higher but not significantly different response rate for the Lonza-manufactured antibody product than for the Coulter-manufactured product.

I-131-B1 Therapy Response Assessment by Antibody Manufacturer		
Antibody Manufacturer	Overall Response Rate (No. responders/total)	Total number of patients treated
Coulter-manufactured antibody	35% (7/20)	20
Lonza-manufactured antibody	52% (21/40)	40
Total	46% (28/60)	60

The following figure illustrates the relative comparison of the duration of response for each patient following treatment with their LQC and following treatment with Bexxar therapeutic regimen. On the left side of the figure are data from 5 patients with a longer duration of response for the LQC; in the center there are data from 29 patients with less than 30 days difference in the duration of response; and on the right side of the figure are data from 26 patients with a longer duration of response after Bexxar therapeutic regimen.

Figure: Paired Comparison of Duration of Response

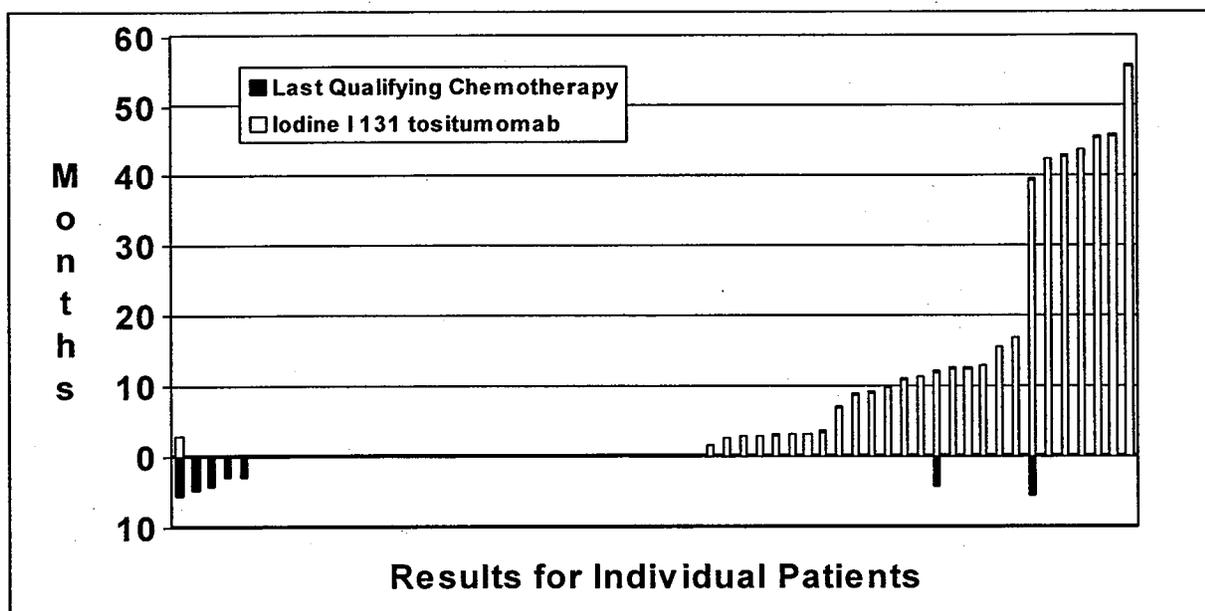


Table of Baseline Variables and Bexxar therapeutic regimen Confirmed Response as assessed by the Masked Independent Randomized Radiology and Oncology Review (MIRROR)

Confirmed Bexxar therapeutic regimen Response – MIRROR Assessed (RIT-II-004)

	No Response	Response	Total
Gender			
Male	20	18	38 (63%)
Female	12	10	22 (37%)
Histology Grade			
Low	14	23	37 (62%)
Transformed	18	5	23 (38%)
Antibody Manufacturer			
Coulter	13	7	20 (33%)
Lonza	19	21	40 (67%)
Age in years			
Median	60.5	57	50
Range	(38-80)	(39-82)	(38-82)
Weight (Kg)			
Median	79.3	83.4	81
Range	(48-115)	(48-107)	(48-115)
Body Surface Area (m²)			
Median	1.95	2.01	2.0
Range	(1.44-2.5)	(1.43-2.38)	(1.43-2.5)
Dose (mci)			
Median	77.9	97.7	90.2
Range	(0-173.4)	(47.2-212)	(0-212)
Dose (mci per m²)			
Median	43.9	49.7	46.4
Range	(0-83.8)	(33-100)	(0 – 100)
Dose (mci per kg)			
Median	1.1	1.2	1.2
Range	(0-2)	(0.9-2.4)	(0 – 2.4)

Duration of Response
Time (in days) to duration of response for responders

Study	Bexxar therapeutic regimen				Last Qualifying Chemo
		Low-grade NHL	Transformed to a higher grade	Total Bexxar therapeutic regimen	
RIT-II-004 (N=60)	N	23	5	28	7
	Median Days	330	..	380	124
	95% CI	(93, ..)	(211, ...)	(18, ...)	(89, 163)
	Q1-Q3	(90, ..)	(267, ...)	(93, ...)	(92, 163)
	Range	(47, 1395+)	(211, 1695+)	(47, 1695+)	(89, 169)
	# Censored (Ongoing)	8 35%	3 60%	11 30%	0
RIT-II-002-A (N=42)	N	21	2	23	30
	Median Days	182
	95% CI	(170, ...)	(51, ...)	(170, ...)	(91, 213)
	Q1-Q3	(170, ...)	(51, ...)	(141, ...)	(91, 213)
	Range	(60, 1734+)	(51, 325+)	(51, 1734+)	(30, 365)
	# Censored (Ongoing)	12 57%	1 (50%)	13 57%	0
RIT-II-002-B (N=36)	N	3	4	7	27
	Median Days	237	...	856	182
	95% CI	(232, ...)	(147, ...)	(147, ...)	(152, 273)
	Q1-Q3	(232, ...)	(856, ...)	(232, ...)	(121, 334)
	Range	(232, 1025+)	(147, 1234+)	(147, 1234+)	(30, 547)
	# Censored (Ongoing)	1 33%	2 (50%)	3 43%	0
RIT-II-002-X Crossover B to A (N= 19)	N	12	1	13	14
	Median Days	402	...	402	182
	95% CI	(143, ...)	(..., ...)	(179, ...)	(121, 304)
	Q1-Q3	(319, ...)	(..., ...)	(319, ...)	(152, 304)
	Range	(120, 1023+)	(287+, ...)	(120, 1023)	(91, 334)
	# Censored (Ongoing)	5 42%	1 (100%)	6 46%	0

The duration of confirmed response in days –expanded MIRROR is significantly longer for the Bexxar therapeutic regimen group (median = 380 days, n = 28) than the prior chemo group (median = 124 days, n = 7) logrank p= 0.02.

