Long-term responders

In the July 2, 2002 submission to the FDA, the sponsor identified 75 long-term responders from the five clinical studies. In the October 4, 2002 submission, the sponsor identified 78 patients with long-term responses following tositumomab therapeutic regimen. This subset was also derived from Studies RIT-II-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP 97-012. The criterion for selection of this subset was time to disease progression of more than 12 months. The basis for this criterion as being a clinical relevant cut-point remains unclear.

The sources of the sponsor-defined long-term responder population and distribution across the efficacy/activity study population are as follows:

Study No./description	Enrollment dates	Data Cutoff date	Number of Patients
RIT-I-000 Single Center Phase I	24 Apr 90 to 17 Jan 96	8 Dec 01	16
RIT-II-001 Multicenter Phase II Dosimetry/Validation Study	5 Dec 95 to 20 Nov 96	21 Sept 01	10
RIT-II-002 Randomized Study of I-131 Anti-B1 Antibody vs. Unlabeled Anti-B1 Antibody	18 Sept 96 to 7 Jan 00	28 Jan 02	20
RIT-II-004 Phase III Study in Chemotherapy Refractory Patient Population	22 Nov 96 to 6 Mar 98	28 Jan 02	15
CP-97-012 Phase II Study of I-131 Anti-B1 Antibody in Patients Previously Treated with Rituximab	17 Jul 98 to 19 Nov 99	08 Feb 02	17

A: Study Population in the Long-Term Responder Data Set

FDA's review of the case report forms and other documentation identified the following two patients in whom long-term response could not be confirmed.

1. 004-014-001: Patient was responding to previous chemotherapy (Fludarabine) before study entry. The sponsor agreed that data from this patient are non-informative. In the primary efficacy analysis for study RIT-II-004, this patient was excluded by the sponsor, but included in the long-term responder data set. For the purposes of labeling, the sponsor will correct all analyses to reflect exclusion of this patient

2. 000-002-056: Patient underwent modified radical mastectomy for metastatic breast cancer 5 weeks before the dosimetric dose. The sponsor agreed that the confounding effects of metastatic breast cancer in this patient make assessment of lymphoma response problematic. The sponsor will remove this patient from the long-term responder data set.

After teleconferences on October 24, and November 7, 2002, between FDA and the sponsor, agreement was reached to exclude these two patients from the "Long-term responder" subset. Due to insufficient time to re-analyze the dataset, some of the analyses below include these 2 patients, however inclusion of

these patients does not alter the conclusions drawn from these analyses. The analyses will be updated for the December 17, 2002 ODAC meeting. Based on the agreement with the sponsor, the "long-term responder" data set contains 76 patients.

Among the 76 patients, eight patients received a dose and/or schedule of the tositumomab therapeutic regimen that differs from the regimen under review for licensure and for which approval is being sought. FDA believes that the following eight patients from study RIT-II-000 should be treated as a separate group, since they received more than one dosimetric dose: These patients (by patient ID number) are: 000-002-006, 000-002-010, 000-002-013, 000-002-015, 000-002-016, 000-002-020, 000-002-022, 000-002-025.

The confounding factor introduced by receiving more than one dose of unlabelled antibody is illustrated by the observation that in study RIT-II-002, when comparing the efficacy of labeled and unlabeled antibody therapy, there were also some patients with long-term responses in the unlabelled antibody group.
The following case included in the long-term responder group by the sponsor further underscores the point.

> Patient # 000-002-006 was a 36 year old male at entry and diagnosed in February 1989 with follicular mixed (<50% large cell) lymphoma. He received non-radiolabeled (cold) tositumomab as a component of dosimetric doses administered on 5/8/92, 5/15/92 and 5/28/92 before receiving the therapeutic dose of the labeled antibody on 6/18/92. He was noted to have a CCR until disease progression after 477 days. However, a CT scan done on 6/17/92, prior to the therapeutic dose of antibody, showed that the patient already had a substantial response to the multiple doses of tositumomab given during dosimetric studies.

Since pooling the data from patients who have received multiple doses of unlabeled antibody may not be appropriate, FDA analyses were conducted both including and excluding this subset of patients who received an alternate tositumomab regimen.

B: What Were The Disease Parameters Being Measured?

The eligibility requirements regarding measurable disease differed among the five studies. The Phase I study, RIT-II-000, required 'evaluable and measurable' disease with no specific requirements in terms of tumor dimensions. Study RIT-II-001 required either evaluable disease (which included unidirectionally measurable disease if it had ill defined margins and lesions <0.5 cm diameter, or less then distance between two CT cuts) or bi-dimensionally measurable disease. Study RIT-II-002 at its inception required patients to have evaluable or –bi-dimensionally measurable disease that was amended on 7/9/97 to require lesions of ≥2 cm in both perpendicular dimensions. Study RIT-II-004 required at its inception bi-dimensionally measurable or evaluable disease, which was amended to requiring bi-dimensionally measurable disease on 6/4/97 with at least 1 lesion to be ≥2 cm diameter. The study CP-97-012 required that at least one lesion be ≥ 2 cm in perpendicular diameters from the onset.

C: How Was the Follow-Up Conducted?

The follow-up requirements as specified in the protocols differed among the five studies. .
Study RIT-I-000 required frequent monitoring during the treatment phase and then at 'standard' evaluations during long term follow-up. This was amended on 2/18/94 to tumor response evaluations at appropriate intervals and further amended on 2/17/01 to evaluations every 6 months during the first two years and long term follow up after that. Study RIT-II-001 required follow-up studies every 3 months

during the first 2 years and every six months after that. Study RIT-002 required frequent follow-up during first 12 weeks, then every 3 months for the first two years and every 6 months thereafter. RIT-II-004 also required response evaluation every 3 months for 2 years and every six months thereafter. Study CP-97-012 required frequent follow-ups during first 6 months and then every 6 months for the first two years and long term follow-up after that. The long term follow up consisted of obtaining information about disease status by direct or telephone contact with patient, physician or family member. Radiographic scans and medical notes related to the response evaluation were obtained retrospectively by the sponsor.

D: How was the Long-term Responder Population Derived?

An independent review of the response assessments was performed by the MIRROR (Masked Independent Randomized Radiology and Oncology Review) Panel. This review was performed for all patients enrolled in studies RIT-II-004, RIT-II-002 and CP-97-012. This review was prospectively planned and primary source documentation for review prospectively collected for study RIT-II-004. The collection of data and proposal for MIRROR panel review was performed retrospectively, after the completion of accrual, for studies RIT-II-002 and CP 97-012, per an amendment to the protocols in 2001.

A retrospective review of the Investigator's assessment of response was conducted by the MIRROR panel in October 2001 for patients from studies RIT-I-000, RIT-II-001, RIT-II-002, and RIT-II-004 who were identified by the sponsor as long-term responders. A subsequent, retrospective review of other patients with low-grade NHL was conducted in June/July 2002 for patients from studies RIT-I-000 and RIT-II-001. In July 2002, the FDA requested a confirmatory independent re-review of 37 patients from studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012. Each of the 37 patients had a time to progression of at least 12 months on their original MIRROR Panel review. The majority (26 of 37 patients) were patients enrolled in the earlier studies RIT-I-000 or RIT-II-001, which were the two studies with MIRROR Panel review performed on only a subset of patients. According to the MIRROR2 panel charter, measurable lesions were defined as having a bi-dimensional size of ≥2.0 cm x 2.0 cm. All lesions having a product of greatest perpendicular diameters ≥ 4.0 cm^2 were considered to be measurable disease. Lesions with products of perpendicular diameters between 1.0 cm^2 and 4.0 cm^2, were considered to be evaluable, but not measurable disease. These lesions were documented in the baseline lesion tabulation for reference.

The MIRROR2 Panel, convened to assess long-term responders, identified six patients for whom an earlier response assignment of progressive disease was made in error by them. In each case, the MIRROR2 Panel members re-classified the patient as a responder at later assessment time points. In addition, the MIRROR2 Panel identified three patients without measurable disease, but with evaluable disease, at baseline. Each of the three patients was eligible based on the protocol entry criteria in use at the time of their enrollment and each patient had all lesions decrease to <1 x 1 cm^2.

E: Analyses of the Long-term Responder Subpopulation

1. The data set was generated from a retrospectively identified population across studies. These studies initially relied on investigator assessment for efficacy/activity outcomes and all relied on investigators' discretion for the intensity and degree of follow-up. Investigators at two of the study sites, Michigan and Stanford, had reportable financial and other arrangements with the sponsor and also accounted for a disproportionate percentage of the patients enrolled. As in the major efficacy study, the impact of investigator/site on the study outcome was assessed. The following table summarizes the long-term responder population according to investigational site.

Long-term Responders by Study Site

Study Site	# of patients with long-term PR	# of patients with long-term CCR	# of patients with long-term CR	# of Long-term Responders (% of 78)	Total # of patients Enrolled (% of 271)
Michigan	6	13	4	23 (29%)	101(37%)
Stanford	6	2	7	15 (15%)	33 (12%)
All Other Sites	6	15	19	40 (51%)	137 (51%)

FDA conclusion: There does not appear to be bias in terms of over-representation of long-term responders from sites with financial or other potential conflicts of interest.

2. Assessment of the baseline characteristics.
The baseline entry characteristics of the sponsor defined long-term responder population and FDA derived long-term responder population (i.e. excluding the 2 patients agreed upon as exclusions with the sponsor and the eight multidose patients as described above in the section entitled "Study Population in the Long-Term Responder Data Set") are summarized in the following table:

Baseline Study Entry Characteristics	Sponsor-specified	FDA-specified
N	78	68
Age (Years) Median Range	 52 (23-82)	 53 (23-82)
Gender Male/Female % Male	 46/32 59 %	 41/27 60%
Histology Grade at study entry Low N (%) Transformed N (%)	 61 (78 %) 17 (22%)	 54 (79%) 14 (21%)
Tumor grade at the study entry Low N(%) Intermediate N (%)	 65 (83%) 13 (17%)	 58 (85%) 10 (15%)
Time from diagnosis to study entry, Median in years, (range)	3.5 (0.7, 22)	3.5 (0.7, 22)
Median number of prior chemo therapies (range)	3 (1,8)	3 (1,6)
Stage III/IV disease at entry	69 (88%)	61 (90%)
Bulky disease (>500 g)	**13/77 = 17%**	**11/67 = 16%**
Modified IPI Score 0-1 2 3 4-5	 26/77 (34%) 32/77 (42%) 16/77 (21%) 3/77 (4%)	 19/67 (28%) 30/67 (45%) 15/67 (22%) 3/67 (4%)

No. of prior chemotherapies		
Median	3	3
Q1	2	2
Q3	4	4
Min	1	1
Max	8	6
Response to last chemotherapy		
Response (CR+CCR+PR)	53/76 (70%)	48/66 (73%)
Complete Resp. (CR+CCR)	27/76 (36%)	23/66 (35%)
Last qualifying chemotherapy end day to study day (years)		
Median	1.1	1.1
Range	(0.1, 5.4)	(0.1, 5.4)

3. Assessment of the baseline characteristics of long-term responders vs. transient/non-responders

FDA assessed the baseline entry characteristics of this subset population and contrasted it with the patients enrolled in the same 5 studies who did not achieve long-term responses. In addition, FDA conducted a logistic regression analysis to assess for baseline entry characteristics that correlated with long-term response. FDA identified a series of baseline variables to be investigated likely to be of prognostic importance for long-term response. A stepwise selection using PROC LOGISTIC in SAS was used to identify the prognostic factors for durable response. A significance level of 0.25 was used to allow a baseline variable into the model and a significance level of 0.30 was used to allow a baseline variable to stay in the model. The only baseline variables that entered into the model significantly were tumor grade at the study entry (GRADEE), Investigator assessed response to last qualifying chemotherapy (LQRESP), duration of response to last qualifying chemotherapy (LQDUR), time interval between the last qualifying chemotherapy regimen and study day (LQCEDAY) and number of prior chemotherapy regimens. The results across the 5 studies for the long-term responder population, various subsets, and for the patients without long-term responses are displayed in the table shown below.

Other baseline variables such as age, sex, IPI category, study day of diagnosis of NHL, maximum uni-dimensional lesion measurement (cm) at baseline, Ann Arbor stage at study entry, number of prior chemotherapy received, duration of response to first chemotherapy, etc. did not enter into the model (all p-values >= 0.25).
As can be seen in the following table, compared to patients without long-term response, the long-term responder patients have a lower tumor grade at study entry and a higher and longer response to last qualifying chemotherapy. More importantly, the long term responders had a median of 1.1 year elapsed time between the end of their last qualifying chemotherapy and study entry, compared to 0.4 years for the rest of the group. How much of this observation can be explained by the duration of response to the last chemotherapy, will need to be further explored and updated to the ODAC. Either way, this observation perhaps implies a more indolent disease in this group of patients, either because they had a longer duration of response to their last chemotherapy, and/or that a lack of urgency was shown in their treatment after the end of their last chemotherapy.

Table: Durable Response Analysis

Characteristic	Non-durable Response-Sponsor ISE Pop	Non-durable Response-FDA ISE Pop	Durable Response Sponsor	Eligible Durable Response Sponsor	Single Dose Durable Responders FDA	Multiple Dose Durable Responders FDA
N	193	203	78	76	68	8
Response						
CR (%)	13 (7%)	13 (6%)	30 (38%)	30 (39%)	30 (44%)	
CCR (%)	2 (1%)	8 (4%)	30 (38%)	28 (37%)	24 (35%)	4 (50%)
PR (%)	49 (25%)	53 (26%)	18 (23%)	18 (24%)	14 (21%)	4 (50%)
ORR (%)	64 (33%)	74 (36%)	78	76	68	8
Response Duration						
Median (Years)	0.4	0.5	4.9	4.9	4.9	1.5
95% CI	(0.3, 0.6)	(0.4, 0.7)	(3.0, ---)	(3.0, ---)	(3.4, ---)	(0.9, ---)
Q1	0.3	0.3	1.2	1.3	1.6	1.0
Q3	0.7	0.8	---	---	---	---
Min	0.1+	0.1+	0.9	0.9	0.9	0.9
Max	1.4	7.8+	7.8+	7.8+	7.0+	7.8+
Tumor grade at the study entry						
Low	123 (64%)	130 (64%)	65 (83%)	65 (86%)	58 (85%)	7 (88%)
Intermediate	65 (34%)	68 (33%)	13 (17%)	11 (14%)	10 (15%)	1 (13%)
High	5 (3%)	5 (2%)				
Response to last qualifying chemotherapy (investigator)						
CR	22 (11%)	26 (13%)	25 (32%)	24 (32%)	21 (31%)	3 (38%)
CCR	4 (2%)	4 (2%)	2 (3%)	2 (3%)	2 (3%)	
PR	61 (32%)	62 (31%)	26 (33%)	26 (34%)	25 (37%)	1 (13%)
Duration of response to last qualifying chemotherapy						
Median (Years)	0.4	0.4	0.6	0.6	0.6	0.8
95% CI	(0.3, 0.5)	((0.3, 0.5)	(0.5, 0.9)	(0.5, 0.9)	(0.5, 0.9)	(0.1, ...)
Q1	0.2	0.2	0.4	0.4	0.4	0.3
Q3	0.7	0.7	1.0	1.0	1.0	2.0
Min	0.1	0.1	0	0	0	0.1
Max	3.0	3.0	4.5	4.5	4.5	2.0
Number of prior chemotherapies						
Median	3	3	3	3	3	3
Q1	2	2	2	2	2	2
Q3	5	5	4	4	4	4
Min	1	1	1	1	1	1
Max	13	13	8	8	6	8
Last qualifying chemotherapy end day to study day						
Median (Years)	0.4	0.4	1.1	1.1	1.0	1.2
95% CI	(0.4, 0.6)	(0.4,0.6)	(0.8, 1.2)	(0.9, 1.2)	(0.8, 1.2)	(0.3, 1.8)
Q1	0.2	0.2	0.5	0.5	0.5	0.5
Q3	1.0	1.0	1.6	1.6	1.6	1.8
Min	0	0	0.1	0.1	0.1	0.3
Max	9.3	9.3	5.4	5.4	5.4	2.4

4. Assessment of response to chemotherapy as a predictor of response to the tositumomab therapeutic regimen

The following table displays the results of an analysis of the effect of the response to the last qualifying chemotherapy on the duration of response seen to the tositumomab therapeutic regimen. Among patients with long-term responses, there is no significant difference in response rate in patients who responded to the last qualifying chemotherapy as compared to those who did not (McNemar's test) and, despite the observed differences in median durations of response, there are no statistically significant differences in the durations of responses, as a function of response to last chemotherapy [p-value on duration of response to the tositumomab therapeutic regimen according to response to prior chemo (log-rank, p = 0.4401; Wilcoxon p= 0.3338)].

Efficacy Outcome	Patients without long-term responses Sponsor (271-78)	Patients without long-term responses FDA (271-78)	Long-term Responders Per Corixa	Agreed upon Long-term Responders	Single Dose Long-term Responders	Multiple Dose Long-term Responders
Number of subjects	n=193	N=203	n=78	n=76	n=68	n=8
Response CR (%) CCR (%) PR (%)	 13 (7%) 2 (1%) 49 (25%)	 13 (6%) 8 (4%) 53 (26%)	 30 (38%) 30 (38%) 18 (23%)	 30 (39%) 28 (37%) 18 (24%)	 30 (44%) 24 (35%) 14 (21%)	 4 (50%) 4 (50%)
ORR (%)	64 (33%)	74 (36%)	78	76	68	8
Response Duration (yrs) Median 95% CI Q1 Q3 Min Max	 0.4 (0.3, 0.6) 0.3 0.7 (0.1+ 1.4	 0.5 (0.4, 0.7) 0.3 0.8 0.1+ 7.8+	 4.9 (3.0, ---) 1.2 --- 0.9 7.8+	 4.9 (3.0, ---) 1.3 --- 0.9 7.8+	 4.9 (3.4, ---) 1.6 --- 0.9 7.0+	 1.5 (0.9, ---) 1.0 --- 0.9 7.8+

Relationship between last qualifying chemotherapy response and Bexaar response for CBER defined durable population

Bexaar Responses

Last Qualifying Chemotherapy Response	Count	PR	CCR	CR	Total
	Not Available	1	0	1	2
	PD	0	3	4	7
	SD	7	2	2	11
	PR	5	7	13	25
	CCR	0	0	2	2
	CR	1	12	8	21
	Total	14	24	30	68

Last Qualifying Chemotherapy (LQC) for the tositumomab long-term responders	Number of patients	Median Duration of long-term response to tositumomab therapeutic regimen
LQC-responsive (CR, CCR, or PR)	48/68 (71%)	4.9 years
LQC non-responsive (PD OR SD)	20/68 (29%)	3.9 years

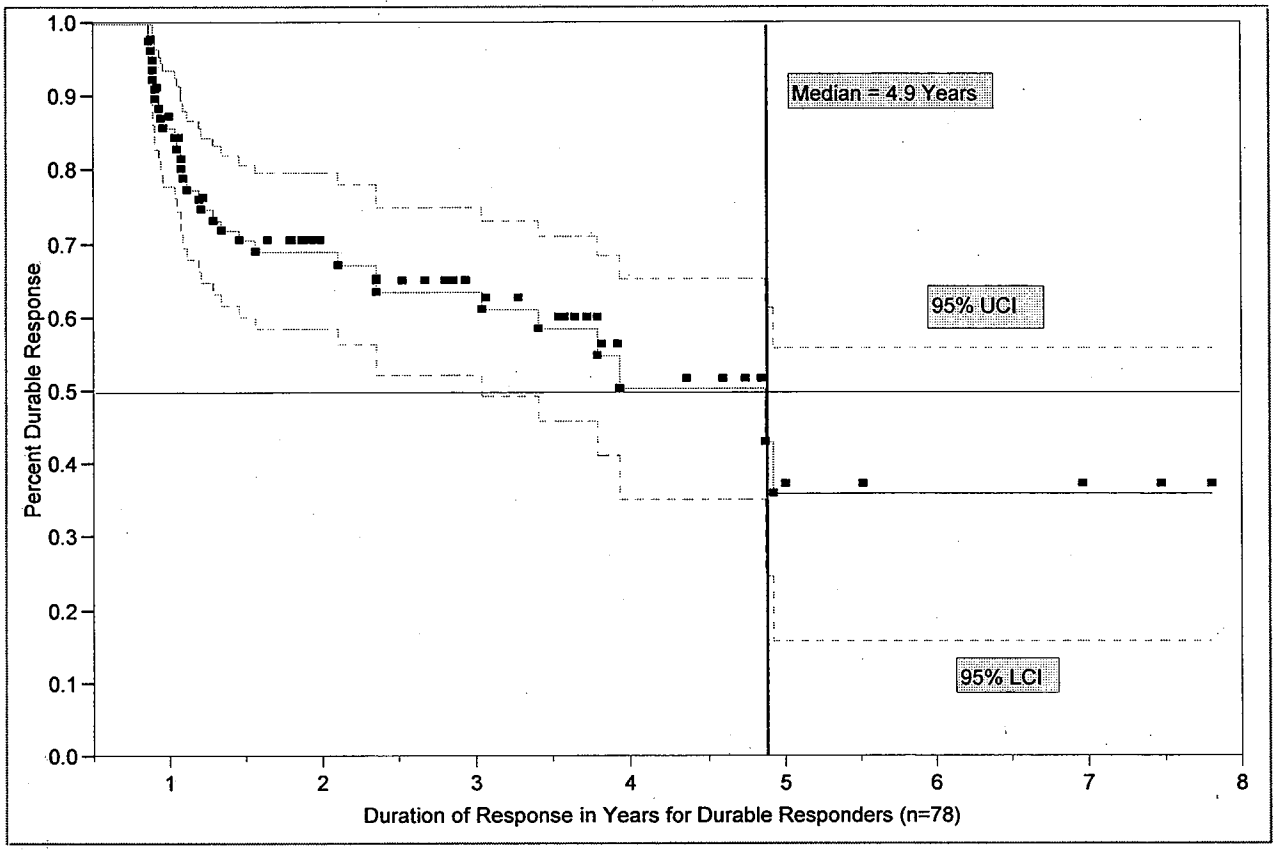
5. Assessment of the efficacy outcomes in long-term responders vs. transient or non-responding patients.

Further analysis across the same 5 studies was done on the efficacy data for the long-term responder population as identified by the sponsor and various subsets of the population as well as the efficacy results from the subset of patients who did not achieve a long-term response (193 patients, i.e., 271 patients [total enrollment in RIT-II-000, 001, 002, 004, CP 97-012] minus the 78 long-term responders). The data are summarized in a tabular form below:

As shown, the long-term responder subset constitutes the majority of the responding patients across these studiesThe median duration of response for all patients across all the studies was approximately one year (ISE data on 271 patients).

6. Duration of response over time (graphical display).

The following graph displays the duration of response for the long-term responder subset. The slope of the curve changes and may indicate the presence of two subpopulations within this single subset. In the period of time between 1 year and 18 months, there is a sharp decrease in the number of responding patients whereas beyond 18 months, the curve is less steep. The "tail" on the curve that begins at 18 months may represent a different and distinctive patient population with a more favorable outcome. Without an internal control, it is difficult, if not impossible, to determine whether the effect seen (long-term responses) is attributable to the Bexxar therapeutic regimen or is the result of retrospective selection of a subset of patients who would have behaved similarly regardless of the treatment.



Additional Review Comments:

The retrospective manner in which the long-term responder population was identified and the duration of response assessed, impinges on the robustness of the findings. Retrospective judgment passed on lesions with the benefit of hindsight may not represent the real time clinical decision-making process regarding whether further treatment is truly contemplated in this indolent lymphoma population. Following the FDA review of long-term responder population, teleconferences were conducted between the FDA reviewers and the sponsor on 10/24/02 and 11/7/02 regarding 17 patients that the FDA reviewers did not feel confident in endorsing the assessment provided by the sponsors. As stated above, the sponsor agreed to remove two patients from the durable response population, bringing the total number of patients in this group to 76.

Transformed Low-Grade NHL

At the initiation of the major efficacy trial (RIT-II-004) FDA informed the sponsor, in the End-of-Phase 2 meeting and in subsequent correspondence, that extending the efficacy date obtained in the treatment of patients with low grade and follicular NHL without evidence of transformation to the treatment of patients with NHL with transformation to a higher grade histology may not be appropriate. The sponsor was asked to provide a justification for pooling the results from these two populations. In addition, the sponsor was informed that subset analyses should be conducted in patients with and without evidence of transformation. At the conclusion of RIT-II-004, the results of the subset analyses showed a marked difference in the response rates in the two subsets (62% vs. 21%). Based on a demonstration of durable responses in patients with low grade and follicular NHL with transformation, recurrent after combination chemotherapy, the sponsor requested Fast Track designation and received for treatment of patients with transformed NHL, that was recurrent or refractory to standard chemotherapy. FDA asked the sponsor to supplement the data from RIT-II-004, which enrolled 23 patients with transformed NHL. The sponsor identified a total of 71 patients with a diagnosis of transformed NHL at the time of study entry who were enrolled in the 4 activity/efficacy trials conducted by the sponsor.

The integrated efficacy analyses of the transformed low-grade NHL patient population include data on the 78 patients who had a diagnosis of transformed low-grade NHL at some point prior to study entry and who received study drug in the 4 studies (RIT-I-000, RIT-II-001, RIT-II-002, and RIT-II-004). In order to be included in the dataset, FDA stated that the histologic diagnosis be confirmed for each subject. Central pathologic review was conducted by Dr. Charles Ross at the University of Michigan of 60 patients with a diagnosis of transformed NHL who were enrolled in studies RTI-I-000, RIT-II-001, RIT-II-002, and RIT-II-004. Dr.Elaine Jaffe performed central pathologic review for 12 patients a diagnosis of transformed NHL who were enrolled in study CP 97-012.

The independent (MIRROR) panel conducted a retrospective review of the clinical data to establish the response rates and duration for this subpopulation.

FDA conducted a review of the information in the case report forms, pathology reports (initial and central review) and the central pathologic review process for the 60 patients who were centrally reviewed at the University of Michigan. FDA has not yet completed its review of the information and central pathologic review process for those subjects assessed by Dr. Jaffe. This report will cover the review of the 60 patients and an updated report on all 72 subjects will be provided as supplemental information and presented at the Dec. 17, 2002 ODAC meeting.

Among the 60 patients reviewed, FDA determined that a diagnosis of low grade NHL with evidence of histologic transformation could be documented for 42 patients. Biopsy material was available for central pathological review at all critical timepoints for each of these 42 patients. There were 31 patients in whom low grade NHL was documented histologically at the time of original diagnosis and intermediate grade NHL was documented histologically at a later time; both diagnoses were confirmed by the central pathologist. There were 11 patients in whom lymphoma with transformed features (low grade and intermediate grade) was documented histologically at the time of diagnosis and confirmed by the central pathologist.

FDA believes that the remaining 18 should be excluded from analysis of the transformed subpopulation due to inability to confirm the pathologic diagnosis. The reasons for exclusion from the dataset are listed in the table below. For most of these 18 patients, the pathologic material (slides) was not available or was inadequate at one or more critical times. In three of the patients where the slides were available for central review, the central reviewing pathologist disagreed with the diagnosis of transformation.

Classification of Transformed Lymphomas From the Transformed Dataset

Reason for exclusion from the subpopulation	Number of patients excluded
Original histological diagnosis of NHL not documented. Transformed (low grade and intermediate grade) documented histologically at a later time.	7
Low grade NHL documented histologically at the time of original diagnosis. Transformation diagnosed by pathologist at a later time, but diagnosis of transformation not upheld by central pathologist.	3
Transformation diagnosed at time of original diagnosis, but slides not available for central pathologic review. Subsequent biopsy(s) show low grade NHL.	1
Insufficient pathologic material for central pathologist to diagnose low grade lymphoma. No material submitted to support diagnosis of transformation.	1
Low grade NHL documented histologically at the time of original diagnosis. Slides documenting transformation not available for central review.	1
Slides documenting original diagnosis of low grade NHL not available for central review. Slides documenting histologic transformation not available for central review. (1 case)	1
No transformation of NHL diagnosed at either original biopsy, or on any subsequent biopsies.	1
Original diagnosis of transformation not documented. Slides not available. No evidence of pre-existing low grade lymphoma. (1 case)	1
Histologic subtype of NHL does not Eligibility Criteria and diagnosis of transformation not upheld by central pathologist.	1
Histologic subtype of NHL does not meet Eligibility Criteria and no transformation diagnosed either at original biopsy or any subsequent biopsies.	1
TOTAL	18

Among the 42 patients, with adequate information to confirm the diagnosis, there were two patients who had been enrolled in single patient IND trials. The sponsor has provided minimal data and has not audited the clinical data for these two patients. These two patients have been excluded from the FDA confirmed group because there was insufficient clinical information to conduct analyses and the quality of the data available are unknown. The baseline entry characteristics for the remaining 40 patients are summarized in the following table.

Baseline Entry Characteristics	Sponsor Identified*	FDA Confirmed
N	**71**	**40**
Age (Years)		
Median	59	58
Range	(37, 80)	(37, 80)
Gender		
Male (% male)	41 (58%)	23 (58%)
Median time from diagnosis to study entry (years) (range)	6.2 (0.7, 27.8)	5.0 (0.7, 27.8)
Median time from diagnosis to transformation date (years) (range)	1.8 (-0.3, 10.3)	1.9 (0.02, 9.9)
Median time from transformation to study entry (years) (range)	3.4 (0, 24.5)	3.3 (0, 24.5)
Ann Arbor Stage at entry		
1	1 (1%)	1 (2%)
2	7 (10%)	1 (2%)
3	17 (24%)	11 (28%)
4	46 (65%)	27 (68%)
Modified IPI Score	(n = 67)	(n = 38)
0-1	9 (13%)	2 (5%)
2	23 (34%)	14 (37%)
3	23 (34%	16 (42%
4-5	12 (18%)	6 (16%)
Number of prior chemotherapies	4	4
Median	(3, 5)	(3, 5)
IQ	(1, 11)	(1, 9)
Range		
Maximum unidimensional lesion measurement (cm)		
0 to ≤5 cm	24 (34%)	12 (30%)
>5 to ≤10 cm	34 (48%)	20 (50%)
> 10 cm	13 (18%)	8 (20%)
Response to last chemotherapy	35 (49%)	22 (55%)
Response (CR+CCR+PR)	16 (23%)	10 (25%)
Complete Response (CR+CCR)		
Tumor grade at the study entry		
Low	9 (13%)	2 (5%)
Intermediate	59 (83%)	35 (88%)
High	3 (4%)	3 (8%)
Last qualifying chemotherapy end day to study day (yrs)	(n = 66)	(n = 35)
Median	0.5	0.5
Range	(0.1, 5.4)	(0.1, 3.1)

Most of the baseline data for these patients is typical for patients with transformed disease. Such patients have had multiple courses of chemotherapy (median 4). Transformation is often suspected clinically when a patient with known lymphoma presents with a rapidly enlarging node, so the presence of nodes greater than 7 cm in 40% of the FDA confirmed study patients is not surprising.

An atypical statistic in this group is the median time from transformation until study entry, which was 3.3 years (range of 0 to 24.5). The literature states that transformed low grade NHL has a poor prognosis, with a median survival of less than one year after transformation. Yuan, et al (JCO 13:1726, 1995) described a group of patients with histologic transformation who had a median survival duration of 81 months after transformation. The predictors of good survival in this study were lack of prior chemotherapy, complete response to chemotherapy after transformation and limited disease. Such factors are not present in the FDA confirmed patients, who, as mentioned above, have had a median of 4 chemotherapy regimens, did not tend to have limited disease, and were less likely to have had a complete response to chemotherapy once they transformed. The implication is that the transformed patients who received iodine ^{131}I tositumomab had already demonstrated a tendency towards a favorable natural history.

Analyses of Baseline Entry Characteristics

FDA performed an analysis of the baseline entry characteristics (as variables) that were associated with a diagnosis of transformed disease. A stepwise selection using PROC LOGISTIC in SAS was used to identify the variables associated with patients who had a diagnosis of transformed disease. A significance level of 0.10 was used to allow a baseline variable into the model and a significance level of 0.15, was used to allow a baseline variable to stay in the model. The baseline variables that entered into the model significantly were tumor grade at the study entry (GRADEE), days between the last qualifying chemotherapy regiment and study day (LQCEDAY), number of prior chemotherapy and Ann Arbor Stage at study entry. Other baseline variables such as age, sex, IPI category, study day of diagnosis of NHL, maximum unidimensional lesion measurement (cm) at baseline, Ann Arbor stage at study entry, number of prior chemotherapy received, duration of response to first chemotherapy, etc. did not enter into the model (all p-values >= 0.25).
The following table summarizes the baseline entry characteristics of the 271 patients enrolled in the 5 efficacy/activity studies, according to the presence or absence of a reported pathologic diagnosis of histologic transformation.

Baseline Entry Characteristics	Non-transformed-ISE Pop	Transformed Population - Sponsor	Transformed Population - FDA
N	200	71	40
Tumor grade at the study entry			
Low	179 (89%)	9 (13%)	2 (5%)
Intermediate	19 (10%)	59 (83%)	35 (88%)
High	2 (1%)	3 (4%)	3 (8%)
Ann Arbor Stage at the study entry			
1	3 (2%)	1 (1%)	1 (3%)
2	17 (9%)	7 (10%)	1 (3%)
3	41 (21%)	17 (24%)	11 (28%)
4	139 (70%)	46 (65%)	27 (68%)
Response to last qualifying chemotherapy (investigator)			
CR	32 (16%)	15 (21%)	9 (23%)
CCR	5 (3%)	1 (1%)	1 (3%)
PR	68 (34%)	19 (27%)	12 (30%)
ORR	105 (53%)	35 (49%)	22 (55%)
Duration of response to last qualifying chemotherapy (years)			
Median (Years)	0.5	0.4	0.3
95% CI	(0.4, 0.6)	(0.2, 0.6)	(0.2, 0.5)
IQ Range	(0.2, 0.9)	(0.2, 0.7)	(0.2, 0.6)
Range	(0.1, 4.5)	(0.0, 2.2)	(0.1, 1.3)
Number of prior chemotherapies			
Median	3	4	4
IQ Range	(2, 4)	(3, 5)	(3, 5)
Range	(1, 13)	(1, 11)	(1, 9)
Last qualifying chemotherapy end day to study day (years)			
Median	0.6	0.5	0.5
95% CI	(0.4, 0.8)	(0.4, 0.7)	(0.3, 0.7)
IQ Range	(0.3, 1.2)	(0.3, 1.1)	(0.3, 1.0)
Range	(0.01, 9.3)	(0.01, 5.4)	(0.1, 3.1)

Efficacy Outcomes and Analyses

The pooled efficacy outcomes (response rates and durations) are provided for the subpopulations of the 271 patients enrolled in the 5 efficacy/activity studies, according to sponsor-reported histologic diagnosis (without [n=200] and with [n=71] evidence of histologic transformation) and in the subset of patients where FDA confirmed that there were adequate evidence to establish a diagnosis of transformed histology on central pathologic review (n=40). The outcome measures are summarized in the following table

Outcome Measures	Non-transformed-ISE Pop	Transformed Population - Sponsor	Transformed Population - FDA
N	196*	71	40
Response		(n=71)	(n=40)
CR (%)	36 (18%)	7 (10%)	3 (8%)
CCR (%)	21 (11%)	11 (15%)	7 (18%)
PR (%)	57 (29%)	10 (14%)	6 (15%)
ORR (%)	114 (58%)	28 (39%)	16 (40%)
Response Duration			
Median (Years)	1.0	1.2	1.6
95% CI	(0.8, 1.5)	(0.9, 3.4)	(0.6, ---)
IQ Range	(0.4, ---)	(0.8, 3.4)	(0.7, 3.4)
Range	(0.1, 7.8+)	(0.1+, 4.9)	(0.1+, 4.9)

* Data not available for 4 of the 200 patients identified by sponsor as without histologic transformation

The response rates for the FDA-confirmed population were 8% CR, 18% CCR (combined CR rate 26%), and 15% PR, for an overall response rate of 41%. The median duration of response to iodine ^{131}I tositumomab was 1.6 years (range: 0.1—4.9 years). While these are impressive responses for patients with transformed NHL, the prolonged median survival after transformation and before study entry needs to be taken into account.

FDA conducted an analysis to assess whether there were predictors of response to iodine ^{131}I tositumomab in this subpopulation. The results of the analysis of the relationship between response to last qualifying chemotherapy and response to iodine ^{131}I tositumomab in the FDA confirmed transformed subpopulation is summarized in the table below.

		Overall Response (ORR = CR+CCR+PR) to iodine ^{131}I tositumomab		
Last Qualifying Chemotherapy Overall Response (ORR = CR+CCR+PR)		Yes	No	Total
	Yes	11	11	22
	No	5	13	18
	Total	16	24	40

There were 11 of 22 (50%) patients responding to chemotherapy and 5 of 18 (28%) who did not respond to chemotherapy who achieved a response to the iodine ^{131}I tositumomab regimen. There is no significant difference in the overall response rates following the last qualifying chemotherapy regimen and ORR following the iodine ^{131}I tositumomab regimen in the FDA-confirmed transformed population (p-value using two-sided McNemar's test for paired samples = 0.2101).

Integrated Summary of Safety

Description of the Safety Population

The sponsor has submitted demographic information on 836 patients enrolled in the 5 clinical efficacy/activity trials and additional experience in expanded access studies. Safety data are provided for 620 patients enrolled in the 5 clinical efficacy/activity trials and interim data from the expanded access experience. FDA has chosen to conduct analyses primarily in the data derived from 229 of the 284 patients enrolled 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.

Protocol	Number of Patients Enrolled [a]	# ISE	# ISS-A	# ISS-B	Total ISS	Explanation of the Differences in the Number of Patients	Data cutoff	Dates of accrual
RIT-I-000	59	59	22	0	22	Excludes 37 patients who received total body doses other than 65 or 75 cGy	Dec. 1, 2000	4/1990 - 1/1996
RIT-II-001	47	47	47	0	47		Dec. 1, 2000	12/1995 - 11/1996
RIT-II-002	42+36 +19	42 + 19	42 + 19	0	61	Excludes 17 patients who only received tositumomab	Jan. 17, 2001	9/1996 - 1/2000
RIT-II-004	61	61	59	0	59	Excludes 1 patient with Mantle Cell NHL	Jan. 31, 2001	11/1996 - 3/1998
CP-97-012	43	43	40	0	40	Excludes 3 patients who did not get any dose	Dec. 17, 2000	7/1998 -
CP-98-020	464	0	0	387	387			
Single Patient	6	0	0	4	4			
Total	854	271	229	391	620			

[a] Number of patients receiving Bexxar therapeutic regimen as of August 31 2000.

Study population for Integrated Summary of Safety

The baseline entry characteristics for the safety database are summarized below according to type of study (activity/efficacy vs. expanded access) for the 620 patients for whom safety data were provided. All studies enrolled patients with a diagnosis of follicular and/or low-grade non-Hodgkin's lymphoma, with or without transformation to a higher grade histology, which had recurred after at least one prior cytotoxic chemotherapy regimen. The baseline entry characteristics of the two groups are generally similar, although those enrolled in the efficacy/activity studies were more heavily pretreated and had a higher proportion of intermediate grade histology and tumors with histologic transformation.

Baseline Entry Characteristics of ISS database according to type of Study		
	ISS-audited studies (n=271)	ISS-expanded access (n=393)
Age (years)		
Median(range)	55 (23-82)	58 (29-88)
Q1; Q3	46; 64	50; 67
Gender		
Males (%)	60%	53%
Race		
Caucasian (%)	92%	93%
Histologic diagnosis at entry		
W/o transformation	199 (73%)	313 (80%)
Low grade	178 (66%)	313 (80%)
Intermediate grade	19 (7%)	0
High grade	2 (<1%)	0
With transformation	72 (27%%)	80 (20%)
Low grade	10 (4%)	3 (1%)
Intermediate grade	59 (22%)	74 (19%)
High grade	3 (1%)	3 (1%)
Stage of disease		
I	4 (1%)	9 (2%)
II	24 (9%)	33 (8%)
III	58 (21%)	100 (25%)
IV	185 (68%)	250 (64%)
Missing	0	1
IPI category		
0	7 (3%)	10 (3%)
1	48 (18%)	27 (7%)
2	103 (38%)	114 (29%)
3	76 (28%)	157 (40%)
4	24 (9%)	50 (13%)
5	2 (1%)	1 (0.3%)
Missing	11 (4%)	34 (9%)
Max. tumor diam		
< 5 cm	153 (56%)	393 (100%)
≥ 5, ≤10 cm	95 (35%)	0
> 10 cm	23 (9%)	0
# Prior chemo regimens		
Median (range)	3 (1-13)	2 (1-10)
25^{th}, 75^{th} quartiles	2, 4	1, 3
# Prior RT regimens		
Median (range)	0 (0-7)	0 (0-1)
25^{th}, 75^{th} quartiles	0, 1	0, 0
Prior BMT	15 (6%)	2 (<1%)
Yrs from diagnosis to entry		
Median (range)	3.7 (0.5-27.8)	3.9 (0.2- 22.9)
25^{th}, 75^{th} quartiles	2.2, 6.8	2.1, 6.7

In the analysis of this application, it became apparent that there were significant amounts of missing data, in part due to a high rate of withdrawal from study, but also due to failure to collect data for patients who remained alive for analysis of survival. In an attempt to identify a subset of subjects with complete information for hematologic toxicity, the dose-limiting toxicity associated with Bexxar therapeutic regimen, FDA initially requested that the sponsor attempt to collect all possible information through a review of the primary medical records and to collect additional safety data from ongoing studies. In response, the sponsor submitted a safety database containing additional data from studies RIT-II-002, CP97-012, and CP98-020.

In review of this dataset, FDA determined that there were even greater amounts of missing information particularly for the patients who were enrolled in the expanded access protocol (CP 98-020). The proportion of patients in the expanded access experience with missing data for hematologic toxicity through the period at risk (weeks 5-9) and for documentation of recovery from hematologic toxicity (week 13) was higher than in the other studies. In addition, there were insufficient numbers of patients followed beyond 4 months post-treatment to permit accurate assessments of prolonged and persistent hematologic toxicity. There was also evidence of lack of reporting of non-hematologic adverse events. Specifically, the proportion of patients in whom any adverse events was reported in the aggregate, the proportion of patients with adverse events within organ system (e.g., GI, respiratory), and the number of adverse events per patient was lower in the expanded access dataset as compared to the efficacy/activity studies. Of note, the sponsor has not audited any of the study sites participating in the expanded access study or in sponsor-investigator studies/single patient INDs. Because of the concerns with regard to under-reporting of the adverse events, the data from CP 98-020 has not been included in the ISS with the following exceptions: Serious adverse events are included in the ISS and analysis presented as time to event data (development of HAMA seropositivity, development of hypothyroidism, development of myelodysplasia and/or secondary leukemia) include data from CP98-020.

Adverse Events- Overall

Ninety-five percent of the patients enrolled in the efficacy activity studies experienced one or more adverse events. The most common toxicities of any severity as well as the most common severe (NCI grade 3-4) toxicities were neutropenia, thrombocytopenia, and anemia. The hematologic toxicity will be presented as a separate section. The most common non-hematologic adverse events were asthenia, fever and chills, gastrointestinal toxicities (nausea, vomiting, anorexia, and diarrhea), musculoskeletal (myalgias, arthralgias), pain (unspecified and abdominal pain), headache, and rash. The most common serious adverse events were infections and second malignancies. Separate discussion will be provided for the following categories of adverse events: hematologic, infection, hemorrhagic events, infusion-related, gastrointestinal, hypersensitivity, thyroid, immune responses (HAMA), MDS and second malignancies.