Time to Response
Time (in days) to response for responders

Study	Bexxar therapeutic regimen				Last Qualifying Chemo
		Low-grade NHL	Transformed to a higher grade	Total Bexxar therapeutic regimen	
RIT-II-004 (N=60)	N	23	5	28	7
	Median Days	48	46	48	80
	95% CI	(47, 50)	(44, ...)	(47, 50)	(43, 95)
	Q1-Q3	(47, 50)	(45, 56)	(46, 50)	(47, 95)
	Range	(41, 172)	(44, 56)	(41, 172)	(43, 144)
	# Censored	0	0	0	0

Time to Response (RIT-II-004) is quicker in Bexxar therapeutic regimen group (median time to respond = 48 days, n = 28) as compared to Prior Chemo with median time to respond = 80 days, n = 7, logrank p<0.01.

Bexxar therapeutic regimen Group (RIT-II-004) for various baseline variables

Variable	Median Time in Days to Duration	Response
Patient Gender		
Male (n=18)	380	50
Female (n=10)	...	48
Log-rank p-value:	0.8729	0.0627
Histology Grade		
Low (n=23)	330	48
Transformed (n=5)	...	46
Log-rank p-value:	0.3659	0.8560
Antibody Manufacturer		
Coulter (n=7)	93	50
Lonza (n=21)	380	48
Log-rank p-value:	0.8919	0.0895

Conclusions:

Males show a trend towards longer duration of response and time to response (though not significant) than Females in Bexxar therapeutic regimen group (Study RIT-II-004).

Low histology grade at protocol entry has similar duration of response and time to response as transformed histology grade at protocol entry in Bexxar therapeutic regimen group.

Antibody manufactured by Lonza has a trend towards longer duration of response and lower time to response days (though not significant) than Antibody manufactured by Coulter in Bexxar therapeutic regimen group.

Study CP-97-012

Title: Phase II Study of Bexxar therapeutic regimen for Non-Hodgkin's Lymphoma Patients who Have Previously Received Rituximab.

Design: Phase 2, single-arm, open-label, multicenter study of Bexxar therapeutic regimen 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.

Accrual initiated – July 17, 1998

Closed to enrollment - November 19, 1999

Data-cutoff – December 17, 2000

Final study report: August 17, 2001

Data cut-off: February 8, 2002

Objectives

1. To assess the response rate and duration of response of Bexxar therapeutic regimen 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 Bexxar therapeutic regimen 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.

Study Population

The subjects enrolled in this study had similar baseline entry characteristics to those enrolled in 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.

Baseline Entry Characteristics for Study Population in Study CP 97-012

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

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.

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 Bexaar 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)

Response Rates and Duration of Response for the Study CP-97-012

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

Response rate to Bexxar therapeutic regimen in subsets of the study population based on prior response to rituximab.

Prior response to most recent rituximab regimen	Response to the Bexxar therapeutic regimen	Median Duration of response to the Bexxar 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:

Patient ID	Rituximab Response	Duration of Response- Rituximab in Years	Bexxar Therapeutic Regimen Response	Duration of Response- Bexaar 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

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

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 Bexxar therapeutic regimen and prior rituximab :

Response	Frequency	% of 43
Equivalent response duration	11	26 %
Longer duration with Bexxar therapeutic regimen	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 Bexaar 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 Bexxar therapeutic regimen and to rituximab

p_2 = proportion of responses with longer duration to the Bexxar 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 non-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 Bexxar therapeutic regimen

ITT population (n=43)				
		Response to Bexxar therapeutic regimen		
		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

SAFETY ASSESSMENT

The most frequent adverse events were hematologic toxicities. The incidence of grade 3-4 toxicities were 43%, 25%, and 10% for neutropenia, thrombocytopenia, and anemia, respectively. The most frequent non-hematologic toxicities were asthenia (35%), fever (30%), infection (28%), increased cough (23%), nausea (20%), pain (15%), pneumonia and dyspnea (13% each), vomiting (13%), rash (13%), vomiting (13%), arthralgia (10%) and myalgias (10%). The major organ systems affected were gastrointestinal (43% of patients) and respiratory (40% of patients). Other than the infectious events, most of the non-hematologic toxicity was mild to moderate in severity (NCI CTC grade 1-2). This study is notable for the relatively high rate of infections. A separate summary is provided for the hematologic toxicity, infectious complications, and infusional reactions.

Infusion related AE . The study required pre-medication with acetaminophen and an antihistamine 30 minutes prior to the dosimetric and the therapeutic infusions. Infusion-related AEs were reported in 10% (4/40) of the dosimetric infusions and 20% (8/40) of the therapeutic infusions. The symptom complex of infusion-related AEs includes nausea, chills and fever, pruritus and vomiting; 85% of these were NCI CTC grade 1 or 2. One patient (012-0360001) experienced grade 3 arthralgia, nausea, hypovolemia and vomiting during the therapeutic infusion on day 14. This reaction lasted 5 days and was not described as serious.

Infections: Infection-specific data case report forms were used during the first 12 weeks following the therapeutic dose. Infections were observed in 55% (22/40) of the patients; 22% of the infections were pneumonia (6 patients) and 7% were sepsis (2 patients). Almost all patients, 24/27, received antibiotics.

**Per-Patient Incidence and Duration of Severe Hematologic Toxicity
Study CP 97-012**

Hematologic toxicity	
Grade 3-4 neutropenia	43%
Median duration (95% CI)	30 days (18, 43)
Grade 3-4 thrombocytopenia	25%
Median duration (days)	32 days (15, 51)
Grade 3-4 anemia	10%
Median Duration (days)	36 days (16, ---)

Deaths during first 90 study days: Three subjects died during the first 90 study days. Summary précis are given below. One of the patients who died (patient 012-035-008) withdrew from the study shortly after an agent related AE (tumor lysis syndrome). See subject précis in last section of this report.