Per-Patient Incidence of Adverse Events Occurring in ≥5% of Subjects (N=229)

AE PREFER NAME	Any Grd	Grd III/IV
Body as a Whole		
Asthenia	46%	2%
Chest Pain	7%	0%
Chills	18%	1%
Neck Pain	6%	<1%
Pain	19%	1%
Cardiovascular		
Vasodilatation	5%	0%
Gastrointestinal		
Nausea	35%	3%
Constipation	6%	<1%
Metabolic		
Weight Loss	6%	<1%
Musculoskeletal		
Arthralgia	10%	1%
Nervous System		
Somnolence	5%	0%
Respiratory		
Pneumonia	5%	2%
Skin		
Rash	17%	<1%
Sweating	8%	<1%

Occurrence of Adverse Events from the day of dosimetric dose

ISS-A patients (n= 229)

Median Number of days = 19
IQ Range = (7, 51)
90^{th} percentile = 78 days
Range in days (-33, 2819)

All patients (n=620)

Median Number of days = 17
IQ Range = (8, 47)
90^{th} percentile = 72 days
Range in days (-33, 2819)

Per-patient incidence of potential allergic reactions- Allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus & serum sickness.

Number of Patients with AE All n=620	23	
Number of AEs in All n=620	24	
Number of Patients with AE ISS-A n=229	14	
Number of AEs in ISS-A n=229	14	
90^{th} percentile for duration of grade 3 or 4 ANC	**ISS-A (ISE)**	**62**
	All	**58**
90^{th} percentile for duration of grade 3 or 4 platelet	**ISS-A (ISE)**	**102**
	All	**89**
90^{th} percentile for duration of grade 3 or 4 hemoglobin	**ISS-A (ISE)**	**40**
	All	**43**

Indusial AEs in the first 7 days

Fever, Asthenia, Nausea, Pain, Chills, Pruritus, Rash, Pharyngitis, Rhinitis, Headache, Cough increased, Diarrhea, Vomiting, Hypotension, Vasodilatation, Artharalgia, injection site reaction, Urticaria, Myalgia

Study	ISS-A	ISS-B
# Patients	229	391
# Patients experiencing any of the above reactions	125	86
% Patient experiencing any of the above reactions	55%	22%
Total number of events	309	169

# of Events	# of Patients experiencing these events	
	ISS-A	ISS-B
9	1	0
8	4	1
6	2	1
5	4	4
4	15	5
3	24	12
2	29	16
1	46	47

Indusial AEs in the 8-14 days

Nausea, Asthenia, Fever, Chills, Vomiting, Anorexia, Headache, Cough increased, Pain, Rash, Diarrhea, Myalgia, Pruritus, Artharalgia, Hypotension, Sweating, Dyspnea, Urticaria, Asthma, Vasodilatation,

Study	ISS-A	ISS-B
# Patients	229	391
# Patients experiencing any of the above reactions	105	105
% Patient experiencing any of the above reactions	46%	27%
Total number of events	222	246

# of Events	# of Patients experiencing these events	
	ISS-A	ISS-B
10	1	0
9	0	1
8	1	0
7	1	4
6	2	4
5	2	3
4	9	11
3	11	10
2	28	24
1	50	48

Per-patient incidence of
Infusion-related (Study days 0-2) Adverse Events

Costart Preferred Term	All Grades N=229
FEVER	39 (17%)
NAUSEA	17 (7%)
PRURITUS	17 (7%)
CHILLS	16 (7%)
ASTHENIA	15 (7%)
RASH	13 (6%)
PAIN	12 (5%)
HEADACHE	11 (5%)
PHARYNGITIS	11 (5%)
RHINITIS	10 (4%)
HYPOTENSION	8 (3%)
VOMITING	8 (3%)
VASODILATATION	7 (3%)
CHEST PAIN	6 (3%)
COUGH INCREASED	6 (3%)
BACK PAIN	5 (2%)
DIARRHEA	5 (2%)
ARTHRALGIA	4 (<2%)

AEs for patients within first two days of the dosimetric dose

PREFER AEs First 2 Days	N Patients first 2 days ISS-A n=229	N Events first 2 days ISS-A n=229	N Patients first 2 days ISS-B n=391	N Events first 2 days ISS-B n=391	N Patients first 2 days ISS n=620	N Events first 2 days ISS n=620
FEVER	39	42	9	9	48	51
NAUSEA	17	17	12	12	29	29
PRURITUS	17	18	15	15	32	33
CHILLS	16	20	14	17	30	37
ASTHENIA	15	15	5	5	20	20
RASH	13	14	9	9	22	23
PAIN	12	14	12	12	24	26
HEADACHE	11	11	4	4	15	15
PHARYNGITIS	11	11	3	3	14	14
RHINITIS	10	12	8	8	18	20
HYPOTENSION	8	8	5	5	13	13
VOMITING	8	8	7	7	15	15
VASODILATATION	7	7	4	5	11	12
CHEST PAIN	6	8	6	6	12	14
COUGH INCREASED	6	6	4	4	10	10
BACK PAIN	5	5			5	5
DIARRHEA	5	5	2	2	7	7
ARTHRALGIA	4	4	3	5	7	9
INFECTION	4	4	1	1	5	5
SOMNOLENCE	4	4	1	1	5	5
URTICARIA	4	4	9	9	13	13
ABDOMINAL PAIN	3	4	6	6	9	10
ASTHMA	3	3			3	3
DYSPEPSIA	3	3	1	1	4	4
DYSPNEA	3	3	3	3	6	6
EDEMA	3	3	2	2	5	5
INJECTION SITE REACTION	3	3			3	3
NECK PAIN	3	3			3	3
SINUSITIS	3	3	1	1	4	4
SKIN DISORDER	3	3			3	3
SWEATING	3	3	2	2	5	5
ANOREXIA	2	2	1	1	3	3
BRONCHITIS	2	2			2	2
DIZZINESS	2	2	4	4	6	6
EAR DISORDER	2	2			2	2
ECCHYMOSIS	2	2			2	2
MYALGIA	2	2	2	2	4	4
PALPITATION	2	2			2	2
PARESTHESIA	2	2	1	1	3	3
SEPSIS	2	2			2	2
WEIGHT LOSS	2	2			2	2
ACCIDENTAL INJURY	1	1			1	1
AMNESIA	1	1			1	1

ANAPHYLACTOID REACTION	1	1			1	1
ANEMIA	1	1			1	1
ANXIETY	1	1			1	1
ATELECTASIS	1	1			1	1
CONFUSION	1	1			1	1
CONSTIPATION	1	1			1	1
DEPERSONALIZATION	1	1			1	1
DRY EYES	1	1			1	1
DRY MOUTH	1	1			1	1
DYSPHAGIA	1	1	1	1	2	2
EAR PAIN	1	1			1	1
ERUCTATION	1	1			1	1
FACE EDEMA	1	1	1	1	2	2
FLATULENCE	1	1	1	1	2	2
FLU SYNDROME	1	1	1	1	2	2
HEMORRHAGE	1	1			1	1
HYPOCHROMIC ANEMIA	1	1			1	1
INSOMNIA	1	1	1	1	2	2
LACRIMATION DISORDER	1	1			1	1
LARYNGISMUS	1	1			1	1
LUNG DISORDER	1	1			1	1
MALAISE	1	1			1	1
MIGRAINE	1	1			1	1
PARALYSIS	1	1			1	1
PELVIC PAIN	1	1			1	1
PERIPHERAL EDEMA	1	1			1	1
PNEUMONIA	1	1			1	1
POSTURAL HYPOTENSION	1	1			1	1
SERUM SICKNESS	1	1			1	1
STOMATITIS	1	1	1	1	2	2
TACHYCARDIA	1	1			1	1
TASTE PERVERSION	1	1			1	1
ULCERATIVE STOMATITIS	1	1			1	1
ALLERGIC REACTION			2	2	2	2
AMBLYOPIA			1	1	1	1
APNEA			1	1	1	1
CONJUNCTIVITIS			1	1	1	1
CREATININE INCREASED			1	1	1	1
DEHYDRATION			1	1	1	1
GUM HEMORRHAGE			1	1	1	1
HYPERTENSION			1	1	1	1
HYPERTONIA			1	1	1	1
MELENA			1	1	1	1
MYASTHENIA			1	1	1	1
NEUROPATHY			1	1	1	1
NEUTROPENIA			1	1	1	1
PHLEBITIS			1	1	1	1
SINUS BRADYCARDIA			1	1	1	1

AEs for patients in First 7 days of the dosimetric dose

PREFER AEs First 7 Days	N Patients First 7 Days ISS-A n=229	N Events First 7 Days ISS-A n=229	N Patients First 7 Days ISS-B n=391	N Events First 7 Days ISS-B n= 391	N Patients first 7 days ISS n = 620	N Events First 7 days n=620
FEVER	45	55	12	12	57	67
ASTHENIA	24	24	8	9	32	33
NAUSEA	24	24	19	19	43	43
PAIN	20	24	16	17	36	41
CHILLS	18	27	15	20	33	47
PRURITUS	17	20	16	17	33	37
RASH	16	21	10	10	26	31
PHARYNGITIS	14	15	3	3	17	18
RHINITIS	14	17	9	9	23	26
HEADACHE	12	14	5	5	17	19
COUGH INCREASED	11	11	5	5	16	16
DIARRHEA	10	11	4	4	14	15
VOMITING	10	10	9	9	19	19
HYPOTENSION	8	9	5	5	13	14
VASODILATATION	8	9	4	5	12	14
ARTHRALGIA	7	7	4	6	11	13
BACK PAIN	7	7			7	7
CHEST PAIN	7	9	7	7	14	16
DYSPEPSIA	7	7	1	1	8	8
INFECTION	7	7	2	2	9	9
ABDOMINAL PAIN	6	8	7	7	13	15
NECK PAIN	6	6			6	6
SOMNOLENCE	6	6	1	1	7	7
ANOREXIA	5	5	2	2	7	7
DYSPNEA	4	4	5	5	9	9
EDEMA	4	4	2	2	6	6
INJECTION SITE REACTION	4	4			4	4
SWEATING	4	4	5	6	9	10
URTICARIA	4	4	10	10	14	14
ASTHMA	3	3			3	3
CONSTIPATION	3	3	1	1	4	4
DIZZINESS	3	3	4	5	7	8
MYALGIA	3	3	4	4	7	7
SINUSITIS	3	3	1	1	4	4
SKIN DISORDER	3	3			3	3
ANEMIA	2	2	3	3	5	5
ANXIETY	2	2			2	2
BRONCHITIS	2	2			2	2
CONFUSION	2	2			2	2
DYSPHAGIA	2	2	1	1	3	3
EAR DISORDER	2	2			2	2
ECCHYMOSIS	2	2			2	2
HYPOCHROMIC ANEMIA	2	2			2	2

INSOMNIA	2	2	4	4	6	6
LUNG DISORDER	2	2			2	2
PALPITATION	2	2			2	2
PARESTHESIA	2	2	2	2	4	4
PELVIC PAIN	2	2			2	2
PERIPHERAL EDEMA	2	2			2	2
PNEUMONIA	2	2			2	2
POSTURAL HYPOTENSION	2	2			2	2
SEPSIS	2	2	1	1	3	3
WEIGHT LOSS	2	2			2	2
ABNORMAL VISION	1	1			1	1
ACCIDENTAL INJURY	1	1			1	1
AMNESIA	1	1			1	1
ANAPHYLACTOID REACTION	1	1			1	1
ATELECTASIS	1	1			1	1
BREAST PAIN	1	1			1	1
CELLULITIS	1	1			1	1
DEPERSONALIZATION	1	1			1	1
DIPLOPIA	1	1			1	1
DRY EYES	1	1			1	1
DRY MOUTH	1	1			1	1
EAR PAIN	1	1			1	1
ERUCTATION	1	1			1	1
FACE EDEMA	1	1	2	3	3	4
FLATULENCE	1	1	1	1	2	2
FLU SYNDROME	1	1	2	2	3	3
HEMORRHAGE	1	1			1	1
HYDRONEPHROSIS	1	1			1	1
HYPERCALCEMIA	1	1			1	1
INCREASED APPETITE	1	1			1	1
INJECTION SITE HYPERSENSITIVITY	1	1	1	1	2	2
INJECTION SITE PAIN	1	1			1	1
LACRIMATION DISORDER	1	1			1	1
LARYNGISMUS	1	1			1	1
LIVER FUNCTION TESTS ABNORMAL	1	1			1	1
LYMPHADENOPATHY	1	1			1	1
MALAISE	1	1			1	1
MIGRAINE	1	1			1	1
PARALYSIS	1	1			1	1
PERIPHERAL VASCULAR DISORDER	1	1			1	1
PNEUMOTHORAX	1	1			1	1
SERUM SICKNESS	1	1			1	1
SHOCK	1	1			1	1
SKIN ULCER	1	1			1	1
STOMATITIS	1	1	2	2	3	3
TACHYCARDIA	1	1			1	1
TASTE PERVERSION	1	1			1	1
ULCERATIVE STOMATITIS	1	1	1	1	2	2

ALLERGIC REACTION			2	2	2	2
AMBLYOPIA			1	1	1	1
APNEA			1	1	1	1
BRADYCARDIA			1	1	1	1
CONJUNCTIVITIS			1	1	1	1
CREATININE INCREASED			1	1	1	1
DEHYDRATION			1	1	1	1
GUM HEMORRHAGE			1	1	1	1
HERPES SIMPLEX			1	1	1	1
HYPERTENSION			1	1	1	1
HYPERTONIA			1	1	1	1
INTESTINAL OBSTRUCTION			1	1	1	1
MELENA			2	2	2	2
MICROCYTIC ANEMIA			1	1	1	1
MYASTHENIA			1	1	1	1
NEUROPATHY			1	1	1	1
NEUTROPENIA			1	1	1	1
PHLEBITIS			1	1	1	1
RECTAL HEMORRHAGE			1	1	1	1
SINUS BRADYCARDIA			1	1	1	1
THINKING ABNORMAL			1	1	1	1
TINNITUS			1	1	1	1
VENTRICULAR EXTRASYSTOLES			1	1	1	1

AEs for patients in 8 to 14 days of the dosimetric dose

PREFER of AE 8-14 Days	N Patients 8-14 Days ISS-A n=229	N Events 8-14 Days ISS-A n=229	N Patients 8-14 Days ISS-B n=391	N Events 8-14 Days ISS-B n=391	N Patients 8-14 Days ISS n=620	N Events 8-14 Days ISS n=620
NAUSEA	36	38	32	32	68	70
ASTHENIA	22	23	31	31	53	54
FEVER	22	25	25	25	47	50
CHILLS	14	16	19	21	33	37
VOMITING	13	13	11	11	24	24
ANOREXIA	11	11	11	11	22	22
HEADACHE	11	11	15	15	26	26
COUGH INCREASED	10	10	5	5	15	15
PAIN	9	9	13	15	22	24
RASH	9	9	12	12	21	21
DIARRHEA	8	8	9	9	17	17
MYALGIA	8	8	14	14	22	22
PRURITUS	8	8	5	5	13	13
ARTHRALGIA	7	7	13	14	20	21
HYPOTENSION	7	7	6	6	13	13
SWEATING	6	7	8	8	14	15
ABDOMINAL PAIN	5	5	3	3	8	8
DYSPNEA	5	5	4	4	9	9
RHINITIS	5	6	3	4	8	10
CHEST PAIN	4	4	3	3	7	7
INFECTION	4	4	1	1	5	5
BACK PAIN	3	3	9	9	12	12
CONSTIPATION	3	3	1	1	4	4
DYSPEPSIA	3	3	2	2	5	5
MALAISE	3	3	1	1	4	4
NECK PAIN	3	3	1	1	4	4
URTICARIA	3	3	3	3	6	6
ANEMIA	2	2	3	3	5	5
ANXIETY	2	2			2	2
ASTHMA	2	2	1	1	3	3
CONJUNCTIVITIS	2	2	1	1	3	3
DEHYDRATION	2	2			2	2
INSOMNIA	2	2	5	5	7	7
LYMPHADENOPATHY	2	2	4	4	6	6
PERIPHERAL EDEMA	2	2	7	8	9	10
PLEURAL EFFUSION	2	2	1	1	3	3
SOMNOLENCE	2	2	1	1	3	3
TACHYCARDIA	2	2	3	3	5	5
VASODILATATION	2	2	4	4	6	6
WEIGHT LOSS	2	2	1	1	3	3
ABNORMAL STOOLS	1	1			1	1
ACCIDENTAL INJURY	1	1			1	1
ARTHROSIS	1	1			1	1

ATAXIA	1	1			1	1
ATRIAL FLUTTER	1	1			1	1
BREAST PAIN	1	1			1	1
BRONCHITIS	1	1			1	1
CONFUSION	1	1	2	2	3	3
DEEP THROMBOPHLEBITIS	1	1	1	1	2	2
DIZZINESS	1	1	3	3	4	4
DRY MOUTH	1	1			1	1
EDEMA	1	1			1	1
ENCEPHALOPATHY	1	1			1	1
FACE EDEMA	1	1			1	1
FUNGAL DERMATITIS	1	1			1	1
GASTRITIS	1	1			1	1
HEMOLYTIC ANEMIA	1	1			1	1
HERPES SIMPLEX	1	1			1	1
HYPERTONIA	1	2			1	2
HYPERURICEMIA	1	1	1	1	2	2
HYPERVENTILATION	1	1			1	1
HYPOCHROMIC ANEMIA	1	1			1	1
HYPOKINESIA	1	1			1	1
HYPOVOLEMIA	1	1			1	1
HYPOXIA	1	1	1	1	2	2
INCREASED APPETITE	1	1			1	1
INJECTION SITE EDEMA	1	1			1	1
INJECTION SITE HYPERSENSITIVITY	1	1			1	1
LYMPHEDEMA	1	1			1	1
MELENA	1	1			1	1
MOUTH ULCERATION	1	1			1	1
NAUSEA AND VOMITING	1	1	1	1	2	2
NERVOUSNESS	1	1			1	1
PALPITATION	1	1			1	1
PARESTHESIA	1	1	1	1	2	2
PATHOLOGICAL FRACTURE	1	1	1	1	2	2
PELVIC PAIN	1	1			1	1
PERIPHERAL NEURITIS	1	1	1	1	2	2
PNEUMONIA	1	1	3	3	4	4
PUSTULAR RASH	1	1			1	1
SEPSIS	1	1	1	1	2	2
STOMATITIS	1	1			1	1
TASTE LOSS	1	1			1	1
THROMBOCYTOPENIA	1	1	3	3	4	4
THROMBOPHLEBITIS	1	1			1	1
URINARY INCONTINENCE	1	1			1	1
ABSCESS			1	1	1	1
ACNE			1	1	1	1
ALLERGIC REACTION			1	1	1	1
ANAPHYLACTOID REACTION			1	1	1	1
DIPLOPIA			2	2	2	2

DYSPHAGIA			3	3	3	3
EAR DISORDER			1	1	1	1
EMOTIONAL LABILITY			1	1	1	1
EPISTAXIS			1	1	1	1
ESOPHAGITIS			1	1	1	1
FLATULENCE			2	2	2	2
FLU SYNDROME			2	2	2	2
GASTROINTESTINAL DISORDER			2	2	2	2
GINGIVITIS			1	1	1	1
HYDRONEPHROSIS			1	1	1	1
HYPERCALCEMIA			1	1	1	1
HYPERKALEMIA			1	1	1	1
HYPERTENSION			1	1	1	1
INJECTION SITE REACTION			1	1	1	1
KIDNEY FAILURE			1	1	1	1
LARYNGISMUS			1	1	1	1
LUNG DISORDER			1	1	1	1
MIGRAINE			1	1	1	1
NEUTROPENIA			2	2	2	2
OLIGURIA			1	1	1	1
ORAL MONILIASIS			1	1	1	1
PERIODONTAL ABSCESS			1	1	1	1
PHARYNGITIS			3	3	3	3
PHOTOPHOBIA			1	1	1	1
PHOTOSENSITIVITY REACTION			1	1	1	1
PTOSIS			1	1	1	1
RECTAL DISORDER			1	1	1	1
RECTAL HEMORRHAGE			1	1	1	1
SINUSITIS			1	1	1	1
SKIN ULCER			1	1	1	1
SYNCOPE			2	2	2	2
URINARY FREQUENCY			1	1	1	1

Pooled AEs for patients

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
Fever, sweating, chills & fever	153	234	91	151	62	83
Chills, sweating, chills & fever	100	152	53	80	47	72
UGI (Nausea, Vomiting, Nausea & Vomiting, Gastrointestinal disorder)	166	251	86	136	80	115
UGI (Nausea, Vomiting, Nausea & Vomiting, Intestinal obstruction)	166	251	86	135	80	116
LGI (Diarrhea, Abdominal pain, Abnormal stools, Gastroenteritis, Intestinal Perforation, Ulcerative colitis, Colitis)	103	136	55	78	48	58
Urinary (Urinary tract infection)	10	11	7	8	3	3
Other Urinary (Urination impaired, Urinary tract disorder, Urinary retention, Dysuria, Oliguria, Nocturia, Urinary incontinence Urinary urgency, Urinary frequency)	19	22	14	16	5	6
Infection (type not specified), Pharyngitis, Pneumonia, Bronchitis, Herpes zoster, Urinary tract infection, Sepsis, Sinusitis, Herpes simplex, Cellulitis, Fungal dermatitis, Periodontal abscess	163	223	98	149	65	74
Hemorrhagic events (epistaxis, ecchymosis, Melena, Gastrointestinal hemorrhage, hemoptysis, Gum hemorrhage, Lung hemorrhage	46	52	28	31	18	21
potential allergic reactions- Allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus & serum sickness.	23	24	14	14	9	10

Summary of all adverse events for ISS-A and ISS-B sorted out in order for patients in ISS-A