- 012-035-008: Tumor lysis syndrome, hypoxia, hypercalcemia, death on study day 51.
- 012-036-005: Death on study day 66
- 012-037-005: Death on study day 35 due to aspiration pneumonia

Serious adverse events: There were 18 serious adverse events (SAE) reported for 8 patients (20% of the study population). Six of the 8 patients who experienced SAE were enrolled at one study site. Two patients who suffered SAE died prior to study day 90.

SUPPORTIVE PHASE 1 & PHASE 2 STUDIES

Study RIT-II-002

Title: Randomized Study of Bexxar therapeutic regimen vs. Anti-B1 Antibody Alone in Chemotherapy-Relapsed and Refractory Low-Grade or Transformed Low-Grade NHL.

Design

Study RIT-II-002 was a randomized two-arm, open-label, multi-center study conducted in patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. The study was designed to determine the incremental benefit of the radioconjugate compared to the unlabeled antibody. The study compared the safety and efficacy of the radiolabeled antibody (Arm A) versus the unlabeled antibody (Arm B). A one-way cross-over at the time of disease progression was permitted for patients in the unlabeled arm (to receive Bexxar therapeutic regimen).

Protocol activated- March 18, 1996

Accrual was from September 18, 1996 to June 1, 2000

Objectives (Final protocol)

Primary objective:

The comparison of the rates of complete response between the Iodine I-131 Anti-B1 antibody (Bexxar therapeutic regimen) and the unlabeled anti-B1 ("cold" tositumomab) arms.

Secondary objectives included comparisons between the Iodine I-131 Anti-B1 antibody and the unlabeled anti-B1 arms for:

- response rates (overall and complete),
- durations of response and complete response,
- comparison of times to progression; and
- safety and tolerance

Randomization (Final protocol, after the inclusion of amendments 1-6)

Randomization was performed at an external site. There were no stratification criteria specified and no details regarding the randomization procedure in the protocol other than that the randomization would allocate patients equally (1:1) to the two study arms.

Treatment Plan (Final protocol, after the inclusion of amendments 1-6):

Arm A

The treatment program consisted of two intravenous infusions; an initial dosimetric infusion followed in 7 to 14 days by a therapeutic infusion.

Arm B

The first day of the dosimetric phase was designated as study day 0. The dosimetric [tracer dose] infusion contained 450 mg of Anti-B1 antibody infused over 70 minutes (includes a 10 minute flush) immediately followed by 35 mg unlabeled anti-B1 antibody. A second dosimetric infusion was administered between study days 7-14, consisting of 450 mg unlabeled anti-B1 IV over 60 minutes followed by 35 mg of unlabeled anti-B1 antibody

Final Analytic Plan

(Final study protocol, after the inclusion of amendments 1-6):

The primary endpoint was the comparison (using Fisher's Exact Test) of the complete response rates between the two treatment arms (A and B), as determined by the assessment of an independent review of films and medical information (MIRROR Panel). A single interim analysis was performed by the Data Safety Monitoring Board (DSMB), who applied the Lan-DeMets implementation of O'Brien-Fleming boundary for correction for the interim look; based on this interim analysis, the final analysis level of significance was adjusted to 0.049.

The secondary endpoints included comparison of overall response rate, the duration of response, time to progression and time to death. Based on results from RIT-I-000 and RIT-II-001, a 30% CR rate was estimated for treatment arm patients (Arm A) and a 5% rate for Arm B patients exposed to the "cold" antibody. Using a 2 sided alpha of 5%, it was calculated that equal randomization of 78 patients would result in 80% power to demonstrate a difference in CR rate. The primary analysis was a comparison of the complete response rate between arms of the intent-to-treat population with calculation of 2 sided 95% confidence intervals. P values would be calculated without adjustments except for any interim analyses. Secondary analyses would be performed for crossover patients for response rate and duration of response (McNemar's test). Mean and median durations of response, time to treatment failure and survival will also be calculated.

Based on amendment 6 to the protocol, the analyses of study endpoints were based upon the determination of responses and response durations derived from an assessment of the CRFs and clinical data by an independent reviewer (MIRROR) panel. The MIRROR panel was composed of two teams of radiologists and oncologists who reviewed the CTs and determined the response assignment and duration of response. MIRROR panel radiographs were masked as to information on treatment arm of the patient and to investigators' assessment of response.

Results

The baseline entry characteristics for the study population by treatment arm and for the patients who cross-over in Arm B are presented in the table below.

Baseline Entry Characteristics: Study RIT-II-002 (N = 78)

**APPEARS THIS WAY
ON ORIGINAL**

Baseline Entry Variable	Arm A N= 42	Arm B N= 36	Arm B patients Cross-over n=19
Age (years)			
Median (range)	56 (28-75)	55 (32-85)	59 (37-81)
Q1; Q3	50, 67	46, 65	53, 70
Gender			
Males (%)	23 (50%)	18 (50%)	11 (58%)
Race			
Caucasian (%)	39 (93%)	33 (92%)	18 (95%)
Histologic diagnosis at entry			
Without transformation			
Low grade	36 (86%)	28 (78%)	17 (89%)
Intermediate grade	0	0	0
High grade	0	0	0
With transformation			
Low grade	3(7%)	2 (5%)	1 (5%)
Intermediate grade	3 (7%)	6 (17%)	1(5%)
High grade	0	0	0
Stage of disease			
I	0	1 (3%)	0
II	5 (12%)	3 (8%)	3 (16%)
III	10 (24%)	9 (25%)	7 (37%)
IV	27 (64%)	23 (64%)	9 (47%)
Missing	0	0	0
IPI category			
0	0	0	0
1	11 (26%)	9 (25%)	3 (11%)
2	17 (40%)	18 (50%)	5 (26%)
3	8 (19%)	7 (19%)	4 (21%)
4	4 (10%)	1 (3%)	2 (11%)
5	0	0	0
Missing	0	0	0
Max. tumor diameter			
< 5 cm	20 (48%)	24 (67%)	9 (47%)
≥ 5, ≤10 cm	18 (43%)	11 (31%)	9 (48%)
> 10 cm	4 (9%)	1 (3%)	1 (5%)
# Prior chemotherapy regimens			
Median (range)	2 (1-4)	2 (1-5)	2 (1-4)
25 th , 75 th quartiles	1, 3	1, 3	1, 3
# Prior radiation therapy regimens			
Median (range)	0 (0-4)	0 (0-5)	0 (0-5)
25 th , 75 th quartiles	0,0	0,0	0,0
No Prior BMT	42 (100%)	36 (100%)	19 (100%)
Time from diagnosis to entry (yrs)			
Median (range)	2.6 (0.5-15.4)	2.4 (0.6-19.7)	2.6 (1.7 -20.2)
25 th , 75 th quartiles	1.6, 3.7	1.9, 3.7	2.3, 4.6

EFFICACY RESULTS

There was a significantly higher complete response rate in patient randomized to Arm A as compared to Arm B as well as a significantly increased overall response rate in Arm A. The duration of response however, not significantly different in the two arms; 10 of the 23 responding patients have relapsed in Arm A and 4 of the 7 responding patients have relapsed in Arm B. There was also no difference in overall survival between the two study arms. The median survival has not been reached in either study arm, with 16 of 42 patients dead in Arm A and 12 of 36 patients dead in Arm B. However, there was a significant difference in time to death or progression between the study arms ($p=0.031$). The survival curves for duration of response, time to progression or death, and time to death are displayed below.

Efficacy Outcomes

MIRROR Panel-Assessed Outcomes: Study RIT-II-002

Efficacy Endpoint	Arm A (N = 42)	Arm B (N = 36)	P-value
Primary endpoint			
Complete response	14/42 (33%)	3/36 (8%)	0.01
Secondary endpoints			
Overall Response	23/42 (55%)	7/36 (19%)	0.001
Median duration (yrs) of response (95% CI)	NR (0.5-NR)	2.3 (0.4, NR)	0.9
Median duration (mos) of complete response (95% CI)	NR (NR, NR)	NR (28, NR)	0.4
Median time to progression or death (yrs) (95% CI)	0.52 (0.35, NR)	0.45 (0.24, 0.5)	0.031