AE PREFER NAME	No Pt with AE Efficacy Group n=229	No_ of AEs Efficacy Group n=229	No_ Pt_with AE Exp Access Group n=391	Sum(N Rows) of AE Exp Access Group n=391
ASTHENIA	105	116	94	104
FEVER	84	131	52	60
NAUSEA	81	95	73	81
COUGH INCREASED	47	54	25	26
INFECTION	47	55	20	22
PAIN	44	55	43	55
CHILLS	41	60	37	49
RASH	39	45	33	35
THROMBOCYTOPENIA	37	41	38	40
HEADACHE	36	43	28	32
ABDOMINAL PAIN	34	41	23	24
ANEMIA	34	38	54	57
VOMITING	34	38	30	30
ANOREXIA	32	35	24	24
MYALGIA	30	31	26	28
DIARRHEA	28	33	27	32
PHARYNGITIS	27	28	12	12
DYSPNEA	26	31	26	27
ARTHRALGIA	24	27	30	36
PRURITUS	24	34	24	27
RHINITIS	24	30	20	21
NEUTROPENIA	22	23	35	36
PERIPHERAL EDEMA	20	21	14	15
BACK PAIN	18	20	17	17
SWEATING	18	19	21	23
MYELOPROLIFERATIVE DISORDER	17	17	1	1
HYPOTENSION	16	18	15	16
CHEST PAIN	15	20	18	19
HYPOTHYROIDISM	15	15	3	3
NECK PAIN	14	15	2	2
WEIGHT LOSS	14	14	10	10
CONSTIPATION	13	14	5	5
DYSPEPSIA	13	15	3	3
DIZZINESS	12	12	16	19
PNEUMONIA	12	13	12	12
SOMNOLENCE	12	12	4	4
VASODILATATION	12	13	11	12
AE NONE	11	11	102	102
TACHYCARDIA	11	11	5	5
EPISTAXIS	10	10	3	3
INSOMNIA	10	10	9	10
LEUKOPENIA	10	11	9	9

MALAISE	10	10	3	3
BRONCHITIS	9	12		
ECCHYMOSIS	9	10	4	4
URTICARIA	9	13	15	15
HERPES ZOSTER	8	8	3	3
EDEMA	7	8	3	3
SEPSIS	7	8	8	8
SKIN DISORDER	7	8	1	1
URINARY TRACT INFECTION	7	8	3	3
ANXIETY	6	6		
CARDIOVASCULAR DISORDER	6	6	1	1
DEHYDRATION	6	6	6	7
INJECTION SITE REACTION	6	6	1	1
LUNG DISORDER	6	6	3	3
PLEURAL EFFUSION	6	6	5	5
SINUSITIS	6	6	3	3
SKIN ULCER	6	6	3	3
ASTHMA	5	6	1	1
CONJUNCTIVITIS	5	5	5	5
DEEP THROMBOPHLEBITIS	5	5	1	1
DYSPHAGIA	5	5	7	7
EAR DISORDER	5	5	1	1
FACE EDEMA	5	5	3	4
FLATULENCE	5	5	6	6
HYPERCALCEMIA	5	5	4	4
LYMPHADENOPATHY	5	6	5	5
PALPITATION	5	5	1	1
PELVIC PAIN	5	5	4	4
STOMATITIS	5	5	6	6
SYNCOPE	5	5	3	3
ACUTE MYELOBLASTIC LEUKEMIA	4	4		
CELLULITIS	4	4	3	3
CONFUSION	4	4	5	5
HERPES SIMPLEX	4	4	6	6
PANCYTOPENIA	4	4	5	5
PARESTHESIA	4	4	8	9
PATHOLOGICAL FRACTURE	4	4	4	5
PETECHIA	4	7		
RECTAL DISORDER	4	4	1	1
URINARY FREQUENCY	4	4	2	2
ABDOMEN ENLARGED	3	3		
ARTHRITIS	3	3	1	1
DEPRESSION	3	3	1	1
DYSURIA	3	3	1	1
FLU SYNDROME	3	3	11	11
GASTRITIS	3	3		
GASTROINTESTINAL CARCINOMA	3	3		
HYPOCHROMIC ANEMIA	3	5	10	11

INJECTION SITE HYPERSENSITIVITY	3	3	1	1
LYMPHOMA LIKE REACTION	3	3		
MELENA	3	3	5	5
MOUTH ULCERATION	3	3	2	2
MYASTHENIA	3	3	1	1
PERIPHERAL NEURITIS	3	3	1	1
POSTURAL HYPOTENSION	3	3	2	2
THROMBOSIS	3	3		
ULCERATIVE STOMATITIS	3	3	2	2
ABNORMAL GAIT	2	2		
ACCIDENTAL INJURY	2	2		
ACNE	2	2	1	1
ALLERGIC REACTION	2	2	3	3
AMBLYOPIA	2	3	1	1
AMNESIA	2	3		
ATAXIA	2	2		
BLADDER CARCINOMA	2	2		
BREAST PAIN	2	2		
DRY EYES	2	3		
DRY MOUTH	2	2	2	2
FUNGAL DERMATITIS	2	2		
GASTROINTESTINAL DISORDER	2	2	3	3
GASTROINTESTINAL HEMORRHAGE	2	2	3	5
HEMOPTYSIS	2	2	1	1
HEMORRHAGE	2	2	1	1
HERNIA	2	2		
HYDRONEPHROSIS	2	2	1	1
HYPERTONIA	2	4	3	3
HYPOKALEMIA	2	2	1	1
INCREASED APPETITE	2	2		
INJECTION SITE PAIN	2	2		
KIDNEY FAILURE	2	2	5	5
KIDNEY FUNCTION ABNORMAL	2	2		
MACULOPAPULAR RASH	2	2	1	1
MIGRAINE	2	2	1	1
NECK RIGIDITY	2	2	1	1
NOCTURIA	2	2		
ORAL MONILIASIS	2	2	3	3
SERUM SICKNESS	2	2		
THINKING ABNORMAL	2	2	1	1
TREMOR	2	2		
URINARY URGENCY	2	2	1	1
VESICULOBULLOUS RASH	2	2		
WEIGHT GAIN	2	2		
ABNORMAL STOOLS	1	1		
ABNORMAL VISION	1	1	2	2
AGITATION	1	1		
ANAPHYLACTOID REACTION	1	1	1	1

AORTIC STENOSIS	1	1		
ARRHYTHMIA	1	1	1	1
ARTHROSIS	1	1		
ASCITES	1	1		
ASPIRATION PNEUMONIA	1	1		
ATELECTASIS	1	1	1	1
ATRIAL FLUTTER	1	1		
BONE DISORDER	1	1	2	2
BONE PAIN	1	1	1	1
CARCINOMA	1	1	1	1
CARDIOMEGALY	1	1		
CHEST PAIN SUBSTERNAL	1	1		
CHILLS AND FEVER	1	1		
CHOLECYSTITIS	1	1		
CHRONIC LEUKEMIA	1	1		
COLITIS	1	1	1	1
CYST	1	1		
DEPERSONALIZATION	1	1		
DIPLOPIA	1	1	2	2
EAR PAIN	1	1		
ENCEPHALOPATHY	1	1		
ERUCTATION	1	1		
ERYTHEMA NODOSUM	1	1		
FOLATE DEFICIENCY ANEMIA	1	1		
FOOT DROP	1	1		
GASTROENTERITIS	1	1		
GENERALIZED EDEMA	1	1		
GENITAL EDEMA	1	1		
GINGIVITIS	1	1	1	1
GLOSSITIS	1	1		
GUM HEMORRHAGE	1	1	2	2
HAIR DISORDER	1	1		
HEMOLYTIC ANEMIA	1	1		
HEPATITIS	1	1		
HYPERURICEMIA	1	1	1	1
HYPERVENTILATION	1	1		
HYPOGLYCEMIA	1	1	1	1
HYPOKINESIA	1	1		
HYPONATREMIA	1	1		
HYPOVOLEMIA	1	1		
HYPOXIA	1	1	1	1
INJECTION SITE EDEMA	1	1		
INTESTINAL OBSTRUCTION	1	1	2	4
JAUNDICE	1	1		
LACRIMATION DISORDER	1	1	1	1
LARYNGISMUS	1	1	1	1
LEUKEMIA	1	1		
LIVER FUNCTION TESTS ABNORMAL	1	1		

LUNG HEMORRHAGE	1	1		
LYMPHEDEMA	1	1		
MUSCLE ATROPHY	1	1		
NAUSEA AND VOMITING	1	1	1	1
NERVOUSNESS	1	1		
NEURALGIA	1	1		
OLIGURIA	1	1	1	1
PARALYSIS	1	1		
PAROSMIA	1	1		
PERIODONTAL ABSCESS	1	1	2	2
PERIPHERAL VASCULAR DISORDER	1	1	1	1
PNEUMOTHORAX	1	1	1	1
PULMONARY EMBOLUS	1	1		
PUSTULAR RASH	1	1		
SHOCK	1	1		
SKIN BENIGN NEOPLASM	1	1		
SKIN CARCINOMA	1	1	1	1
SKIN DISCOLORATION	1	1	1	1
SKIN NODULE	1	1		
SUBDURAL HEMATOMA	1	1		
TASTE LOSS	1	1		
TASTE PERVERSION	1	1	2	2
TENDON DISORDER	1	1	1	1
TENESMUS	1	1		
TENOSYNOVITIS	1	1	1	1
THROMBOPHLEBITIS	1	1		
TINNITUS	1	1	2	2
ULCERATIVE COLITIS	1	1		
URINARY INCONTINENCE	1	1	1	1
URINARY RETENTION	1	1		
URINARY TRACT DISORDER	1	1		
URINATION IMPAIRED	1	1		
VESTIBULAR DISORDER	1	1		
VOICE ALTERATION	1	1	3	3
ABSCESS			2	2
ACIDOSIS			1	1
APNEA			4	4
AV BLOCK COMPLETE			1	1
BRADYCARDIA			1	1
CACHEXIA			2	3
CONGESTIVE HEART FAILURE			1	1
CONVULSION			1	1
CREATININE INCREASED			1	1
DEAFNESS			1	1
DEATH			1	1
DRY SKIN			1	1
EMOTIONAL LABILITY			1	1
ESOPHAGITIS			2	2

EYE PAIN			1	1
FACIAL PARALYSIS			2	2
HEART ARREST			1	1
HYPERGLYCEMIA			1	1
HYPERKALEMIA			2	2
HYPERTENSION			4	5
HYPERTHYROIDISM			1	1
IMPOTENCE			1	1
INTESTINAL PERFORATION			1	1
JOINT DISORDER			2	2
KETOSIS			1	1
LEUKOPLAKIA OF MOUTH			1	1
LEUKORRHEA			1	1
MARROW DEPRESSION			1	1
MASTITIS			1	1
MICROCYTIC ANEMIA			1	1
NEUROPATHY			2	2
PALLOR			1	1
PERICARDIAL EFFUSION			1	1
PHLEBITIS			1	1
PHOTOPHOBIA			2	2
PHOTOSENSITIVITY REACTION			1	1
PTOSIS			1	1
RECTAL HEMORRHAGE			3	3
RESPIRATORY DISORDER			1	1
SCLERITIS			1	1
SINUS BRADYCARDIA			1	1
VAGINAL HEMORRHAGE			2	2
VAGINITIS			1	1
VENTRICULAR EXTRASYSTOLES			1	1
VENTRICULAR TACHYCARDIA			1	1
VERTIGO			1	1
VITREOUS DISORDER			1	1

Summary of Grade 3 or 4 adverse events for ISS-A and ISS-B sorted out in order for patients in ISS-A

PREFER Name of AE gr 3-4	No Pt- AE gr 3-4 ISS-A n=229	No of AE gr 3-4 ISS-A n=229	No Pt gr 3-4 ISS-B n=391	No of AE gr 3-4 ISS-B n=391
THROMBOCYTOPENIA	32	35	33	35
NEUTROPENIA	20	21	28	29
MYELOPROLIFERATIVE DISORDER	17	17	1	1
ANEMIA	14	14	22	23
LEUKOPENIA	8	9	7	7
DYSPNEA	7	9	11	11
ABDOMINAL PAIN	6	6	5	5
NAUSEA	6	6	4	4
PNEUMONIA	6	7	4	4
SEPSIS	5	5	6	6
ACUTE MYELOBLASTIC LEUKEMIA	4	4		
ASTHENIA	4	4	11	11
FEVER	4	4	7	9
PANCYTOPENIA	4	4	2	2
PLEURAL EFFUSION	4	4	4	4
ARTHRALGIA	3	4	4	4
CHILLS	3	3	2	3
CONFUSION	3	3	2	2
GASTROINTESTINAL CARCINOMA	3	3		
PAIN	3	4	9	10
SKIN ULCER	3	3		
VOMITING	3	3	3	3
BACK PAIN	2	2	4	4
CONSTIPATION	2	2		
COUGH INCREASED	2	2	1	1
DEEP THROMBOPHLEBITIS	2	2	1	1
DEHYDRATION	2	2	6	7
DYSPHAGIA	2	2	1	1
GASTROINTESTINAL HEMORRHAGE	2	2	3	5
HYDRONEPHROSIS	2	2	1	1
HYPERCALCEMIA	2	2	2	2
HYPOCHROMIC ANEMIA	2	3	4	5
HYPOTENSION	2	2	2	2
LYMPHOMA LIKE REACTION	2	2		
NECK PAIN	2	2		
PATHOLOGICAL FRACTURE	2	2	2	2
ARRHYTHMIA	1	1	1	1
ARTHRITIS	1	1		
ASCITES	1	1		
ASPIRATION PNEUMONIA	1	1		

ATAXIA	1	1		
BLADDER CARCINOMA	1	1		
BONE DISORDER	1	1	2	2
BONE PAIN	1	1	1	1
BRONCHITIS	1	1		
CHOLECYSTITIS	1	1		
CHRONIC LEUKEMIA	1	1		
DRY EYES	1	1		
DYSPEPSIA	1	1		
ECCHYMOSIS	1	1		
EDEMA	1	1		
ENCEPHALOPATHY	1	1		
ERYTHEMA NODOSUM	1	1		
GASTROENTERITIS	1	1		
GENERALIZED EDEMA	1	1		
HEMOLYTIC ANEMIA	1	1		
HEMORRHAGE	1	1	1	1
HEPATITIS	1	1		
HERNIA	1	1		
HYPERURICEMIA	1	1	1	1
HYPOKALEMIA	1	1		
HYPOVOLEMIA	1	1		
HYPOXIA	1	1		
INFECTION	1	1	4	4
INTESTINAL OBSTRUCTION	1	1	2	3
LEUKEMIA	1	1		
LIVER FUNCTION TESTS ABNORMAL	1	1		
LUNG DISORDER	1	1	1	1
LUNG HEMORRHAGE	1	1		
MALAISE	1	1		
MYALGIA	1	1	1	1
OLIGURIA	1	1	1	1
ORAL MONILIASIS	1	1		
PARALYSIS	1	1		
PULMONARY EMBOLUS	1	1		
RASH	1	1		
SERUM SICKNESS	1	1		
SHOCK	1	1		
SKIN CARCINOMA	1	1		
STOMATITIS	1	1		
SUBDURAL HEMATOMA	1	1		
SWEATING	1	1		
SYNCOPE	1	1	2	2
THINKING ABNORMAL	1	1	1	1
THROMBOSIS	1	1		
ULCERATIVE COLITIS	1	1		

URINARY TRACT DISORDER	1	1		
WEIGHT LOSS	1	1		
ABSCESS			2	2
ACIDOSIS			1	1
ANAPHYLACTOID REACTION			1	1
ANOREXIA			3	3
APNEA			4	4
AV BLOCK COMPLETE			1	1
CACHEXIA			2	2
CARDIOVASCULAR DISORDER			1	1
CELLULITIS			2	2
CHEST PAIN			2	2
COLITIS			1	1
CONGESTIVE HEART FAILURE			1	1
CONVULSION			1	1
DEATH			1	1
DIARRHEA			1	1
DIZZINESS			1	2
ESOPHAGITIS			1	1
GASTROINTESTINAL DISORDER			1	1
HEADACHE			1	1
HEART ARREST			1	1
HEMOPTYSIS			1	1
HYPERGLYCEMIA			1	1
HYPERTENSION			1	1
HYPERTHYROIDISM			1	1
HYPOGLYCEMIA			1	1
INSOMNIA			1	1
INTESTINAL PERFORATION			1	1
KETOSIS			1	1
KIDNEY FAILURE			4	4
LARYNGISMUS			1	1
LYMPHADENOPATHY			1	1
MARROW DEPRESSION			1	1
MELENA			1	1
PARESTHESIA			1	1
PELVIC PAIN			1	1
SKIN DISCOLORATION			1	1
SOMNOLENCE			1	1
TACHYCARDIA			1	1
URTICARIA			3	3
VENTRICULAR TACHYCARDIA			1	1

Summary of all adverse events for **Durable Response Population (n=70)**

AE Preferred Name **Durable Response Population (n=70)**	Durable Response Number of Patients with AE n=70	Durable Response Number of AEs n=70
AE NONE	4	4
NAUSEA	24	29
FEVER	21	28
INFECTION	18	21
HEADACHE	13	16
COUGH INCREASED	11	14
CHILLS	10	12
PAIN	10	12
ARTHRALGIA	9	10
RASH	9	12
RHINITIS	9	12
MYALGIA	8	9
PHARYNGITIS	8	8
THROMBOCYTOPENIA	8	9
DIARRHEA	7	10
NEUTROPENIA	7	7
ABDOMINAL PAIN	6	9
DYSPNEA	6	7
MYELOPROLIFERATIVE DISORDER	6	6
DYSPEPSIA	5	5
EPISTAXIS	5	5
PRURITUS	5	7
VOMITING	5	5
BACK PAIN	4	4
INSOMNIA	4	4
MALAISE	4	4
SWEATING	4	4
URTICARIA	4	4
ANEMIA	3	3
ANOREXIA	3	3
CONJUNCTIVITIS	3	3
DIZZINESS	3	3
DYSPHAGIA	3	3
ECCHYMOSIS	3	3
HYPOTHYROIDISM	3	3
INJECTION SITE REACTION	3	3
NECK PAIN	3	3
PERIPHERAL EDEMA	3	3

SKIN DISORDER	3	3
SOMNOLENCE	3	3
ULCERATIVE STOMATITIS	3	3
CHEST PAIN	2	2
CONSTIPATION	2	2
DYSURIA	2	2
FACE EDEMA	2	2
FLU SYNDROME	2	2
HERPES SIMPLEX	2	2
HERPES ZOSTER	2	2
HYPOTENSION	2	2
LEUKOPENIA	2	2
LYMPHADENOPATHY	2	3
MYASTHENIA	2	2
PNEUMONIA	2	2
THROMBOSIS	2	2
URINARY TRACT INFECTION	2	2
VASODILATATION	2	3
WEIGHT GAIN	2	2
ACCIDENTAL INJURY	1	1
ACNE	1	1
ACUTE MYELOBLASTIC LEUKEMIA	1	1
AMNESIA	1	2
AORTIC STENOSIS	1	1
ARTHROSIS	1	1
BREAST PAIN	1	1
BRONCHITIS	1	1
CARDIOVASCULAR DISORDER	1	1
CHILLS AND FEVER	1	1
CHOLECYSTITIS	1	1
DEPERSONALIZATION	1	1
DRY MOUTH	1	1
EAR DISORDER	1	1
EDEMA	1	1
FLATULENCE	1	1
FOOT DROP	1	1
GASTRITIS	1	1
GASTROINTESTINAL CARCINOMA	1	1
HAIR DISORDER	1	1
HEMOPTYSIS	1	1
HEMORRHAGE	1	1
HERNIA	1	1
HYPERTONIA	1	3
HYPOCHROMIC ANEMIA	1	1
HYPOKINESIA	1	1
INJECTION SITE HYPERSENSITIVITY	1	1

LUNG DISORDER	1	1
LUNG HEMORRHAGE	1	1
LYMPHOMA LIKE REACTION	1	1
MACULOPAPULAR RASH	1	1
MIGRAINE	1	1
MOUTH ULCERATION	1	1
NEURALGIA	1	1
PALPITATION	1	1
PATHOLOGICAL FRACTURE	1	1
PERIODONTAL ABSCESS	1	1
PERIPHERAL NEURITIS	1	1
PERIPHERAL VASCULAR DISORDER	1	1
PETECHIA	1	1
SINUSITIS	1	1
SUBDURAL HEMATOMA	1	1
TASTE PERVERSION	1	1
TENDON DISORDER	1	1
TENOSYNOVITIS	1	1
URINARY FREQUENCY	1	1
URINARY URGENCY	1	1

Summary of all Adverse Events for **Transformed Population (n = 65)**

AE Preferred Name **Transformed Population (n = 65)**	Transformed Population Number of Patients with AE n = 65	Transformed Population Number of Aes n = 65
FEVER	30	46
ASTHENIA	29	31
NAUSEA	20	22
COUGH INCREASED	13	15
PAIN	13	18
RASH	13	16
ANOREXIA	12	13
CHILLS	12	18
ANEMIA	11	11
MYALGIA	10	10
ARTHRALGIA	9	10
DIARRHEA	9	9
HEADACHE	9	9
INFECTION	9	9
PRURITUS	9	11
VOMITING	9	9
ABDOMINAL PAIN	8	10
DYSPNEA	7	9
THROMBOCYTOPENIA	7	7
HYPOTENSION	6	8
SWEATING	6	6
BACK PAIN	5	6
NEUTROPENIA	5	6
PERIPHERAL EDEMA	5	6
PNEUMONIA	5	5
CHEST PAIN	4	6
CONSTIPATION	4	5
DEEP THROMBOPHLEBITIS	4	4
MYELOPROLIFERATIVE DISORDER	4	4
NECK PAIN	4	4
PHARYNGITIS	4	4
PLEURAL EFFUSION	4	4
RHINITIS	4	7
SOMNOLENCE	4	4
URTICARIA	4	4
VASODILATATION	4	4
	3	3
BRONCHITIS	3	4
CONFUSION	3	3
DYSPHAGIA	3	3

EDEMA	3	4
HYPERCALCEMIA	3	3
HYPOTHYROIDISM	3	3
MALAISE	3	3
SEPSIS	3	4
SINUSITIS	3	3
SKIN ULCER	3	3
TACHYCARDIA	3	3
ABNORMAL GAIT	2	2
ACCIDENTAL INJURY	2	2
ACUTE MYELOBLASTIC LEUKEMIA	2	2
ATAXIA	2	2
DEHYDRATION	2	2
DIZZINESS	2	2
DYSPEPSIA	2	2
DYSURIA	2	2
ECCHYMOSIS	2	2
HERNIA	2	2
LYMPHOMA LIKE REACTION	2	2
MELENA	2	2
NECK RIGIDITY	2	2
PALPITATION	2	2
SKIN DISORDER	2	2
SYNCOPE	2	2
THINKING ABNORMAL	2	2
ULCERATIVE STOMATITIS	2	2
URINARY FREQUENCY	2	2
URINARY TRACT INFECTION	2	2
URINARY URGENCY	2	2
WEIGHT LOSS	2	2
ABDOMEN ENLARGED	1	1
ABNORMAL VISION	1	1
ALLERGIC REACTION	1	1
AMBLYOPIA	1	1
ARRHYTHMIA	1	1
ARTHRITIS	1	1
ARTHROSIS	1	1
ASPIRATION PNEUMONIA	1	1
ASTHMA	1	2
ATELECTASIS	1	1
ATRIAL FLUTTER	1	1
BONE PAIN	1	1
CARCINOMA	1	1
CARDIOMEGALY	1	1
CARDIOVASCULAR DISORDER	1	1
CELLULITIS	1	1

CHEST PAIN SUBSTERNAL	1	1
DEPRESSION	1	1
DIPLOPIA	1	1
DRY MOUTH	1	1
ENCEPHALOPATHY	1	1
ERYTHEMA NODOSUM	1	1
FACE EDEMA	1	1
FLATULENCE	1	1
FLU SYNDROME	1	1
GASTROENTERITIS	1	1
GASTROINTESTINAL CARCINOMA	1	1
GASTROINTESTINAL DISORDER	1	1
GASTROINTESTINAL HEMORRHAGE	1	1
GENERALIZED EDEMA	1	1
GLOSSITIS	1	1
HEMORRHAGE	1	1
HERPES SIMPLEX	1	1
HERPES ZOSTER	1	1
HYPERTONIA	1	3
HYPERVENTILATION	1	1
HYPOCHROMIC ANEMIA	1	1
HYPOGLYCEMIA	1	1
HYPONATREMIA	1	1
INCREASED APPETITE	1	1
INJECTION SITE HYPERSENSITIVITY	1	1
INJECTION SITE REACTION	1	1
INSOMNIA	1	1
KIDNEY FAILURE	1	1
LACRIMATION DISORDER	1	1
LEUKOPENIA	1	1
LUNG DISORDER	1	1
LYMPHADENOPATHY	1	1
LYMPHEDEMA	1	1
MACULOPAPULAR RASH	1	1
MOUTH ULCERATION	1	1
MUSCLE ATROPHY	1	1
NOCTURIA	1	1
OLIGURIA	1	1
ORAL MONILIASIS	1	1
PANCYTOPENIA	1	1
PARALYSIS	1	1
PARESTHESIA	1	1
PATHOLOGICAL FRACTURE	1	1
PERIPHERAL VASCULAR DISORDER	1	1
PETECHIA	1	1
PULMONARY EMBOLUS	1	1

RECTAL DISORDER	1	1
SERUM SICKNESS	1	1
SKIN BENIGN NEOPLASM	1	1
SKIN NODULE	1	1
URINARY TRACT DISORDER	1	1
VOICE ALTERATION	1	1

Hematologic Adverse Events and Toxicity

The acute, dose-limiting toxicity of Bexxar therapeutic regimen therapy is severe neutropenia and/or thrombocytopenia with a median time from initiation of treatment (dosimetric dose) to nadir of 6 weeks (neutropenia) and 4.2 weeks (thrombocytopenia) and median duration of grade 3-4 toxicity of approximately 4 weeks. 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 620 patients, including 271 from studies RIT-II-000, 001, 002, 004 and CP 97-012 and 393 patients enrolled in the expanded access experience (6 patients in single patient INDs and 387 in the expanded access study CP98-020).