Fisher's exact test for response rates

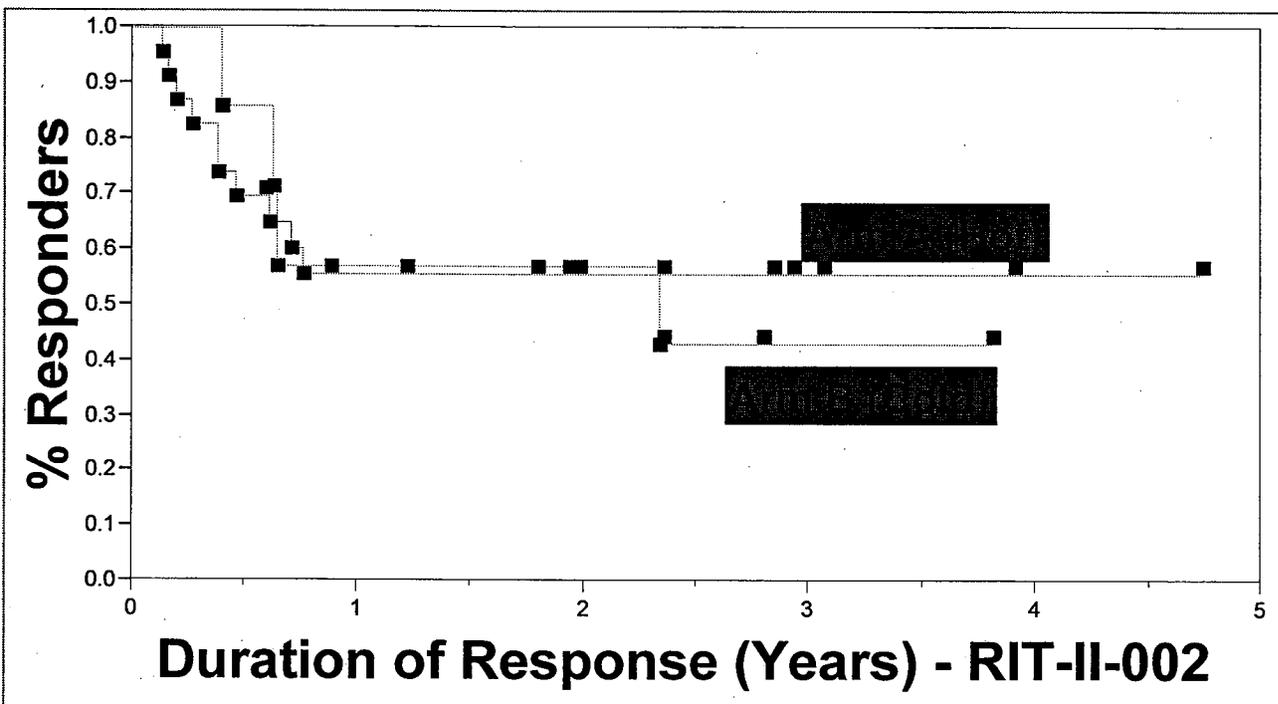
Log-rank test for duration measures

NR = Not reached

CI = 95% confidence interval

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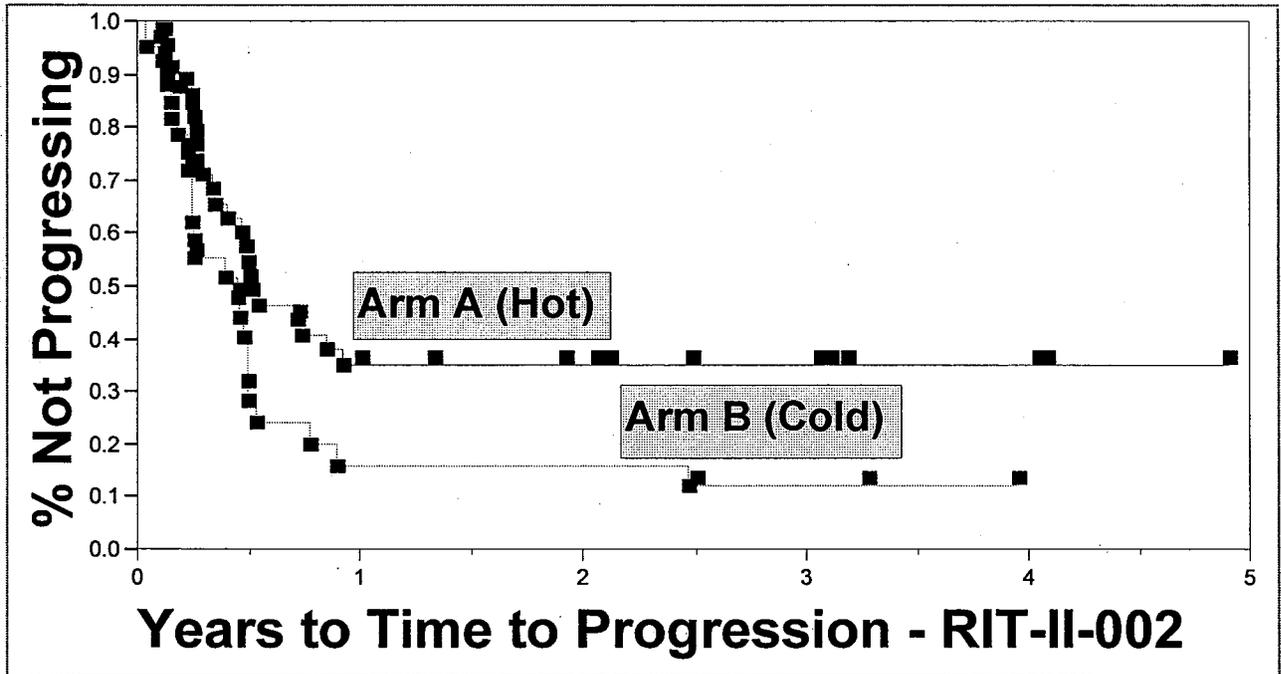
Study RIT-II-002 –Duration of Response in Years (n=78)



p-value (Log-Rank) = 0.8769

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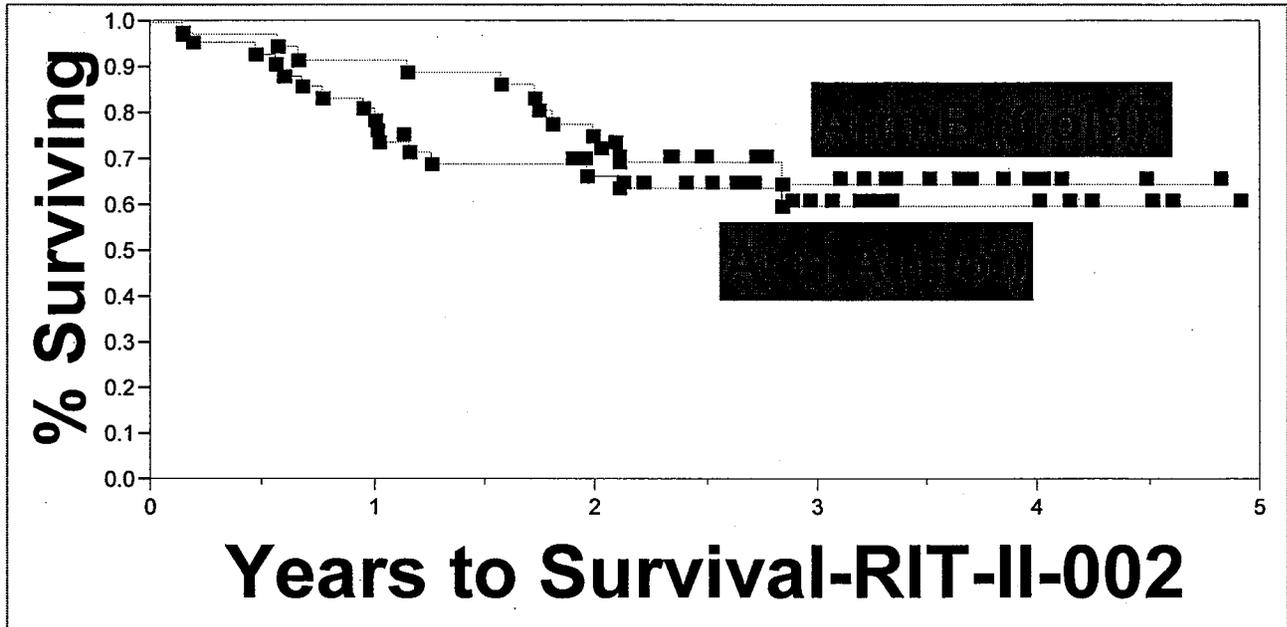
Time to Progression or death in Years Hot (Arm A, n=42) vs Cold (Arm B, n=36) -- Study RIT-II-002



p-value (Log-Rank) = 0.0313

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Study RIT-II-002 – Time to Survival (Years)



p-value (Log-Rank) = 0.4822

Safety Assessment

Adverse events: The most frequent adverse events were nausea, asthenia, fever, rash, chills and pain. Adverse events, both the incidence of all adverse events and of serious adverse events (26% vs. 11%), were higher in patients receiving Bexxar therapeutic regimen than in those who received the unlabeled antibody. Gastrointestinal adverse events, particularly nausea, were significantly more frequent in patients receiving radiolabeled antibody as compared to those receiving unlabeled antibody. NCI CTC grade 3-4 non-hematologic adverse events that were reported in >5% of patients included myeloproliferative disorder, chronic leukemia, and lymphoma like reaction and pneumonia. Adverse events reported in \geq 5% of patients, regardless of relationship to study drug, are shown in the following table.

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Per-patient incidence of adverse events regardless of severity or relationship to study agent

<u>Body System</u> COSTART Preferred term	Arm A	Arm B %	Arm X %	<u>Body system</u> COSTART Preferred term	Arm A %	Arm B %	Arm X %
N	42	36	19		42	36	19
<u>Body as a Whole</u>				<u>Metabolic system</u>			
Abdominal pain	17	8	16	Edema	5	6	0
Asthenia	40	36	42	Peripheral edema	7	8	11
Back pain	12	8	11	Weight loss	5	0	16
Chest pain	10	11	0	Dehydration	0	6	0
Chills	24	19	16	<u>Musculoskeletal</u>			
Face edema	0	8	5	Arthralgia	19	19	5
Fever	33	22	16	Myalgia	17	17	0
Headache	14	19	21	<u>Nervous system</u>			
Infection	5	17	16	Anxiety	5	3	5
Injection site pain	10	6	0	Dizziness	7	8	0
Malaise	10	3	0	Insomnia	10	8	5
Neck pain	10		16	Depression	0	6	0
Pain	10	10	21	Parasthesia	2	6	5
Pelvic pain	21	3	0	Somnolence			
Sepsis	7	6	0	<u>Respiratory system</u>			
<u>Cardiovascular</u>				Cough increased	17	8	32
Palpitation	7	0	0	Dyspnea	14	3	16
Vasodilatation	14	11	0	Pharyngitis	19	11	16
Syncope	0	8	0	Rhinitis	10	14	16
<u>Digestive system</u>				Bronchitis	2	8	5
Anorexia	14	8	0	Epistaxis	5	0	0
Constipation	7	6	0	Lung disorder	5	0	0
Diarrhea	17	11	5	Pleural effusion	2	8	5
Dyspepsia	10	6	11	<u>Skin & appendages</u>			
Dysphagia	5	0	0	Pruritus	5	14	11
Flatulence	5	3	5	Rash	31	14	16
Nausea	48	17	11	Sweating	14	8	11
Vomiting	7	6	0				

Hematologic toxicity:

The most frequent adverse event (all severity) and the most frequent severe adverse events were hematologic. In the 19 subjects in arm X there were 11 patients with documented hematologic toxicity and 3 with undocumented toxicity for a cumulative total of 14 (74%). Source was FDA analysis using CRTs submitted 9/7/01.

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Grade 3-4 hematologic toxicity in patients receiving Bexxar therapeutic regimen			
Toxicity Measure	Arm A N=42	Arm B N=36	Arm X N=19
Neutropenia			
% Documented Grade 3-4 toxicity	33%	3/36=8%	58%
Median days to nadir (95% CI)	47 (42, 49)	22, 38, 46	43 (39, 47)
Median duration of documented Grade 3-4 toxicity	21 (14, 36)	4, 56, 68	31 (15,49)
Thrombocytopenia			
% Documented Grade 3-4 toxicity	33%	0	47%
Median days to nadir (95% CI)	36 (29, 38)		35 (28,36)
Median duration of documented Grade 3-4 toxicity	29 (22, 54)		28 (16,90)
Anemia			
% Documented Grade 3-4 toxicity	14%	0	11%
Median days to nadir	48 (40, 51)		47 (36, 61)
Median duration of documented Grade 3-4 toxicity	18 (6, ---)		35 (10, ---)

Hematologic toxicity in crossover population: The table below compares documented hematologic toxicity in the three arms and shows a higher incidence of grade 3-4 toxicity in arm A as compared to B, as well as a higher incidence of hematologic grade 3-4 toxicity in arm X as compared to Arm A. Notable is the rate of grade 3-4 neutropenia (8%) with the unlabeled tositumomab, which exceeds that generally observed with other anti-CD20 antibodies. If this is a real finding, the mechanism is unclear. In addition, the incidence of severe cytopenias and of bleeding events in patients who were treated in Arm B and crossed over to treatment with Bexxar therapeutic regimen in the 3-month interval permitted in this study is higher than observed in patients in Arm A (initial treatment with the Bexxar therapeutic regimen). Again, given the small patient numbers it is unclear whether this finding is real or a chance event. Recovery from hematologic toxicity was evaluated at week 13. There were 35 (of the 42 patients) actively followed in Arm A for hematologic toxicity at week 13. Two patients among the 35 had persistent hematologic toxicity (grade 3 and one grade 4 neutropenia). There were 2 patients, among the 22 being actively followed for toxicity at week 13 in Arm B, who had persistent toxicity (both had Grade 4 neutropenia).

Percent subjects with grade 3-4 hematologic toxicity

	Arm A n=42			Arm B N=36			Arm X n=19		
	%			%			%		
	3&4	3	4	3&4	3	4	3&4	3	4
Hematologic toxicity									
ANC < 1000 cells/mm	33	17	17	8	6	3	58	21	37
Platelets < 20,000/ mm	33	21	12	0	0	0	47	21	26
Hgb	8			0			11		
Bleeding events	10			3			16		

HAMA: HAMA was detected at week 7 (5 cases), week 13 (2 cases) and at 6 months in one case. As noted, 32 patients in Arm B with progressive disease had an option of a one-way cross-over to Arm X. Nineteen of the 32 patients crossed over to arm X (to receive Bexxar therapeutic regimen therapy). The 13 patients with progressive disease who did not crossover included 8 who could not be crossed over because of positive HAMA tests.

Serious adverse events:

There were 15 patients in the randomized portion of the study who suffered one or more serious adverse events. The Bexxar therapeutic regimen arm had an approximately 2-fold higher rate of SAE. A similarly high rate of SAE were observed in the patients who crossed over to Bexxar therapeutic regimen after disease progression on Arm B.

- 26% (11/42) of patients randomized to Bexxar therapeutic regimen (tositumomab therapeutic regimen) experienced one or more SAEs. Ten patients (24%) were hospitalized for the following adverse events: acute cholecystitis; abdominal pain; back pain; constipation; spinal cord compression; pleural effusion; bacteremia (2 patients); dyspnea; GI hemorrhage; small bowel obstruction; deep vein thrombosis. There was one patient with a serious adverse event who experience septicemia that did not require hospitalization.
- 11% (4/36) patients randomized to unlabelled tositumomab experienced at least one SAE. Four patients (11%) were hospitalized for the following adverse events: chest and abdominal pain; syncope /dehydration and hypothermia; retroperitoneal bleed; hydronephrosis; bacteremia; fungemia; febrile neutropenia.
- 37% (7/19) of patients who crossed over to receive Bexxar therapeutic regimen (crossed-over after progression) experienced one or more SAEs. Five patients (21%) were hospitalized for the following adverse events: ulcerated node; thrombocytopenia; basal cell carcinoma; bronchitis; abdominal bloating and dyspnea and edema. The patients with SAEs not requiring hospitalization experienced CML and gastric adenocarcinoma, respectively.