Patients Excluded from Hematology Safety Analyses:

Patients were excluded from all analyses of hematologic toxicity, including sensitivity analyses, if they had no laboratory data following study entry. There are nine patients in this category are summarized below. Of the 620 patients, 8 had no post-treatment platelet counts, 7 had no post-treatment hemoglobin values, and 9 had no post-treatment ANC values.

	MISSING FOLLOW-UP DATA			
Patient ID	**Platelet**	**Hemoglobin**	**ANC**	**Reason for Missing Data**
004-018-001	X	X	X	Patient died on study day 14
020-013-467	X		X	Patient died on study day 10
020-028-126			X	ANC (differentials) not done in follow-up
020-039-016	X	X	X	Patient withdrew; did not receive therapeutic dose; no follow-up lab
020-042-138	X	X	X	Patient withdrew; did not receive therapeutic dose; no follow-up lab
020-047-365	X	X	X	Patient died on study day 39
020-052-159	X	X	X	Patient died on study day 57
020-053-326	X	X	X	Patient lost to follow-up-Had ANC missing at the baseline
020-061-179	X	X	X	Patient died on study day 41
Total w/ Missing Data	8	7	9	
Patients included in Analyses	612	613	611	

Among the remaining patients in the ISS database, 47 patients enrolled in RIT-II-000 who received a therapeutic dose below the MTD (which was based on hematologic toxicity) were excluded from analyses the analyses below. The remaining 229 subjects constitute the most complete dataset for assessment of efficacy

Missing Data

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). Approximately 10% of the 229 patients enrolled in the activity/efficacy studies did not have CBC data during ≥2 of the 5 weeks of expected toxicity (weeks 5-9) or a recovery time point (week 13). Approximately 15% of the 393 patients in the expanded access studies did not have CBC data during ≥2 of the 5 weeks of expected toxicity.

The reasons provided for lack of hematology data, in descending order of frequency, were: missing, died, withdrew from study, not required by protocol, received alternate therapy, shifted outside window. Subjects who withdrew from study or died should not be censored in the analysis of safety, as it is likely that such patients experienced toxicity more often than those who remained on study. In order to adjust for the large amount of missing data and to determine the possible extent of the risk of severe hematologic toxicity, FDA conducted sensitivity analyses for the incidence and duration of severe hematologic toxicity. In the worst-case sensitivity analyses below, all subjects with missing data were assumed to have NCI CTC grade 3 or 4 neutropenia, thrombocytopenia, or anemia, respectively. The number of subjects in the analyses for whom an adverse event was documented and those for whom it was imputed are also provided. The data are provided only for those patients enrolled in the efficacy/activity studies (n=229) since there is a lower proportion of patients with missing data in this subset. The incidence and duration of severe hematologic toxicity was slightly lower in the expanded access subset than observed in the patients in the more controlled studies.

Algorithm

Source – HEMOUT and FEMAT datasets submitted on October 30, 2002

* Nine patients did not have ANC follow-up, including one patient who had WBC recovery but no differentials documenting ANC recovery; 8 patients did not have platelet count follow-up; and 7 patients did not have hemoglobin follow-up.

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.
95% CI is 95% Confidence Interval and IQ range is interquartile range.

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.

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Statistical- 1

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ANC Hematology Summary for ISS data

Characteristics	ISS-A	RIT-I-000	RIT-II-001	RIT-II-002 A	RIT-II-002 X	RIT-II-004	CP-97-012	ISS-B CP-98-020 (387) + Single Pt (4)	ISS All
N -All	229	22	47	42	19	59	40	391	620
N-data available	228	22	47	42	19	58	40	383	611
Nadir Value									
Median Nadir	1.0	1.0	0.8	1.3	0.8	0.8	1.2	1.2	1.1
95% CI	(0.8, 1.1)	(0.6, 1.8)	(0.6, 1.0)	(1.0,1.6)	(0.4,1.2)	(0.6,1.2)	(0.8,1.5)	(1.1, 1.3)	(1.0,1.2)
Q1	0.5	0.6	0.5	0.7	0.4	0.5	0.7	0.7	0.6
Q3	1.6	1.8	1.4	1.8	1.2	1.5	1.8	1.9	1.8
Min									
Max									
Days to Nadir									
Median (Days)	43	47	43	47	43	42	42	42	43
95% CI	(42, 46)	(40,56)	(41,48)	(42, 49)	(39, 47)	(41.45)	(39,46)	(42, 43)	(42,43)
Q1	39	40	40	38	39	39	35	37	38
Q3	49	61	55	53	48	48	47	50	49
Min									
Max									
Grade 3/4	116	11	29	14	11	34	17	140	256
% Grade 3/4	51%	50%	62%	33%	58%	59%	43%	37%	42%
95% CI									
Duration (Days) of Grade 3/4									
Median (Days)	29	29	39	21	31	30	30	30	30
95% CI	(27, 35)	(15, 39)	(24, 43)	(14,36)	(15,49)	(22, 43)	(18, 43)	(24, 36)	(29,35)
Q1	21	22	23	15	27	21	22	19	20
Q3	43	39	44	36	49	49	45	54	47
90th Percentile	62	42	62	73	88	57	59	104	58
Min									
Max									

+ Censored – continuing

Nadir value is within 120 days of therapeutic dose

Platelet Hematology Summary for ISS data

Characteristics	ISS-A	RIT-I-000	RIT-II-001	RIT-II-002 A	RIT-II-002 X	RIT-II-004	CP-97-012	ISS-B CP-98-020 (387) + Single Pt (4)	ISS All
N -All	229	22	47	42	19	59	40	391	620
N-data available	228	22	47	42	19	58	40	384	612
Nadir Value									
Median Nadir	57	65	43	69	50	50	83	68	62
95% CI	(50, 65)	(43,102)	(27, 61)	(52, 80)	(23, 85)	(39, 61)	(56, 94)	(61, 75)	(60,69)
Q1	29	43	20	36	23	28	43	41	36
Q3	93	114	80	87	87	82	99	102	99
Min									
Max									
Days to Nadir									
Median (Days)	34	35	36	36	35	34	34	33	34
95% CI	(33, 35)	(30, 40)	(33,40)	(29, 38)	(28, 36)	(32, 35)	(30, 34)	(31. 34)	(33,34)
Q1	29	30	31	28	28	28	28	28	28
Q3	40	41	43	39	39	40	35	36	38
Min									
Max									
Grade 3/4	95	7	27	14	9	28	10	128	223
% Grade 3/4	42%	32%	57%	33%	47%	48%	25%	33%	36%
95% CI									
Duration (Days) of Grade 3/4									
Median (Days)	30	15	34	29	28	29	32	29	29
95% CI	(28, 36)	(8, 80)	(27, 49)	(22, 54)	(16, 90)	(23, 40)	(15, 51)	(24, 29)	(27,30)
Q1	22	14	26	22	22	22	26	22	22
Q3	51	80	50	54	66	43	49	47	50
90th Percentile	102	122	72	144	90	68	54	86	89
Min									
Max									

b(4)

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+ Censored – continuing
Nadir value is within 120 days of therapeutic dose

Hemoglobin Summary for ISS data

Characteristics	ISS-A	RIT-I-000	RIT-II-001	RIT-II-002 A	RIT-II-002 X	RIT-II-004	CP-97-012	ISS-B CP-98-020 (387) + Single Pt (4)	ISS All
N -All	229	22	47	42	19	59	40	391	620
N-data available	228	22	47	42	19	58	40	385	613
Nadir Value									
Median Nadir	10.5	11	10.2	11	10.2	10	11.2	11	10.8
95% CI	(10.1, 10.9)	(9.5, 11.9)	(8.9, 11.1)	(10.1, 11.7)	(8.3, 12.1)	(9.4, 10.6)	9.9 12.3	(10.7, 11.2)	(10.6, 11.0)
Q1	8.9	9.5	8.1	9.4	8.3	8.3	9.5	9.4	9.2
Q3	12.1	12.1	11.9	12.3	13.2	11.2	12.8	12.4	12.3
Min									
Max									
Days to Nadir									
Median (Days)	47	37	49	48	47	48	42	46	47
95% CI	(45, 49)	(5, 47)	(47,55)	(40,53)	(36,61)	(42, 55)	(35,53)	(43,48)	(44, 48)
Q1	35	5	42	36	36	39	34	35	35
Q3	61	54	62	61	64	60	57	57	60
Min									
Max									
Grade 3/4	35	2	10	6	2	11	4	34	69
% Grade 3/4	15%	9%	21%	14%	11%	19%	10%	9%	11%
95% CI									
Duration (Days) of Grade 3/4									
Median (Days)	19	14	16	18	35	22	36	17	19
95% CI	(15, 22)	(7, ---)	(10, 34)	(6, ---)	(10,---)	(6, 36)	(16, ---)	(15, 31)	(15, 22)
Q1	14	7	14	15	10	16	23	15	15
Q3	34	14	22	27	35	36	78	35	35
90th Percentile	40	14	39	32	35	40	61	43	43
Min									
Max									

b(4)

b(4)

b(4)

+ Censored – continuing
Nadir value is within 120 days of therapeutic dose

Worst-case Hematology (Modified IIT population)

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. Four (4) patients (004-018-001, 020-039-016, 020-042-138, 020-052-159) who did not receive a therapeutic dose and did not have any hematologic follow-up were excluded from the worst-case analyses. Eight additional patients who did not receive the therapeutic dose or the radiolabeled portion of the therapeutic dose, but who had hematologic follow-up, were included in the worst-case analyses (two of the eight patients had Grade 3/4 hematologic toxicity). Thus, a total of 616 patients are included in the worst-case analysis (Modified IIT population). (Ref: ISS-Lab data submitted March 4, 2002).

Based on the worst-case analysis:

1. 256 patients had documented Grade 3/4 neutropenia, and 94 patients without documented Grade III/IV toxicity were classified as Grade 3/4 toxicity due to having incomplete data during Weeks 5–9.
2. 223 patients had documented Grade 3/4 thrombocytopenia, and 78 patients without documented Grade III/IV toxicity were classified as having Grade 3/4 toxicity due to incomplete data during Weeks 5–9.
3. 69 patients had documented Grade 3/4 anemia, and 95 patients without documented Grade 3/4 toxicity were classified as having Grade 3/4 toxicity due to incomplete data during Weeks 5–9.

Based on the worst-case analysis for all three hematologic parameters, 322 patients had documented Grade 3/4 thrombocytopenia, neutropenia, or anemia, and 113 patients without documented Grade 3/4 thrombocytopenia, neutropenia or anemia toxicity were classified as having Grade 3/4 toxicity due to incomplete data during Weeks 5–9.

The following table displays the numerical values for this worst-case analysis.

Grade 3/4 Hematologic Toxicity of Integrated Efficacy (ISS-A) Population under Worst-Case Scenario (N = 228)

	ANC	Platelet	Hemoglobin	ANC or Platelet	ANC or Platelet or Hgb
Documented Grade 3/4	116 (51%)	95 (42%)	35 (15%)	134 (59%)	136 (60%)
Undocumented Grade 3/4	29 (13%)	27 (12%)	31 (14%)	26 (11%)	26 (11%)
Total Grade 3/4	145 (64%)	122 (54%)	66 (29%)	160 (70%)	162 (71%)

Grade 3/4 Hematologic Toxicity of ISS-B Population under Worst-Case Scenario (N = 388)

	ANC	Platelet	Hemoglobin	ANC or Platelet	ANC or Platelet or Hgb
Documented Grade 3/4	140 (36%)	128 (33%)	34 (9%)	182 (47%)	186 (48%)
Undocumented Grade 3/4	65 (17%)	51 (13%)	64 (16%)	54 (14%)	54 (14%)
Total Grade 3/4	205 (53%)	179 (46%)	98 (25%)	236 (61%)	240 (62%)

Grade 3/4 Hematologic Toxicity of All Integrated Safety (ISS) Population under Worst-Case Scenario (N = 616)

	ANC	Platelet	Hemoglobin	ANC or Platelet	ANC or Platelet or Hgb
Documented Grade 3/4	256 (42%)	223 (36%)	69 (11%)	316 (51%)	322 (52%)
Undocumented Grade 3/4	94 (15%)	78 (13%)	95 (15%)	80 (13%)	80 (13%)
Total Grade 3/4	350 (57%)	301 (49%)	164 (27%)	396 (64%)	402 (65%)

Grade 4 Hematologic Toxicity of Integrated Efficacy (ISE or ISS-A) Population under Worst-Case Scenario (N = 228)

	ANC	Platelet	Hemoglobin	ANC or Platelet	ANC or Platelet or Hgb
Documented Grade 4	49 (21%)	42 (18%)	8 (4%)	60 (26%)	60 (26%)
Undocumented Grade 4*	8 (4%)	5 (2%)	3 (1%)	8 (4%)	8 (4%)
Total Grade 4	57 (25%)	47 (21%)	11 (4%)	68 (30%)	68 (30%)

Grade 4 Hematologic Toxicity of ISS-B Population under Worst-Case Scenario (N = 388)

	ANC	Platelet	Hemoglobin	ANC or Platelet	ANC or Platelet or Hgb
Documented Grade 4	60 (15%)	56 (14%)	5 (1%)	87 (22%)	88 (23%)
Undocumented Grade 4*	8 (2%)	10 (3%)	5 (1%)	13 (3%)	13 (3%)
Total Grade 4	68 (18%)	66 (17%)	10 (3%)	100 (26%)	101 (26%)

Grade 4 Hematologic Toxicity of Integrated Safety Population under Worst-Case Scenario (N = 616)

	ANC	Platelet	Hemoglobin	ANC or Platelet	ANC or Platelet or Hgb
Documented Grade 4	109 (18%)	98 (16%)	13 (2%)	147 (24%)	148 (24%)
Undocumented Grade 4*	16 (3%)	15 (2%)	8 (1%)	21 (3%)	21 (3%)
Total Grade 4	125 (20%)	113 (18%)	21 (3%)	168 (27%)	169 (27%)

* These were defined as equaling 1 (undocumented grade 4 toxicity) if the patient had grade 3 toxicity but did not have complete Week 5-9 data.

Per-Patient Incidence of

Grade 3-4 Hematologic Toxicity

Hematologic Toxicity	ISS-A N=229	ISS-B N=391
Neutropenia		
% Documented Grade 3-4 toxicity	51%	36%
% Grade 3/4 toxicity ((worst case scenario, accounting for missing values)	64%	53%
Median days to nadir (95% CI)	43 (42, 46)	42 (42, 43)
25th and 75th percentiles for days to Nadir	39; 49	37; 50
Median duration of documented Grade 3-4 toxicity	29 (27, 35)	30 (24,36)
25th - 75th percentile -duration of documented Gr 3-4	21: 43 days	19: 54 days
90Th percentile -duration of documented Gr 3-4	62 days	104 days
Maximum observed	383+ days	259 days
% documented Grade 4	21%	15%
% Grade 4 (worst case scenario, accounting for missing values)	25%	18%
Thrombocytopenia		
% Documented Grade 3-4 toxicity	42%	33%
% Grade 3-4 toxicity ((worst case scenario, accounting for missing values)	54%	46%
Median days to nadir (95% CI)	34 (33, 35)	33 (31, 34)
25th and 75th percentiles for days to Nadir	29: 40	28; 36
Median duration of documented Grade 3-4 toxicity	30 (28, 36)	29 (24, 29)
25th , 75th percentile duration of documented Gr ¾	22; 51 days	22; 47 days
90Th percentile -duration of documented Gr 3-4	102 days	86 daya
Maximum duration observed	211 days	659+
% documented Grade 4	18%	14%
% Grade 4 (worst case scenario, accounting for missing values)	21%	17%
Anemia		
% Documented Grade 3-4 toxicity	15%	9%
% Grade 3-4 toxicity ((worst case scenario, accounting for missing values)	29%	25%
Median days to nadir (95% CI)	47 (45, 49)	46 (43, 48)
25th and 75th percentiles for days to Nadir	35; 61	35; 57
Median duration of documented Grade 3-4 toxicity	19 (15, 22)	17 (15, 31)
25th, 75th percentile duration of documented Gr ¾	14; 34 days	15; 35 days
90Th percentile -duration of documented Gr 3-4	40 days	43 days
Maximum duration observed	78 days	60 daya
% documented Grade 4	4%	1%
% Grade 4 (worst case scenario, accounting for missing values)	4%	3%

Per-Patient Incidence of
Grade 3-4 Hematologic Toxicity

Hematologic Toxicity	ISS-A N=229	ISS-B N=391
Neutropenia and/or thrombocytopenia		
% Documented Grade 3-4 toxicity	59%	47%
% Grade 3-4 toxicity ((worst case scenario, accounting for missing values)	70%	61%
% Documented Grade 4	26%	26%
% Grade4 (worst case scenario, accounting for missing values)	30%	26%
Neutropenia, anemia, and/or thrombocytopenia		
% Documented Grade 3-4 toxicity	60%	48%
% Grade 3-4 toxicity (worst case scenario, accounting for missing values)	71%	62%
% Documented Grade 4 toxicity	26%	23%
% Grade 4 toxicity (worst case scenario, accounting for missing values)	30%	26%

Both infections and hemorrhagic events may occur as a complication of treatment induced cytopenias. The following analyses pooled preferred terms that may relate to either infection or to hemorrhagic events to obtain a clearer picture of the overall risks.

Infections

- fever reported in 84 patients (31%)
- infections (type not specified) reported in 47 patients (20%)
- pharyngitis reported in 27 patients (12%)
- pneumonia reported in 12 patients
- bronchitis reported in 9 patients
- Herpes zoster reported in 8 patients
- urinary tract infections reported in 7 patients
- sepsis reported in 7 patients
- sinusitis reported in 6 patients
- Herpes simplex reported in 4 patients
- cellulitis reported in 4 patients
- fungal dermatitis reported in 2 patients
- periodontal abscess reported in 1 patient
-

Hemorrhagic events

- epistaxis reported in 10 patients
- ecchymosis reported in 9 patients
- melena reported in 3 patients
- GI hemorrhage reported in 2 patients
- hemorrhage (not specified) reported in 2 patients
- hemoptysis reported in 2 patients
- gum hemorrhage reported in 2 patients

- lung hemorrhage reported in 1 patient

Analyses were conducted to assess the per-patient incidence of infections and of hemorrhagic events, which pooled the terms listed in the table below to avoid "double-counting" multiple infections in the same patient. The analysis of infectious events does not include fever as a term nor does it include febrile neutropenia. In FDA's review, the incidence of febrile neutropenia has been under-reported in the database and the figures are not reliable. FDA will conduct an analysis of fevers occurring during a period of documented neutropenia in order to derive a more appropriate figure. An updated analysis will be available at the time of the Dec. 17, 2002, ODAC meeting.

The per-patient incidence of infection in the efficacy/activity studies was 48% (98/229) with 149 events reported in these 98 patients. The incidence in the expanded access (17%) is substantially lower and deemed unreliable by FDA. The per-patient incidence of hemorrhagic events is 12% (28/229) with 31 events reported among 28 patients enrolled in the efficacy/activity studies. The 5% incidence reported in the expanded access population is deemed unreliable.