Deaths: There were 13 total deaths in RIT-II-002 of which 2 were prior to day 90, 3 by day 189, 4 by day 270, and 8 by one year. Arm A had 2 deaths (weeks 8 & 10) and 6 patients who withdrew (weeks 3, 6, 7,9 and 11) during the first 90 study days.

Patients who died in first ninety days of study

<u>Patient ID #</u>	<u>Age in yrs</u>	<u>Sex</u>	<u>NHL grade*</u>	<u>Study arm</u>	<u>Study Day of death</u>
002-030-002	69	F	L	A	54
002-030-009	51	M	T	A	69
002-030-018	62	F	T	B	53

- L = low grade lymphoma without transformation and T = transformed low grade lymphoma

Studies supporting dosing Strategy

STUDY RIT-I-000 Phase 1

Title: Phase I/II Study of Radiolabeled Anti-B1 Monoclonal Antibody for the Treatment of B-Cell Lymphomas

Background: This initial study of Bexxar therapeutic regimen was a Phase 1/2, single-center, open-label, dose-escalation study. The study was conducted in two Phases. Phase A assessed the impact of a range of cold antibody loading doses on the biodistribution of I 131 tositumomab while simultaneously assessing the toxicity and maximum tolerated dose of I 131 labeled antibody in patients with low-grade, transformed low-grade, intermediate-grade, or high-grade NHL and no prior stem cell transplantation. Phase B assessed the maximum tolerated dose, the dose-limiting toxicity of I 131 labeled antibody in patients with potentially impaired marrow reserve (due to prior hematopoietic stem cell transplants), and the activity at the MTD in patients who had not undergone transplantation.

Study initiated April 24, 1990

Phase B initiated October 5, 1994

Closed on January 17, 1996

Date cut-off: Dec. 1, 2000

Objectives:

1. To evaluate the activity (response) of a pan anti-B cell antibody, B1, that has been conjugated with I-131 in patients with refractory B cell lymphomas
2. To define the toxicity of B1 conjugated with I-131 in patients with refractory B cell lymphomas
3. To determine if B1 conjugated with I-131 can be used as a vehicle to deliver effective radiation to tumor sites and establish the biodistribution, dosimetric parameters, clearance, and tumor specificity
4. To assess the effect of total antibody protein dose on the biodistribution of radiolabeled B1
5. To assess degrees of localization and antigen saturation within tumors by immunohistochemical techniques
6. To assay for human anti-murine antibody (HAMA) production following administration of the murine antibody

Analytic Plan

The analytic plan was modified over time. The major objectives were to determine the optimal biologic dose of unlabeled antibody as a component of the dosimetric dose and the maximum tolerated dose (MTD) of the therapeutic dose. The definition of dose-limiting toxicity (DLT), upon which the MTD was based, was revised during the course of the study. The final protocol defined the MTD as the level below the dose level at which there was a one-third or greater incidence of DLT. DLT was defined as any non-hematologic Grade 3 or 4 dose-related toxicity, any Grade 3 hematologic toxicity of >2 weeks duration, or any Grade 4 hematologic toxicity of >1 week duration. The determination of the optimal biologic dose of unlabeled antibody was described in qualitative terms in the analytic plan.

Results:

Study Population:

The study population contained a mixture of patients with chemosensitive and chemotherapy-refractory disease. Of the 59 patients enrolled, 30 (51%) had responded to the most recent chemotherapeutic regimen. Of these 19 (33% of the overall study population) had achieved a complete or clinical complete response to the most recent treatment regimen.

BASELINE ENTRY CHARACTERISTICS – RIT-II-004

RIT-II-000	Total enrollment n=59
Age (years)	
Median (range)	50 (23-75)
Q1; Q3	41, 59
Gender	
Males (%)	37 (63%)
Race	
Caucasian (%)	54 (92%)
Histologic diagnosis at entry	
W/o transformation	
Low grade	28 (48%)
Intermediate grade	15 (25%)
High grade	2 (3%)
With transformation	
Low grade	0
Intermediate grade	12 (22%)
High grade	2 (3%)
Stage of disease	
I	3 (5%)
II	4 (7%)
III	13 (22%)
IV	39 (66%)
Missing	
IPI category	
0	2 (3%)
1	11 (19%)
2	24 (41%)
3	19 (32%)
4	3 (5%)
5	0
Missing	0
Max. tumor diameter	
< 5 cm	41 (70%)
≥ 5, ≤10 cm	16 (27%)
> 10 cm	2 (3%)
# Prior chemotherapy regimens	
Median (range)	3 (1-11)
25 th , 75 th quartiles	2, 5
# Prior radiation therapy regimens	
Median (range)	0 (0-4)
25 th , 75 th quartiles	0, 1
No Prior BMT	45 (76%)
Time from diagnosis. to entry (years)	
Median (range)	3.8 (0.5-17.8)
25 th , 75 th quartiles	2.5, 7.2

Efficacy Analyses

The study enrolled a heterogeneous group of patients and was not intended to provide more than anecdotal information on clinical activity. In addition, because of the patient heterogeneity and the small numbers of patients who received a particular TBD, it is difficult to draw conclusions regarding the dose-response relationship. The data presented below are not an ITT analysis. For example, no patient was intended to receive "0 cGy" TBD- each of these patients was unable to receive study drug in a treatment cohort for various reasons, including toxicity with dosimetric infusion, development of HAMA, and/or disease progression. The dose selected by the sponsor for use in Phase 2 studies is based upon determination of the MTD and not necessarily the optimal biologic dose (OBD), which cannot be determined in a study of this size and with this degree of heterogeneity. The data presented in the table below are provided only for information.