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
Infection (type not specified), Pharyngitis, Pneumonia, Bronchitis, Herpes zoster, Urinary tract infection, Sepsis, Sinusitis, Herpes simplex, Cellulitis, Fungal dermatitis, Periodontal abscess	163	223	98	149	65	74
Hemorrhagic events (epistaxis, ecchymosis, Melena, Gastrointestinal hemorrhage, hemoptysis, Gum hemorrhage, Lung hemorrhage	46	52	28	31	18	21

B-cell lymphopenia.

The impact of Bexxar therapeutic regimen therapy on the number of circulating lymphocytes was assessed in patients enrolled in two studies: RIT-1-000, the Phase 1 study conducted previously treated subjects) and RIT-1-003, a single arm Phase 2 study conducted in patients with low grade NHL who had received no prior chemotherapy. As can be observed, there is considerable drop-off in the number of patients followed over time. The comparisons of time points is likely to be biased by selective retention of patients who are responding. Therefore, FDA will attempt to conduct analyses within patients over time in addition to the pooled analyses at various time points displayed below. Of note, the majority of the samples was obtained in a patient population (chemotherapy naïve) which differs from the population for which 131-Iodine tositumomab would be indicated. While the data may be qualitatively representative of the effects on CD20+ cells, the quantitative results would likely differ, as chemotherapy naive patients would be expected to have higher pretreatment counts.

CD20+ cells in the Peripheral blood Samples obtained in Selected Patients with Sampling in RIT-I-000 & RIT-II-OO3

PERIPHERAL CD20+ CELLS COUNTS PRE-TREATMENT AND POST-TREATMENT					
Time point (number of samples)	Baseline (n=125)	7 wks (n=111)	13 wks (n=74)	6 mos (n=57)	12 mos (n=14)
Mean (cells/μl)	197	15	35	75	168
25TH Quartile (cells/μl)	63	0	0	19	42
Median (cells/μl)	118	2	13	49	101
75TH Quartile (cells/μl)	196	14	38	100	177

The sponsor cites a normal range for peripheral CD20+ cells as 14-246 cells/ μl

Infusional Toxicity

A constellation of symptoms, including fever, rigors or chills, hypotension, dyspnea, bronchospasm, and nausea, have been reported in the peri-infusional period. This constellation of adverse events is commonly observed with infusions of large proteins in doses of tens to hundreds of milligrams. 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.

The following table provides a listing of adverse events that occurred within 2 days of the dosimetric infusion.

Per-patient incidence of Infusion-related (Study days 0-2) Adverse Events

Costart Preferred Term	All Grades N=229
Fever	17%
Pruritus	7%
Nausea	7%
Chills	7%
Rash	6%
Asthenia	6%
Pain	5%
Headache	5%
Pharyngitis	5%
Rhinitis	4%
Hypotension	3%
Vomiting	3%
Vasodilatation	3%
Cough Increased	3%
Chest pain	3%
Urticaria	2%
Arthralgia	2%
Diarrhea	2%
Back pain	2%
Anaphylactoid reaction	<1%

Toxicities related to the antibody itself rather than the radioisotope were observed within 28 of days of the dosimetric infusion (21-14 days of the therapeutic infusion). These toxicities are attritubuted to infusion of a large protein load and to direct antibody binding. In assessing case reports, infusion-related toxicities included fever, chills, sweating, rigors, hypotension, and nausea. The table below provides the per-patient incidence for some of the commonly observed infusion-related toxicities. Analysis including a more comprehensive listing of the symptoms in this symptom complex that are temporally related to the dosimetric or therapeutic infusion, will be conducted. Based upon the list of preferred terms cited in the table below, and unrestricted by study day, the per-patient incidence of 40% for a pooled analysis of the preferred terms for fever, sweating, chills & fever and 23% for chills, sweating, and chills and fever. The latter grouping is probably more representative of the infusion-related events since fever is also a component on infectious events.

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
Fever, sweating, chills & fever	153	234	91	151	62	83
Chills, sweating, chills & fever	100	152	53	80	47	72

Hypersensitivity reactions

Tositumomab is a murine (mouse) antibody; administration of murine proteins to humans can result in the development of a serologic immune response commonly referred to as HAMA (human anti-murine antibody) response. Prior to the 2001 amendment for long-term follow-up, the clinical studies assessed patients for HAMA for a relatively limited period following treatment. Unfortunately, unlike antibodies directed against other targets, tositumomab therapy directly causes a reduction in the number of circulating CD20+ (B) lymphocytes, may transiently mask any immune response that may occur. This phenomenon has been observed with other CD20+-directed antibodies as well. In these circumstances, evidence of an immune response may not be detectable until the CD20+ cell population returns to pretreatment levels

A pooled analysis was conducted using only those preferred terms that may denote a severe hypersensitivity reaction. Specifically, the preferred terms were allergic reaction, face edema, injection site hypersensitivity, anaphylactoid reaction, laryngismus & serum sickness.

There were 14 patients in the efficacy/activity studies identified with one or more of these terms for a per-patient incidence of 6%. In the expanded access experience there were 10 events reported among 9 of the 391 patients for a per-patient incidence of 2%.

In review of the narrative summaries of the serious adverse events, there is one additional significant allergic reaction that was reported as hypotension in a single patient. The narrative summaries and CRFs are being re-assessed to identify any additional subjects with allergic reactions coded under other terms to further refine the estimated incidence.

Gastrointestinal Toxicity

Images obtained following the dosimetric dose have demonstrated localization of the radioisotope in the gastrointestinal tract. This localization is felt to be direct binding of tositumomab to CD20+ cells in the gastrointestinal mucosa (e.g, Peyer's patches). The clinical studies have demonstrated a range of

gastrointestinal toxicities, which are temporally related to the infusion of the antibody. These toxicities are increased higher in patients who receive 131-Iodine tositumomab as compared to those who receive only the unlabeled tositumomab antibody. For example, in study RIT-II-002, the incidence of nausea (48% vs. 17 %) and abdominal pain (17 vs. 8%) were higher in Arm A (receiving 131-Iodine tositumomab) than in Arm B (unlabeled tositumomab). Infusion-related gastrointestinal toxicities appear to be related to upper GI symptoms, however lower GI symptoms are also frequent but generally occur more distant from infusion. As such, the lower GI events may reflect not only antibody binding but localized irradiation. FDA conducted a pooled analysis of the following gastrointestinal adverse events to identify the per-patient incidence of upper GI and lower GI toxicity.

AE Preferred Name	All Number of Patients with AE All n=620	All Number of AEs in All n=620	ISS-A Number of Patients with AE Efficacy n=229	ISS-A Number of AEs in Efficacy n=229	ISS-B Number of Patients with AE Other n=391	ISS-B Number of AEs in Other n=391
UGI (Nausea, Vomiting, Nausea & Vomiting, Gastrointestinal disorder)	166	251	86	136	80	115
UGI (Nausea, Vomiting, Nausea & Vomiting, Intestinal obstruction)	166	251	86	135	80	116
LGI (Diarrhea, Abdominal pain, Abnormal stools, Gastroenteritis, Intestinal Perforation, Ulcerative colitis, Colitis)	103	136	55	78	48	58

The per-patient incidence of UGI adverse events is 38% (86/229) with 136 events observed among 86 patients. The per-patient incidence in the expanded access study is 20% (80/391). FDA believes that this figure is falsely low and is likely due to under-reporting of non-serious events. The per-patient incidence of LGI adverse events is 24% (55/229) with 78 events observed among 55 patients. The per-patient incidence in the expanded access study is 12% (48/391).

EXPANDED ACCESS EXPERIENCE

The expanded access experience includes serious adverse events reported among 387 subjects enrolled across 60 sites under Protocol CP 98-020 and 6 patients enrolled under single patient studies in investigator-sponsored INDs. The sponsor-investigator experience includes three patients treated at the University of Michigan Medical Center (Protocols CP-97-014c, CP 97-016c, CP 98-023c), two patients treated at Memorial Sloan-Kettering Cancer center (Protocols CP 98-024c, CP-98-029c), and one patient treated at Stanford University Medical Center (Protocol CP-00-039c). None of these studies were audited by the sponsor. The protocol specified requirements for adverse event monitoring and reporting of adverse events were different from those in the activity and efficacy studies conducted by the sponsor, with the exception of the requirement for reporting of serious adverse events. Data from these studies are less reliable but can be included in limited safety assessments, specifically, reports of serious adverse events and time-to-event analyses (e.g., for HAMA, hypothyroidism).

Hypothyroidism

Hypothyroidism can be reliably achieved through the delivery of radioactive iodine. All protocol required that patients be "blocked" with Lugol's solution, SSKI or potassium perchlorate tablets administered from 24 hours prior to the first dosimetric infusion until 14 days after infusion of the

dosimetric dose or therapeutic dose (whichever is the last infusion). The investigators have documented that patient compliance was a problem and this is confirmed by visual evidence of thyroid uptake on gamma camera images obtained for calculating the therapeutic dose.

Thyroid (TSH) Evaluation

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 598 patients (out of 620 patients in the Safety database) who had TSH measured at baseline. Forty-eight of 598 (8%) patients had an elevated TSH prior to the therapeutic dose, and an additional 22 patients had a history of thyroid medication. Thus 70 of 620 (11%) patients had a history of hypothyroidism prior to receiving their therapeutic dose. These patients were excluded from analyses of post–Bexxar therapeutic regimen hypothyroidism. There were 528 patients who had normal TSH values at the baseline and did not have Thyroid medication prior to Bexxar therapeutic regimen treatment. The data are summarized below:

Elevated TSH Values at Baseline prior to therapeutic dose					
Any Thyroid Medication Pre-Bexxar therapeutic regimen		No (0)	Yes (1)	Missing	Total
	No (0)	528	41	21	590
	Yes (1)	22	7	1	30
	Total	550	48	22	620

There were 362 patients (out of 620 patients in the Safety database) who had a TSH value after treatment. There were 34 patients who had an elevated TSH (event) during the course of follow-up. For these 34 patients, the median time to TSH elevation 10.9 months (95% CI on median 6.0 to 13.6 months; range: 1.8 months to 76.3 months, IQ range 5.7 to 18.6 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 34 patients. The remaining 328 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 125011.030, clinstat\iss\iss.pdf, page 67, March 4, 2002 Siurce: 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).

Laboratory TSH Followup: Integrated Safety Population (N=620)

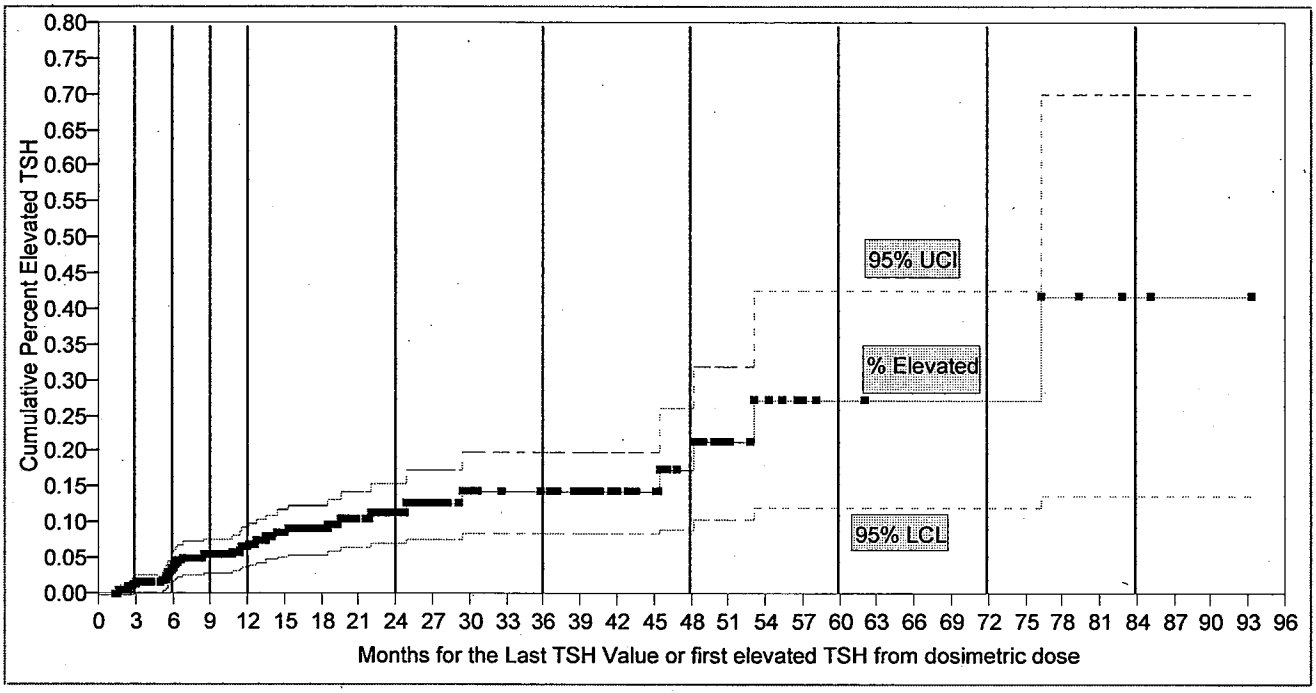
Time Interval	Number of Patients with a TSH Value within or after Interval[a]	Number Initially Elevated[b] in Time Interval	Number of Patients with a TSH Value or Thyroid Medication Assessment within or after Interval[a]	Number Initially Elevated or Initiating Thyroid Medication[b] in Time Interval
>0 – 3 months	362	4	516	3
>3 – 6 months	346	7	469	10
>6 – 12 months	298	9	421	10
>12 – 24 months	226	8	347	10
>24 months	90	6	170	9
Overall	362	34	507	42

[a] Excludes patients with elevated baseline TSH or prior history of thyroid medication. There were 533 patients who did not have elevated TSH at the baseline or Pre-Bexxar therapeutic regimen treatment. Out of 533 patients, 170 patients had missing TSH after treatment and 362 patients had a TSH value after treatment (34 elevated and 328 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 34 of 362 (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 and 42 patients (8%) with low/normal baseline TSH level became hypothyroid (i.e., developed an elevated TSH or initiated thyroid medication).

Analyses were conducted assessing the time to hypothyroidism based on elevated TSH value alone and based on elevated TSH value and/or initiation of thyroid supplementation. The latter analysis provided a lower cumulative incidence. This appeared to be due to that fact that when a patient did not have TSH assessment, the patient was censored in the former analysis but would not be censored in the latter analysis if he/she indicated that he was not taking thyroid supplementation. FDA was concerned that the latter assay may have been falsely reassuring by use of data from patients who were not appropriately followed for this adverse event. Therefore, FDA has chosen only to provide the analysis based on TSH testing (shown below).

Percent Elevated TSH by Months Censored at the Last available TSH Value (Cumulative)

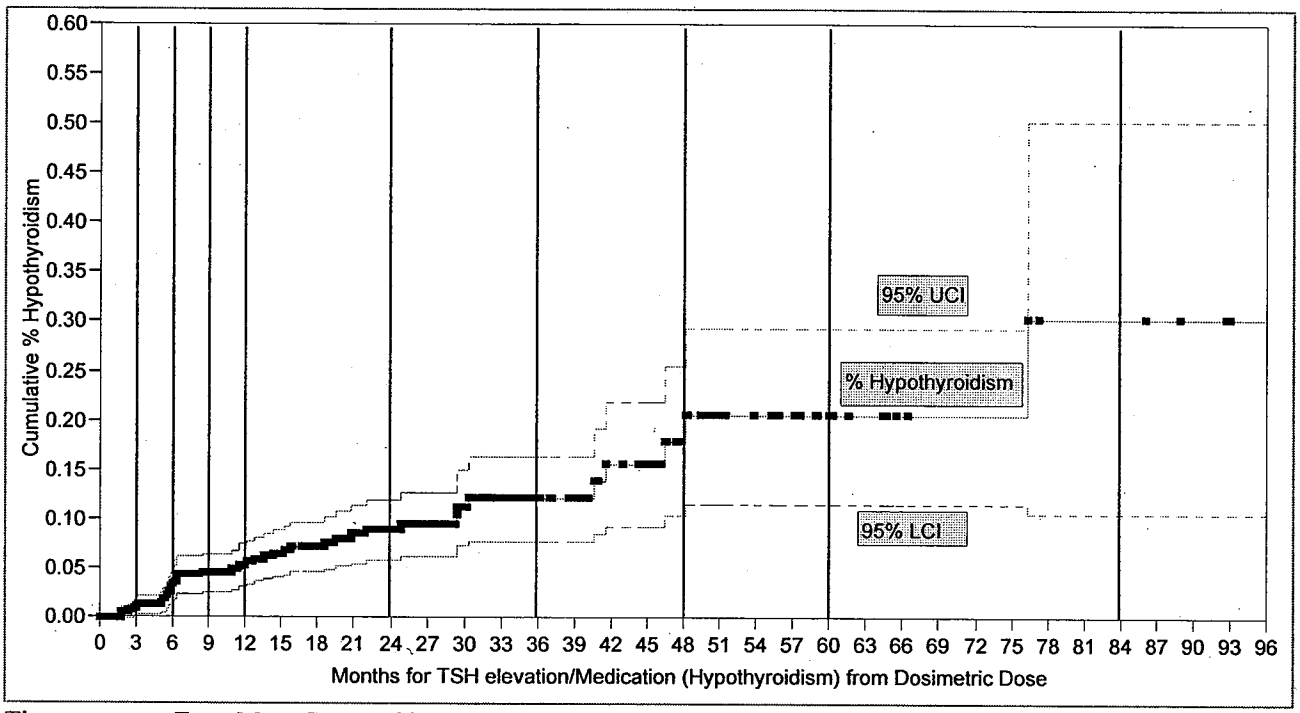


Time to event: Months Last TSH or first elevated; Censored by: Censor Day at Last TSH value

Months	0	3	6	12	24	36	48	60	72	84	96
Elevated	0	4	11	20	28	30	31	33	33	34	34
#Censored	0	14	60	128	252	288	309	323	324	326	328
# at Risk	362	344	291	214	82	44	22	6	5	2	0

#s are cumulative

Percent Hypothyroid (i.e., developed an elevated TSH or initiated thyroid medication) by Months Censored at the Last available TSH Value or thyroid medication (Cumulative)



Time to event:: EventMon; Censored by: EVENTDYC

Months	0	3	6	12	24	36	48	60	72	84	96
Hypothyr	0	4	13	23	33	37	40	41	41	42	42
#Censored	0	45	79	138	305	408	435	451	458	459	463
# at Risk	507	458	415	346	202	62	32	15	8	6	2

#s are cumulative

HAMA

HAMA Values (Site or Central Evaluation)

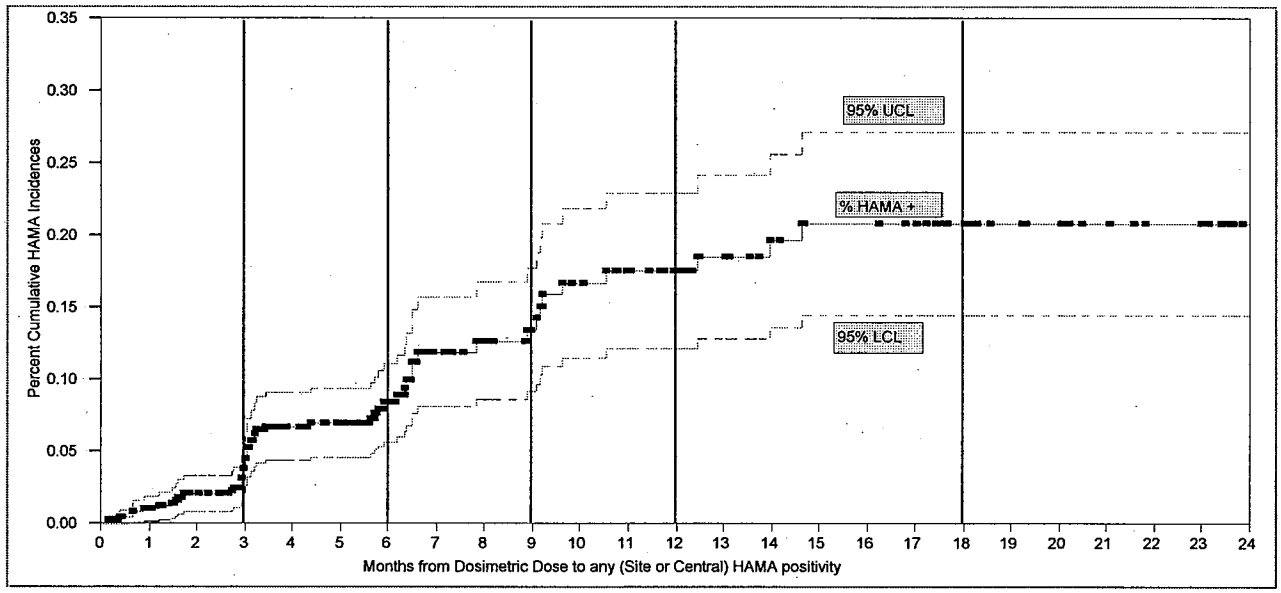
For the **site or central assay**, the data were pooled and patients were classified as HAMA positive if they were positive either the site or central assay. There were 604 patients (out of 620 patients in the Safety database) who had a negative baseline HAMA, 10 had a positive baseline HAMA and 6 had missing value. Out of 604 with negative baseline HAMA, 515 patients had had at least one follow-up assessment. A total of 51of the 515 patients (10%) with a negative baseline HAMA and follow-up HAMA converted to HAMA positivity. For these 51 patients, the median time to HAMA positivity converting to HAMA positivity was 96 days (range: 5–446 days, IQ range 90 to 198 days). Forty-one of 51 (80%) patients converting to HAMA positivity on or prior to their Month 6 scheduled evaluation (228 days), and 10 of the 51 (20%) converted to HAMA positivity after the Month 6 evaluation. Only three of the 84 (4%) patients who were HAMA negative prior to 12 months and were later assayed became HAMA positive. No patient converted to HAMA positivity after 15 months.

The event (HAMA positive) was assumed to have occurred the first time a patient was HAMA positive for these 51 patients. The remaining 464 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.

Ref: Safety update (BLA Submission 125011.030, March 4, 2002, clinstat\iss\iss.pdf, page 63- the 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 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)



Time to event:: APOSMON, Censored by : APOSDAYC

Months	0	3	6	9	12	18	24
# HAMA+	0	18	35	43	48	51	51
# Censored	0	84	273	364	383	406	427
# at Risk	515	413	207	108	84	58	88

#s are cumulative

HAMA Values (Central Evaluation)

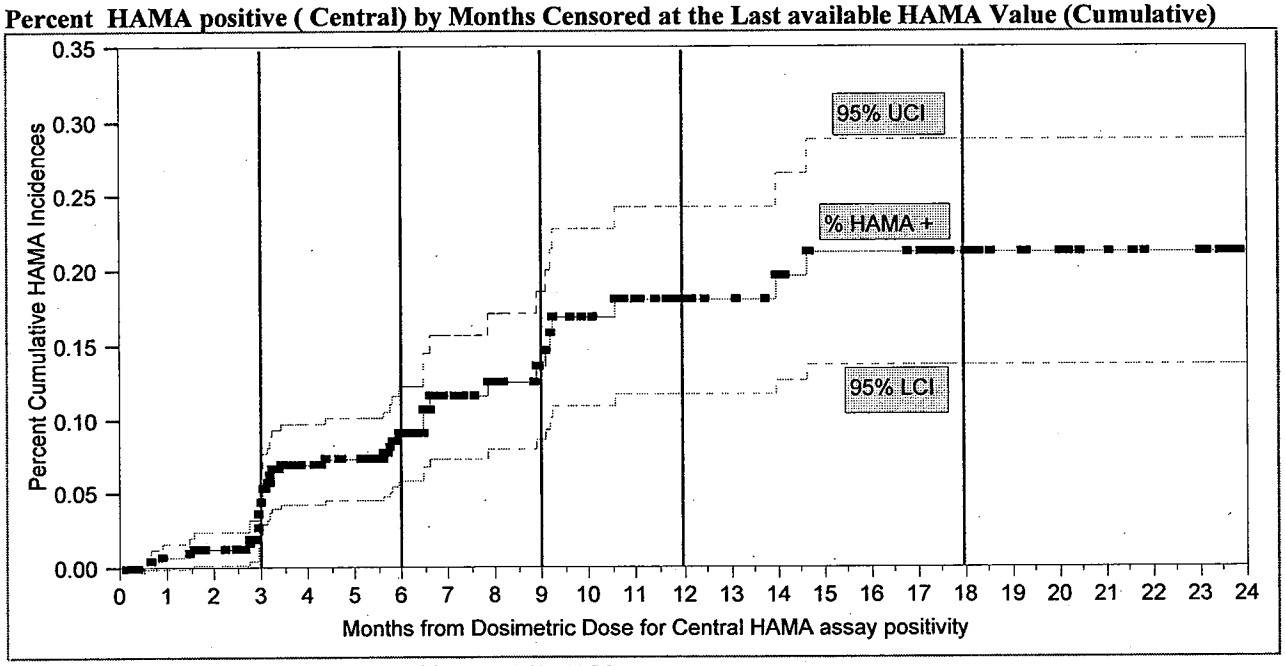
The **central assay** was approved after Studies RIT-I-000 and RIT-II-001 completed enrollment . There were 472 patients (out of 620 patients in the Safety database) who had a negative baseline HAMA by central evaluation (10 positive and 138 missing). Out of 472 with negative baseline central HAMA, 385 patients had at least one follow-up assessment. A total of 40 of the 385 patients (10%) with a negative baseline central HAMA and follow-up central HAMA converted to HAMA positivity. For these 40 patients, the median time to HAMA positivity converting to HAMA positivity was 96 days (95% CI on median 92-172 days; range: 21–446 days, IQ range 90-198 days). Only two of the 57 (4%) patients who were HAMA negative prior to 12 months and were later assayed became HAMA positive based on the central assay. No patient converted to HAMA positivity after 15 months.

The event (HAMA positive) was assumed to have occurred the first time a patient was HAMA positive for these 40 patients. The remaining 345 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.

Ref: Safety update (BLA Submission 125011.030, March 4, 2002, clinstat\iss\iss.pdf, page 63- the **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 cumulative incidence for conversion to HAMA positivity is presented in the figure below.

Percent HAMA positive (Central) by Months Censored at the Last available HAMA Value (Cumulative)



Time to event:: CPOSMON; Censored by: CPOSDAYC

Months	0	3	6	9	12	18	24
# HAMA+	0	13	29	34	38	40	40
# Censored	0	49	195	271	290	306	327
# at Risk	385	323	190	80	57	79	18

#s are cumulative

Table: Laboratory HAMA follow-up

	Central HAMA Assay		Site or Central HAMA Assay	
Time Interval	**Number of Patients with a HAMA Value in Time Interval**	**Number Initially Elevated[a] in Time Interval**	**Number of Patients with a HAMA Value in Time Interval**	**Number Initially Elevated[a] in Time Interval**
>0 – 3 months	213	13	354	18
>3 – 6 months	264	16	362	17
>6 – 12 months	130	9	170	13
>12 – 24 months	47	2	61	3
>24 months	38	0	42	0
Overall	385	40	515	51

[a] Patients with conversion to HAMA positivity in time interval, no HAMA positivity in previous time intervals, and a negative HAMA at baseline. Thus 40 patients with a negative baseline HAMA converted to HAMA positivity for the Central HAMA Assay and 51 patients with a negative baseline HAMA converted to HAMA positivity for the Site or Central HAMA Assay. (SOURCE: dataset, LAB)

The concordance between the site central HAMA assays was 96% with 417 of 436 blood samples assayed by both the site and central HAMA assays in agreement. For site or central HAMA assay, almost all evaluable patients had at least one HAMA assessment at Week 7, Week 13, and/or Month 6. This is the time interval of the greatest incidence of conversion to HAMA positivity.

Source: HAMAOUT data - 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. Ref: Safety update (BLA Submission 125011.030, March 4, 2002, clinstat\iss\iss.pdf, page 63- 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.

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. These findings would suggest that use of Bexxar therapeutic regimen in less heavily pretreated patients who are more immunocompetent will .

Study - RIT-II-003 (HAMA)

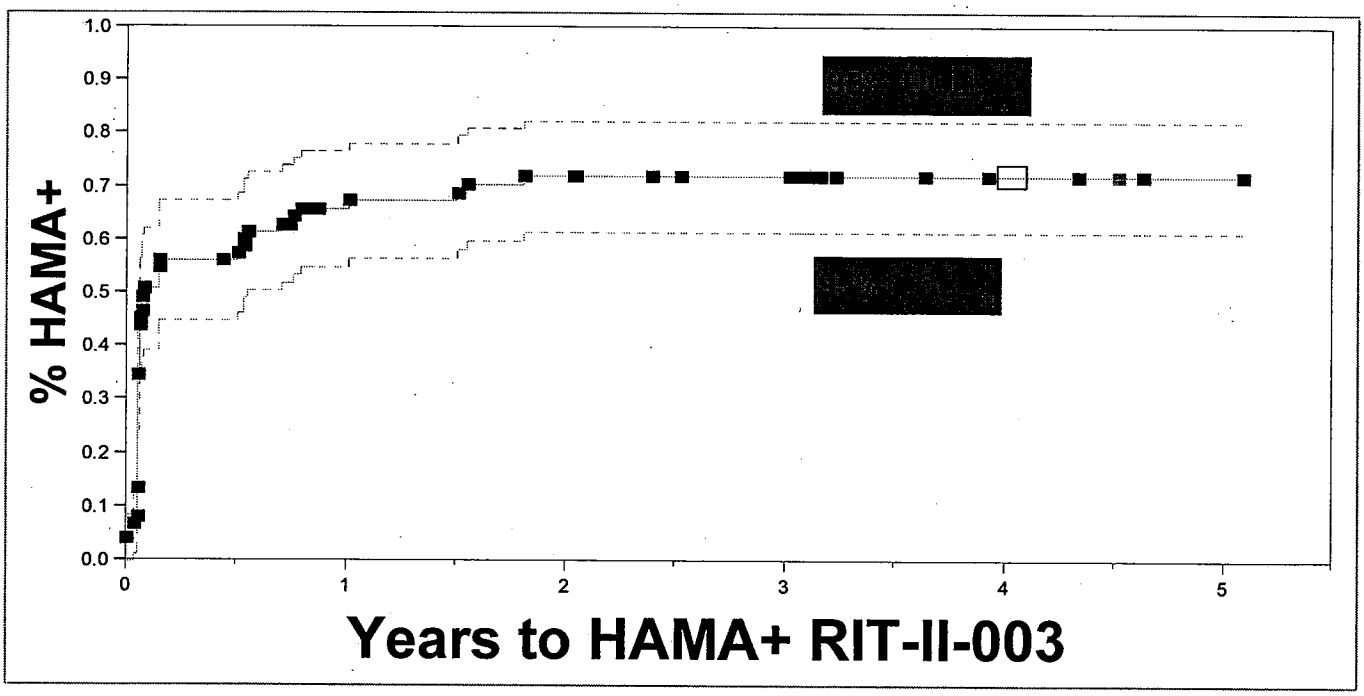
Total of 77 patients

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 = 0.074 years (27 days)
95% CI (0.063, 0.5534 years) or 23 to 202 days
Q1 = 0.0603 years or 23 days
Q3 NR
N Failed = 54
N Censored = 22
Min = 0 years
Max = 5.1 years

Years to any HAMA positivity (site or central) for the study RIT-II-003



Serious Adverse Events

FDA's review of the serious adverse events is ongoing. The data provided below are based upon the sponsor's preferred terms for reported events. In the majority of cases, FDA agrees with the sponsor's assessment of the event and categorization by preferred term. However, in review of the narrative summaries of these events, FDA would categorize certain events differently. Discussions of specific cases will be conducted with the sponsor to discuss FDA's concerns and arrive at an acceptable categorization of disputed terms. Examples of such cases are patients with febrile neutropenia coded as "fever" or as "neutropenia" and patients with apparent hypersensitivity reactions recorded as "hypotension". Any changes in the incidence of serious adverse events will be provided as an update at the Dec. 17, 2002, ODAC meeting.

The listing of serious adverse events, in descending order according to number of events observed in the efficacy/activity trials, are presented in the following table. This is not a per-patient incidence of events.

List of all serious events for the ISS-A data (n=229), ISS-B data (n=391) and all ISS data (n=620)

PREFER	N Patients ISS-A n=229	N Events ISS-A n=229	N Patients ISS-B n=391	N Events ISS-B n=391	N Patients ISS n=620	N Events ISS n=620
MYELOPROLIFERATIVE DISORDER	17	17	1	1	18	18
FEVER	9	9	1	12	19	21
SEPSIS	7	8	1	8	15	16
PNEUMONIA	6	6	1	6	12	12
DYSPNEA	5	7	1	6	11	13
PLEURAL EFFUSION	5	5	1	3	8	8
THROMBOCYTOPENIA	5	5	1	6	10	11
ACUTE MYELOBLASTIC LEUKEMIA	4	4			4	4
ANEMIA	4	4	1	5	9	9
HYPERCALCEMIA	4	4	1	2	6	6
HYPOTENSION	4	4	1	2	6	6
ABDOMINAL PAIN	3	3	1	4	7	7
DEEP THROMBOPHLEBITIS	3	3			3	3
GASTROINTESTINAL CARCINOMA	3	3			3	3
LEUKOPENIA	3	3	1	2	5	5
NEUTROPENIA	3	3	1	6	9	9
ABDOMEN ENLARGED	2	2			2	2
ARTHRALGIA	2	2	1	1	3	3
ASTHENIA	2	2	1	8	8	10
BLADDER CARCINOMA	2	2			2	2
BRONCHITIS	2	2			2	2
CONSTIPATION	2	2			2	2
KIDNEY FAILURE	2	2	1	4	6	6
LYMPHOMA LIKE REACTION	2	2			2	2
PAIN	2	3	1	8	9	11
PANCYTOPENIA	2	2	1	1	3	3
POSTURAL HYPOTENSION	2	2			2	2
VOMITING	2	2	1	6	8	8

ARRHYTHMIA	1	1	1	1	2	2
ARTHRITIS	1	1			1	1
ASPIRATION PNEUMONIA	1	1			1	1
ATAXIA	1	1			1	1
ATRIAL FLUTTER	1	1			1	1
BACK PAIN	1	1	1	3	4	4
BONE DISORDER	1	1	1	2	3	3
CARCINOMA	1	1			1	1
CARDIOMEGALY	1	1			1	1
CELLULITIS	1	1	1	2	3	3
CHILLS	1	1	1	3	3	4
CHOLECYSTITIS	1	1			1	1
CHRONIC LEUKEMIA	1	1			1	1
CONFUSION	1	1	1	3	4	4
COUGH INCREASED	1	1	1	1	2	2
DEHYDRATION	1	1	1	6	7	7
DYSPHAGIA	1	1	1	1	2	2
EDEMA	1	1			1	1
ENCEPHALOPATHY	1	1			1	1
ERYTHEMA NODOSUM	1	1			1	1
FLATULENCE	1	1			1	1
GASTROINTESTINAL HEMORRHAGE	1	1	1	4	3	5
HEMOPTYSIS	1	1			1	1
HEMORRHAGE	1	1	1	1	2	2
HERNIA	1	1			1	1
HERPES ZOSTER	1	1			1	1
HYPERURICEMIA	1	1	1	1	2	2
HYPOCHROMIC ANEMIA	1	3	1	1	2	4
HYPOXIA	1	1	1	1	2	2
INJECTION SITE REACTION	1	1			1	1
INTESTINAL OBSTRUCTION	1	1	1	2	3	3
LEUKEMIA	1	1			1	1
LUNG DISORDER	1	1	1	1	2	2
LUNG HEMORRHAGE	1	1			1	1
MALAISE	1	1			1	1
MELENA	1	1			1	1
NAUSEA	1	1	1	4	5	5
OLIGURIA	1	1			1	1
PATHOLOGICAL FRACTURE	1	1	1	2	2	3
PERIPHERAL EDEMA	1	1	1	1	2	2
PULMONARY EMBOLUS	1	1			1	1
RECTAL DISORDER	1	1			1	1
SERUM SICKNESS	1	1			1	1
SHOCK	1	1			1	1
SKIN CARCINOMA	1	1			1	1
SKIN ULCER	1	1			1	1
SUBDURAL HEMATOMA	1	1			1	1
SYNCOPE	1	1	1	1	2	2

THROMBOSIS	1	1			1	1
ULCERATIVE COLITIS	1	1			1	1
URINARY TRACT DISORDER	1	1			1	1
URINARY TRACT INFECTION	1	1			1	1
ABSCESS			1	2	2	2
ACIDOSIS			1	1	1	1
ANOREXIA			1	1	1	1
APNEA			1	4	4	4
AV BLOCK COMPLETE			1	1	1	1
CACHEXIA			1	1	1	1
CHEST PAIN			1	2	2	2
COLITIS			1	1	1	1
CONVULSION			1	1	1	1
DEATH			1	1	1	1
DIARRHEA			1	1	1	1
ESOPHAGITIS			1	1	1	1
FACIAL PARALYSIS			1	1	1	1
GASTROINTESTINAL DISORDER			1	1	1	1
HEART ARREST			1	1	1	1
HYDRONEPHROSIS			1	1	1	1
HYPERKALEMIA			1	1	1	1
HYPERTHYROIDISM			1	1	1	1
HYPOGLYCEMIA			1	1	1	1
INFECTION			1	2	2	2
INTESTINAL PERFORATION			1	1	1	1
KETOSIS			1	1	1	1
PARESTHESIA			1	1	1	1
PELVIC PAIN			1	1	1	1
PERICARDIAL EFFUSION			1	1	1	1
PHARYNGITIS			1	1	1	1
PNEUMOTHORAX			1	1	1	1
SOMNOLENCE			1	1	1	1
TACHYCARDIA			1	2	2	2
THINKING ABNORMAL			1	1	1	1
VENTRICULAR TACHYCARDIA			1	1	1	1

Myelodysplasia (MDS)

There were a total of 19 reported cases of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML); 18 cases in the 271 patients enrolled in the 5 efficacy/activity studies and one case in the expanded access experience (CP98-020).

A masked, independent review was performed by an expert hemato-morphologist, Dr. John Bennett of the University of Rochester. Based on Dr. Bennett's masked review, 5 patients (1 in the EAP and 4 in the other studies) had preexisting MDS by morphological and clinical criteria before administration of Bexxar therapeutic regimen therapy and 1 patient was found to have a morphologically normal marrow and peripheral blood. Given the limited duration of follow-up in the expanded access experience, data are only summarized for the other studies. Thus, based on the masked independent review, 11 of the 229 (4.8%, 95% CI: 2.4%–8.4%) patients were diagnosed with MDS/AML following Bexxar therapeutic regimen therapy for an annualized incidence of 2.2%/year (95% CI: 1.2%/year–3.9%/year).

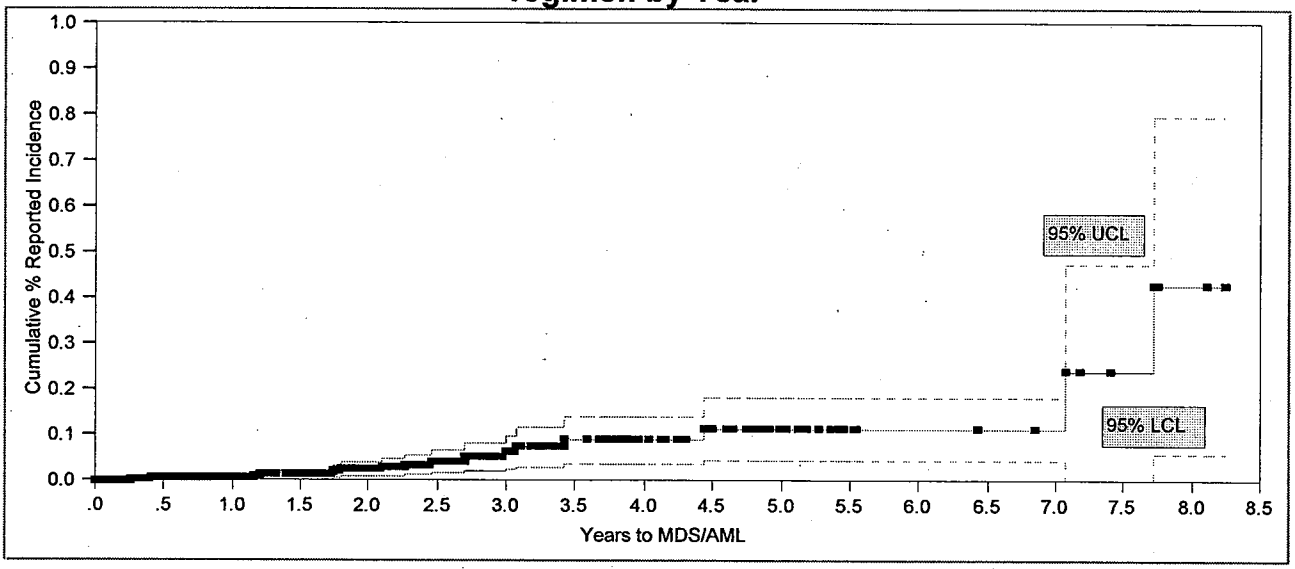
INCIDENCE RATE OF MYELODYSPLASIA/ACUTE LEUKEMIA (MDS or AML)

Study	N	# Incidence	Crude Rate Percent	Median Time to MDS/AML (Years)	IQ Range (Years)	Mean (Years)	95% CI on Mean
RIT-I-000	22	5	22.7%	3.9	1.5 to 7.4	4.2	0.3 to 8.1
RIT-II-001	47	5	10.6%	1.8	1.3 to 3.4	2.2	0.6 to 3.9
RIT-II-002	61	3	4.9%	1.2	0.9 to 1.2	1.2	0.0 to 2.1
RIT-II-004	59	4	6.8%	2.7	1.9 to 3.3	2.7	1.5 to 3.8
CP-97-012	40	1	2.5%				
CP-98-020	387	1	0.3%				
Overall	620	19	3.1%	2.1	1.2 to 3.1	2.5	1.5 to 3.5

Over all: N = 19 with 1 AML and 18 MDS. The crude incidence of MDS/AML is 3.1% (95% CI: 1.9%–4.7%) and the annualized incidence is 1.7%/year (95% CI: 1.1%/yr–2.7%/yr).

There is no apparent marked increase in MDS/AML during the first 18 months post treatment with Bexxar therapeutic regimen. Only one patient in the expanded access experience (n= 387) was diagnosed with MDS/AML, which would be expected given the shorter duration of follow-up in the expanded access experience (median follow-up 1.5 years vs. 2.4 years in the efficacy/activity studies). Among the 233 patients enrolled in the efficacy/activity other studies, eighteen patients developed MDS and/or acute leukemia with a crude incidence of MDS/AML of 7.7% (95% CI: 4.6%–11.9%) and an annualized incidence of 3.0%/year (95% CI: 1.9%/yr–4.8%/yr). 18 patients died after MDS and 1 alive up to follow-up time (day of occurrence of MDS 2.5 years, follow-up 7.8 years). Data from the Expanded Access Program are not as useful in estimating the incidence of MDS/AML, due to the shorter follow-up in that patient population (median follow-up equals 1.5 years).

Cumulative Incidence of MDS/AML in patients treated with Bexxar therapeutic regimen by Year



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	8.0	8.5
# MDS/ AML	0	3	4	6	9	12	13	16	16	17	17	17	17	17	17	18	19	19
Censored	0	97	177	283	388	469	524	543	559	567	583	592	594	595	596	598	599	601
# at Risk	620	520	439	337	223	139	83	61	45	36	20	11	9	8	7	4	2	0

#s are cumulative; Time to event: :MDSYr; Censored by : MDSYrC

Second malignancies

There were 5 secondary hematologic malignancies reported. These included 4 patients who developed AML and one patient who developed CML. Non-hematologic secondary neoplasms were also reported. The most common included non-melanomatous skin cancers, colon cancer, superficial bladder cancer and breast cancer. Some of these events included recurrence of an earlier diagnosis of cancer. The excretion of the radioisotope is through the gastrointestinal tract rather than the genitourinary system. Therefore, surveillance for gastrointestinal malignancies as a delayed toxicity should be conducted.