Response Rate Analysis for RIT-I-000 by Total Dose (cGy) received

Response Variable	0 cGy n=6	25 cGy n=3	35 cGy n=4	45 cGy n=9	55 cGy n=8	65 cGy n=6	75 cGy n=20	85 cGy n=3	All n=59
CR			1			1	2	1	5
CCR			1	1	3	2	4		11
PR	1	1		3	2	3	2		12
% ORR	17%	33%	50%	44%	62%	100%	40%	33%	48%
95% CI	(0.4, 64)	(0.8, 91)	(1, 99)	(14, 79)	(24, 91)	(54, 100)	(19, 64)	(0.8, 91)	(34, 61)

Safety Analyses

Study RIT-I-000 was designed to determine the optimal unlabeled (cold) predose of Anti-B1 Antibody to maximize tumor targeting and the maximum tolerated non-myeloablative radiation dose level.

The sponsor anticipated that bone marrow toxicity would be dose limiting. The sponsor elected the dose escalation design based on whole body radiation-absorbed dose, on the assumption that the whole body radiation dose would be more closely related to levels of bone marrow toxicity as compared to an escalation based on mCi/kg, mCi/m², or mCi.

Because the direct estimation of radiation dose to bone marrow is not feasible with unsealed source radiation therapy and marrow dosimetry from blood is not considered to be reliable in NHL subjects with normal B-cell populations as well as variable bone marrow involvement, the Total Body Dose (TBD) of radiation exposure was utilized as a surrogate for bone marrow dosimetry. Therefore, dose cohorts were escalated based on TBD and subjects were followed for dose-limiting toxicity (DLT) with expectations that the DLT would be related to declines in peripheral blood assessments, e.g. neutropenia, thrombocytopenia and anemia.

The MTD was set at one level below the dose level at which there was a one-third or greater incidence of DLT. The DLT was defined as any non-hematologic Grade 3 or 4 dose-related toxicity, a Grade 3 hematologic toxicity of >2 week's duration, or a Grade 4 hematologic toxicity of >1 week duration.

The dose escalation was performed in subjects without prior bone marrow transplantation (BMT).

The maximum non-myeloablative TBD level was established in study RIT-I-000, based on 2 of 3 patients who had a DLT at 85 cGy TBD. Therefore, the MTD was established to be 75 cGy TBD for patients with no prior BMT

**Dose-Dependent Hematologic Toxicity for Study RIT-I-000:
Patients without Prior Bone Marrow Transplant**

Dose Cohort	ANC	Platelets	Hemoglobin
TBD (cGy)			
25-55			
N	13	13	13
Mean Nadir	2000 cells/mm ³	134,000 cells/mm ³	11.5 g/dL
SD of Nadir	1000 cells/mm ³	41,000 cells/mm ³	1.4 g/dL
Grade III ^a (%)	1 (8%)	0 (0%)	0 (0%)
Grade IV ^a (%)	1 (8%)	0 (0%)	0 (0%)
65-75			
N	24	24	24
Mean nadir	1300 cells/mm ³	76,000 cells/mm ³	10.7 g/dL
SD of nadir	1200 cells/mm ³	49,000 cells/mm ³	1.9 g/dL
Grade III ^a (%)	8 (33%)	4 (17%)	1 (4%)
Grade IV ^a (%)	4 (17%)	4 (17%)	1 (4%)
85			
N	3	3	3
Mean nadir	900 cells/mm ³	78,000 cells/mm ³	8.8 g/dL
SD of nadir	1300 cells/mm ³	115,000 cells/mm ³	2.9 g/dL
Grade III ^a (%)	0 (0%)	0 (0%)	2 (67%)
Grade IV ^a (%)	2 (67%)	2 (67%)	0 (0%)

**APPEARS THIS WAY
ON ORIGINAL**

Study RIT-II-001

Title: Multicenter Phase II Dosimetry/Validation Study of Dosimetry for Bexxar therapeutic regimen for the Treatment of Patients with Relapsed and Refractory Low-Grade and Transformed Low-Grade NHL

Design: Multicenter, single arm study to assess the reproducibility of the dosimetry methods developed in RIT-II-000.

Study initiated December 5, 1995

Study closed to enrollment November 20, 1996

Date cut-off December 1, 2000

Objectives

The primary objective of this multi-center study was to demonstrate that each independent site could reproducibly and accurately conduct the whole body dosimetry. Additional objectives of this study were to evaluate the efficacy and safety of Bexxar therapeutic regimen therapy in a multicenter study. Dosimetry methods and calculations from each participating site were validated by a central dosimetry center at the University of Michigan.

Study Results

Patient Enrollment and Disposition

Forty-seven patients with relapsed/refractory low-grade or transformed low-grade NHL were enrolled. All 47 patients received the dosimetric dose, and 98% (46/47) of the patients received the therapeutic dose. The median follow-up from the dosimetric dose was 34.0 months (range: 0.2–58.3 months).

Patient Entry Characteristics Study RIT-II-001 (n=47)

Male/female	25/22
Median age (years) (range)	51 (23-74)
Time from diagnosis to study entry (months) (range)	41 (8-264)
Median number of prior chemotherapy regimens (range)	4 (1-8)
Grade	
Low grade	33/47 (70%)
Transformed low grade	14/47 (30%)
Bone marrow involvement	24/47 (51%)
Bulky disease (>500 g)	17/47 (44%)
Elevated LDH	18/47 (38%)
Response to last chemotherapy^a	
Response (PR + CCR + CR)	24/47 (51%)
Complete response (CCR + CR)	8/47 (17%)
^a Unconfirmed response rates.	

Dosimetry Endpoints

Assessment of all of the onsite calculations and the administered activity of Bexxar therapeutic regimen (mCi) by the independent dosimetry center indicated that the calculations performed at the treating centers were within 10% of those calculated at the dosimetry center.

Activity Results

The overall response rate was 49% (23/47). The complete response rate (CR + CCR) was 30% (14/47).

Safety Results

Non-hematologic toxicities were qualitatively similar to that reported in other studies. Hematologic toxicities were somewhat more frequent than in the other studies.

Toxicity Measure	N=47
Neutropenia	
% Documented Grade 3-4 toxicity	62%
Thrombocytopenia	
% Documented Grade 3-4 toxicity	57%
Anemia	
% Documented Grade 3-4 toxicity	21%