Growth Factors – ISS-A Population (n=229)

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%)	

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%)	

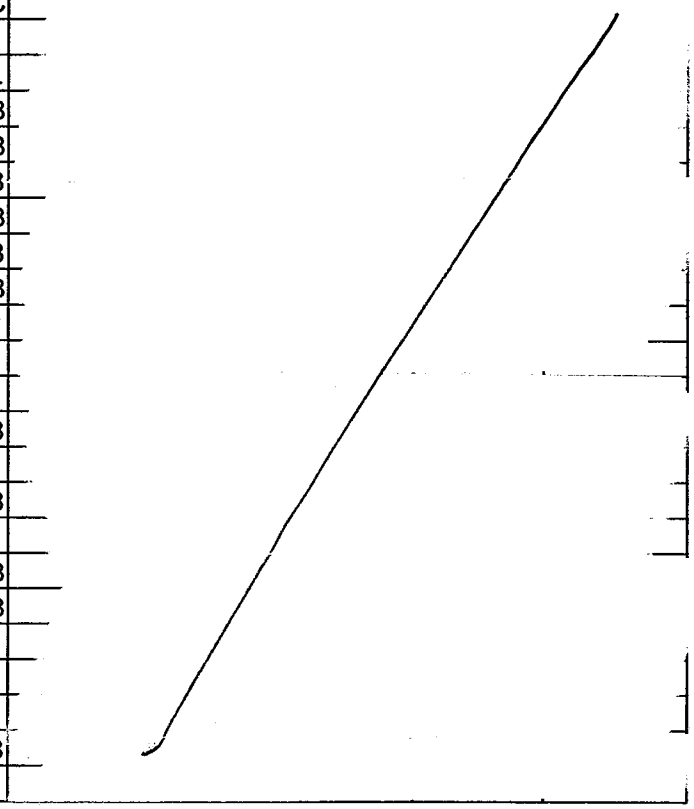
Median Days of EPO = 52
95% CI = 9 - 123 days
Q1 : Q3 = 32 : 123 days
Min = 1 day
Max = 258 days

Toxicity with no resolution (ISS-A Population)

Patients with no evidence of resolution of hematologic toxicity at the time of last follow-up

ANC

PATID	MAXTOX	DURATION	DURTX3C	NADRVAL	NADRTIME
001-009-006 45M L75C					
002-011-917 50F L75C					
004-013-005 63M T75L					
012-036-005 77M T75B					
020-014-350 59M T75B					
020-014-399 42M L75B					
020-017-430 55M T75B					
020-021-019 56M L65B					
020-021-035 53M T75B					
020-028-044 73F L75B					
020-028-099 54F L75B					
020-034-095 65F L75B					
020-034-132 66M L75B					
020-042-055 58F T75B					
020-047-092 48M L75B					
020-048-228 71F L75B					
020-050-134 73M T75B					
020-054-214 56M T75B					
020-056-409 66F L75B					
020-063-377 71F L65B					
020-066-198 73F T65B					
020-074-316 72M L75B					
020-075-289 72F T75B					



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PLT

PATID	MAXTOX	DURATION	DURTX3C	NADRVAL	NADRTIME
001-009-001 60F T65C					
001-009-006 45M L75C					
002-030-002 69F L75L					
002-030-019 52M L65B					
002-030-023 54M L65B					
002-034-008 71M L65B					
004-013-005 63M T75L					
004-013-006 38F L75L					
020-014-350 59M T75B					
020-016-285 59M T65B					
020-017-430 55M T75B					
020-020-047 66M T75B					
020-021-019 56M L65B					
020-021-025 59M L65B					
020-028-044 73F L75B					
020-028-099 54F L75B					
020-028-114 71F T75B					
020-034-005 68M T65B					
020-034-083 73F L75B					
020-034-085 53F L65B					
020-034-095 65F L75B					
020-038-022 53M L65B					
020-042-113 64F L65B					
020-045-059 46F T75B					
020-050-134 73M T75B					
020-050-337 59M L75B					
020-054-214 56M T75B					
020-056-409 66F L75B					
020-060-178 54F T75B					
020-065-233 54F L75B					
020-066-198 73F T65B					
020-068-279 70M L75B					
020-072-373 36M L75B					
020-074-316 72M L75B					
020-075-289 72F T75B					
012-036-005 77M T75B					

b(4)

HGB

PATID	MAXTOX	DURATION	DURTX3C	NADRVAL	NADRTIME
001-008-002 30F L00C					
004-013-006 38F L75L					
020-021-019 56M L65B					
020-028-044 73F L75B					
020-028-114 71F T75B					
020-040-402 67F L75B					
020-042-055 58F T75B					
020-065-233 54F L75B					
020-067-266 70M L75B					
020-068-259 34M L75B					

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Appendix A

Summary of Baseline for all the studies

Intent-to-Treat Population

Table A1

b(4)

Baseline Variables- Demographics

	All	ISS-A ISE	ISS-B	Dur Res	ISE–Dur Resp	RIT-I-000	RIT-II-001	RIT-II-002A	RIT-II-002B	RIT-II-002X	RIT-II-003	RIT-II-004	CP-97-012	CP-98-020	Tran Pop
N	**835**	271	393	**78**	**193**	59	47	42	36	19	77	61	43	387	**71**
Age (Years)															
Median	56	55	58	52	57	50	49	56	55	59	49	59	56	58	59
Q1	47	46	50	43	48	41	40	50	46	53	42	52	49	50	49
Q3	66	64	67	60	71	59	60	67	65	70	55	68	65	58	67
Min															
Max															
Gender															
Male	465	163	208	46	117	37	25	23	18	11	41	38	29	205	41
% Male	56 %	60	53	59	61	63	53	55	50	58	53	62	67	53	58
Female	370	108	185	32	76	22	22	19	18	8	36	23	14	182	30
Race															
White	774	250	365	66	184	54	45	39	33	18	74	59	35	360	67
% White	93 %	92	93	85	95	92	96	93	92	95	97	97	81	93	94
Other	61	21	28	12	9	5	2	3	3	1	3	2	8	27	4
Histology Grade at study entry															
Low															
N	644	178	313	61	117	28	33	36	28	17	77	37	27	310	
%	77 %	66	80	78	61	47.5	70.2	86	78	89	100	61	63	80	
Transformed															
N	168	72	80	17	55	14	14	6	8	2		23	13	77	71
%	20 %	27	20	22	29	24	30	14	22	11		38	30	20	100
Intermediate															
N	21	19			19	15						1	3		
%	2.5 %	7			10	25	0.0					1.6	7.0		
High															
N	2	2			2	2									
%	0.3 %	1			1	3									
Tumor Grade at study entry															
1-Low															
N	661	188	316	65	123	28	36	39	30	18	77	37	30	312	9
%	79 %	69	80	83	64	48	77	93	78	95	100	61	70	81	13
2-Intermediate															
N	164	78	74	13	65	27	10	3	6	1		24	13	72	59
%	19.6	29	19	17	34	46	21	7	22	5		39	30	19	83
3-High															
N	10	5	3		5	4	1							3	3
%	1 %	2	1		3	7	2							1	4

Table A1 (Continued)
Baseline Variables

	All	ISS-A (ISE)	ISS-B	Dur Resp	ISE–Dur Resp	RIT-I-000	RIT-II-001	RIT-II-002A	RIT-II-002B	RIT-II-002X	RIT-II-003	RIT-II-004	CP-97-012	CP-98-020	Trans Pop
N	835	271	393	78	193	59	47	42	36	19	77	61	43	387	71
Cell type at study entry															
0	1	1			1	1									1
%						2									1
1	18	4	10	2	2		1					2	1	10	
%	2	1	3	3	1		2					3	2	3	
2	43	6	27	2	4		2	2				2		26	
%	5	2	7	3	2		4	5				3		7	
3	344	99	155	30	69	12	20	20	18	11	55	22	14	153	6
%	41	37	39	38	36	20	43	48	50	58	71	36	33	40	8
4	240	76	113	31	45	15	12	17	12	7	22	11	14	112	3
%	29	28	29	40	23	25	26	40	33	37	29	18	33	29	4
5	32	15	9	7	8	5	2	1	4			4	3	9	12
%	4	6	2	9	4	8	4	2	11			7	7	2	17
6	13	4	8	1	3							2	2	8	4
%	2	1	2	1	2							3	5	2	6
7	31	13	17	1	12	2	3		1			6	2	16	11
%	4	5	4	1	6	3	6		3			10	5	4	15
8	69	32	36	4	28	14	3	2	1	1		8	4	36	24
%	8	12	9	5	15	24	6	5	3	5		13	9	9	34
9	7	4	1		4	4								1	2
%	1	1			2	7									3
0															
%															
11	1		1											1	
%															
12	3	1	2		1		1							2	
%							2								
13	6	5			5	4						1			
%		2			3	7						2			
14	4		3											3	
%															
99	23	11	11		11	2	3					3	3	10	8
%	3	4	3		6	3	6					5	7	3	11

Key:
0= unknown, 1= small lymphocytic with plasmacytoid differentiation, 2= small lymphocytic without plasmacytoid differentiation, 3= follicular small-cleaved cell, 4= follicular mixed (<50% large cell), 5=follicular large cell, 6= diffuse small-cleaved cell, 7= diffuse mixed small-cleaved cell & large cell, 8= diffuse large cell, 9= large cell immunoblastic, 10= lymphoblastic, convoluted, 11= lymphoblastic, non-convoluted, 12= monocytoid B-cell, 13 = mantle cell, 14, 99= other

Table A1 (Continued)
Baseline Variables

	All	ISS-A (ISE)	ISS-B	Dur Res	ISE–Dur Resp	RIT-I-000	RIT-II-001	RIT-II-002A	RIT-II-002B	RIT-II-002X	RIT-II-003	RIT-II-004	CP-97-012	CP-98-020	Tran Pop
N	**835**	271	393	**78**	**193**	59	47	42	36	19	77	61	43	387	**71**
Ann Arbor Stage at study entry															
0=Unknown															
N	1		1											1	
%	.1 %														
1															
N	18	4	9		4	3			1				1	9	1
%	2 %	1	2		2	5			3				2	2	1
2															
N	71	24	33	9	15	4	4	5	3	3		1	7	31	7
%	9 %	9	8	12	8	7	9	12	8	16		2	16	8	10
3															
N	201	58	100	20	38	13	6	10	9	7	24	13	9	100	17
%	24 %	21	25	26	20	22	13	24	25	37	31	21	21	26	24
4															
N	544	185	250	49	136	39	37	27	23	9	53	47	26	246	46
%	65 %	68	64	63	70	66	79	64	64	47	69	77	61	64	65
IPI (%) Categories															
0															
N	19	7	10	3	4	2	2	0	0	1	0	0	2	10	2
%	2 %	3	3	4	2	3	4			5	0	0	5	3	3
1															
N	113	48	27	23	25	11	4	11	9	3	23	7	12	27	7
%	14 %	18	7	30	13	19	9	26	25	11	30	12	28	7	10
2															
N	289	103	114	32	71	24	20	17	18	5	36	22	15	114	23
%	35 %	38	29	41	37	41	43	40	50	26	47	36	35	29	32
3															
N	273	76	157	16	60	19	18	8	7	4	15	22	5	157	23
%	33 %	28	40	21	31	32	38	19	19	21	20	36	12	41	32
4															
N	86	24	50	2	22	3	3	4	1	2	1	7	4	50	11
%	10 %	9	13	3	11	5	6	10	3	11	1	12	9	13	15
5															
N	4	2	1	1	1	0	0	0	0	0	0	1	1	1	1
%	.5 %	1	.3	1.3	0.5	0	0					1.6	2.3		1
Missing															
N	51	11	34	1	10			1	1	4	2	2	4	28	4
%	6 %	4	9	1	5			2	3	21	3	3	9	7	6

Table A1 (Continued)
Baseline Variables

	All	ISS-A (ISE)	ISS-B	Dur Res	ISE–Dur Resp	RIT-I-000	RIT-II-001	RIT-II-002 A	RIT-II-002 B	RIT-II-002 X	RIT-II-003	RIT-II-004	CP-97-012	CP-98-020	Tran Pop
N	**835**	271	393	**78**	**193**	59	47	42	36	19	77	61	43	387	**71**
Maximum Tumor Diameter 0 to < = 5 cm															
N	549	163	249	43	120	48	34	20	24	9	77	25	24	243	31
%	66 %	60	63	55	62	81	72	48	67	47	100	41	56	63	44
5cm, <=7cm															
N	120	43	65	15	28	5	6	8	6	6		14	5	65	15
%	14 %	16	17	19	15	8	13	19	17	32		23	12	17	21
7cm, <=10cm															
N	104	44	47	15	29	5	3	10	5	3		15	9	47	14
%	12 %	16	12	19	15	8	6	24	14	16		25	21	12	20
> 10 cm															
N	62	21	32	5	16	1	4	4	1	1		7	5	32	11
%	7 %	8	8	6	8	2	9	10	3	5		11	12	8	15
Years from Diagnosis to Study Entry															
Median	3.4	3.7	3.9	3.5	3.7	3.8	3.4	2.6	2.4	2.6	0.7	4.4	4.2	3.9	6.2
Q1	1.8	2.2	2.1	2.1	2.3	2.5	1.8	1.6	1.9	2.3	0.3	2.6	2.7	2.1	3.2
Q3	6.3	6.8	6.7	6.9	6.6	7.2	6.2	3.7	3.7	4.6	1.9	7.2	7.0	6.7	10.0
Min															
Max															
Missing N	5	4			4						1	1	3		
# Prior Chemo															
Median	2	3	2	3	3	3	4	2	2	2	0	4	4	2	4
Q1	1	2	1	2	2	2	2	1	1	1	0	3	3	1	3
Q3	4	4	3	4	5	5	5	3	3	3	0	5	5	3	5
Min															
Max															
Missing N	5														
# Prior Radio															
Median	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Q3	0	1	0	1	1	1	1	0	0	0	0	1	1	0	2
Min															
Max															
Prior BMT															
No (2)	818	256	391	72	184	45	47	42	36	19	77	61	42	387	67
% No	98 %	94	99	92	95	76	100	100	100	100	100	100	98	100	94
Yes (1)	17	15	2	6	9	14	0	0	0	0	0	0	1		4

b(4)

b(4)

b(4)

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

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.

Study CP-98-020 is Expanded Access Study - All low-grade or transformed low-grade NHL patients.

Appendix B

Summary of Responses for all the studies

Integrated Summary of Efficacy (ISE)

Table B1: Response Rate Analysis –Intent-to-Treat

Response Variable	ISE Data	RIT-I-000	RIT-II-001	RIT-II-002-A	RIT-II-002-B	RIT-II-002-X	RIT-II-002 (A+X)	RIT-II-004	CP-97-012	Tran Pop	Dur Res	ISE-Dur Resp
N	271	59	47	42	36	19	61	61	43	71	78	193
CR	43	5	2	11	3	7	18	7	11	7	30	13
CCR	32	11	10	3		1	4	5	2	11	30	2
PR	67	12	11	9	4	5	14	16	14	10	18	49
SD	15	1	1	5	11	3	8	4	1	2		15
PD	110	30	23	14	18	3	17	28	12	41		110
Missing	4							1	3			
ORR = CR+CCR +PR	142	28	23	23	7	13	36	28	27	28	78	64
% ORR	52.4	47.5	48.9	54.8	19.4	68.4	59.0	45.9	62.8	39.4	100	33.2
95% CI	(46,58)	(34 , 61)	(34 , 64)	(39 , 70)	(8 , 36)	(43 , 87)	(46 , 71)	(33 , 59)	(47 , 77)	(28 , 52)	(95, 100)	(27 , 40)
p-value comparing ORR for A vs B for RIT-I-002 trial = 0.0013 (Fisher's Exact Test)												

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

	Doses (cGy)								
Response Variable	0	25	35	45	55	65	75	85	All
N	6	3	4	9	8	6	20	3	59
CR (5)			1			1	2	1	5
CCR (4)			1	1	3	2	4		11
PR (3)	1	1		3	2	3	2		12
SD (2)							1		1
PD (1)	5	2	2	5	3		11	2	30
ORR = CR+CCR+ PR	1	1	2	4	5	6	8	1	28
% ORR	16.7	33.3	50.0	44.4	62.5	100.0	40.0	33.3	47.5
95% CI	(0.4, 64)	(0.8, 91)	(1, 99)	(14, 79)	(24, 91)	(54,100)	(19, 64)	(0.8,91)	(34, 61)

Algorithm: Confirmed responses for the final analyses were used which require two separate response evaluations at least 28 days apart with final MIRROR2 confirmation if present (includes resolved assessment for 9 patients)or if no final MIRROR2 confirmation, then MIRROR2 confirmation, or if no MIRROR2 confirmation, then Original MIRROR Panel or if no Original MIRROR Panel, then Investigator assessment.

Integrated Summary of Efficacy (ISE)

Duration of Response in Years for CBER derived ISE data

Duration (Years)	ISE Data	RIT-I-000	RIT-II-001	RIT-II-002-A	RIT-II-002-B	RIT-II-002-X	RIT-II-002 (A+X)	RIT-II-004	CP-97-012	Tran Pop	Dur Res	ISE-Dur Resp
N	271	59	47	42	36	19	61	61	43	71	78	193
Median	1.1	1.0	1.2	...	2.3	1.1	1.1	1.0	1.3	1.2	4.9	0.4
95%CI	(0.9,1.5)	(0.7,3.0)	(0.4,4.9)	(0.5, ...)	(0.4, ...)	(0.5, ...)	(0.7,...)	(0.3, ...)	(0.8, ...)	(0.9, 3.4)	(3.0 ,...)	(0.3, 0.6)
Q1	0.5	0.6	0.4	0.4	0.6	0.9	0.5	0.3	0.8	0.8	1.2	0.3
Q3	4.9	3.8	4.9	...	...	...	---	3.9	...	3.4	...	0.7
Min	[redacted]											
Max												
# relapsed	88	22	16	10	4	7	17	18	15	17	32	56
# Ongoing (censored)	54	6	7	13	3	6	19	10	12	11	40	8
# non-responders	129	31	24	19	29	6	25	33	16	43	0	129
p-value comparing ORR for A vs B for RIT-I-002 trial = 0.8769 (Log-rank Test)												

b(4)

Duration of response is computed only for responders (CR, CCR, PR). Patients who continued to be responders at their last response evaluation were censored.

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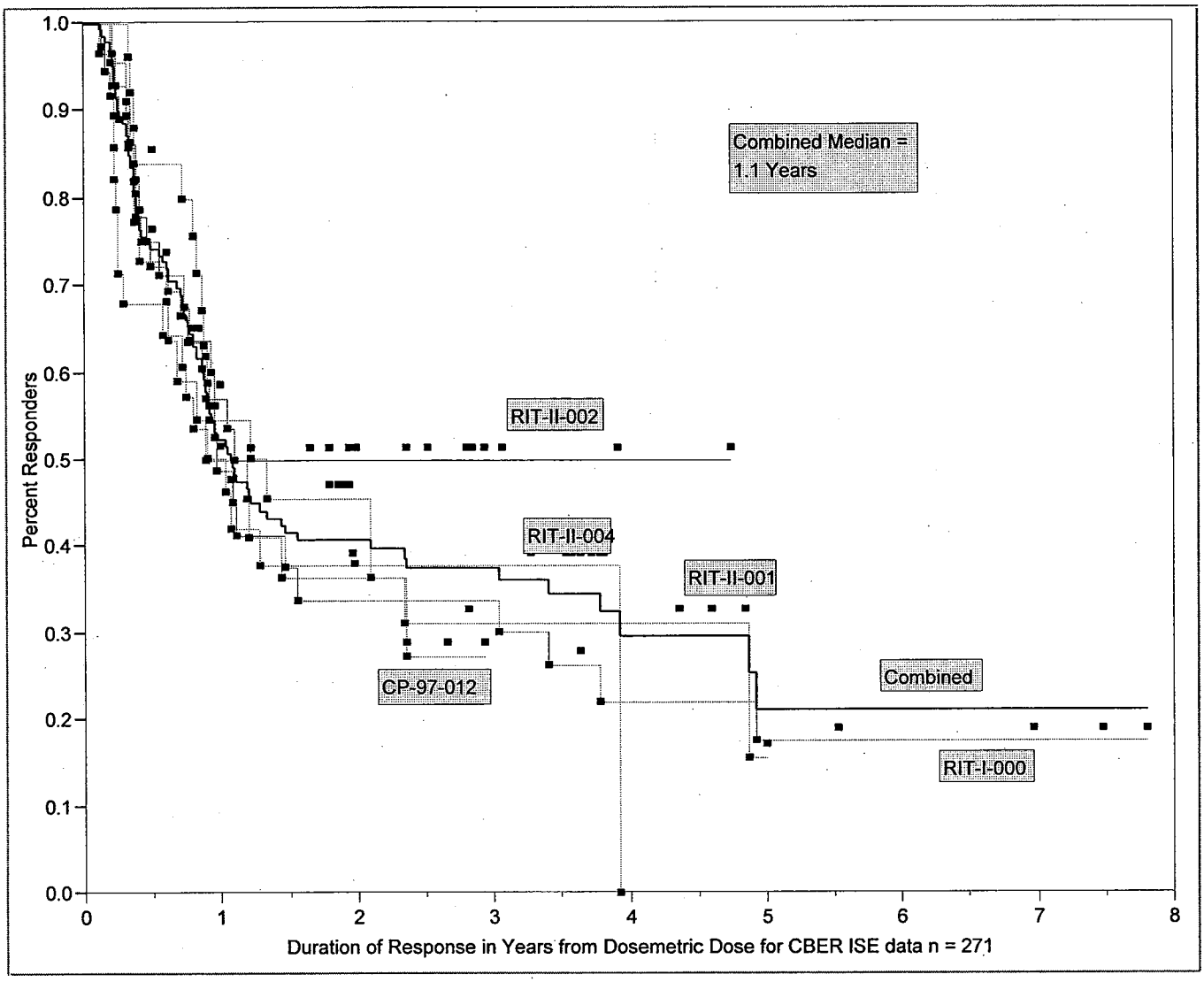
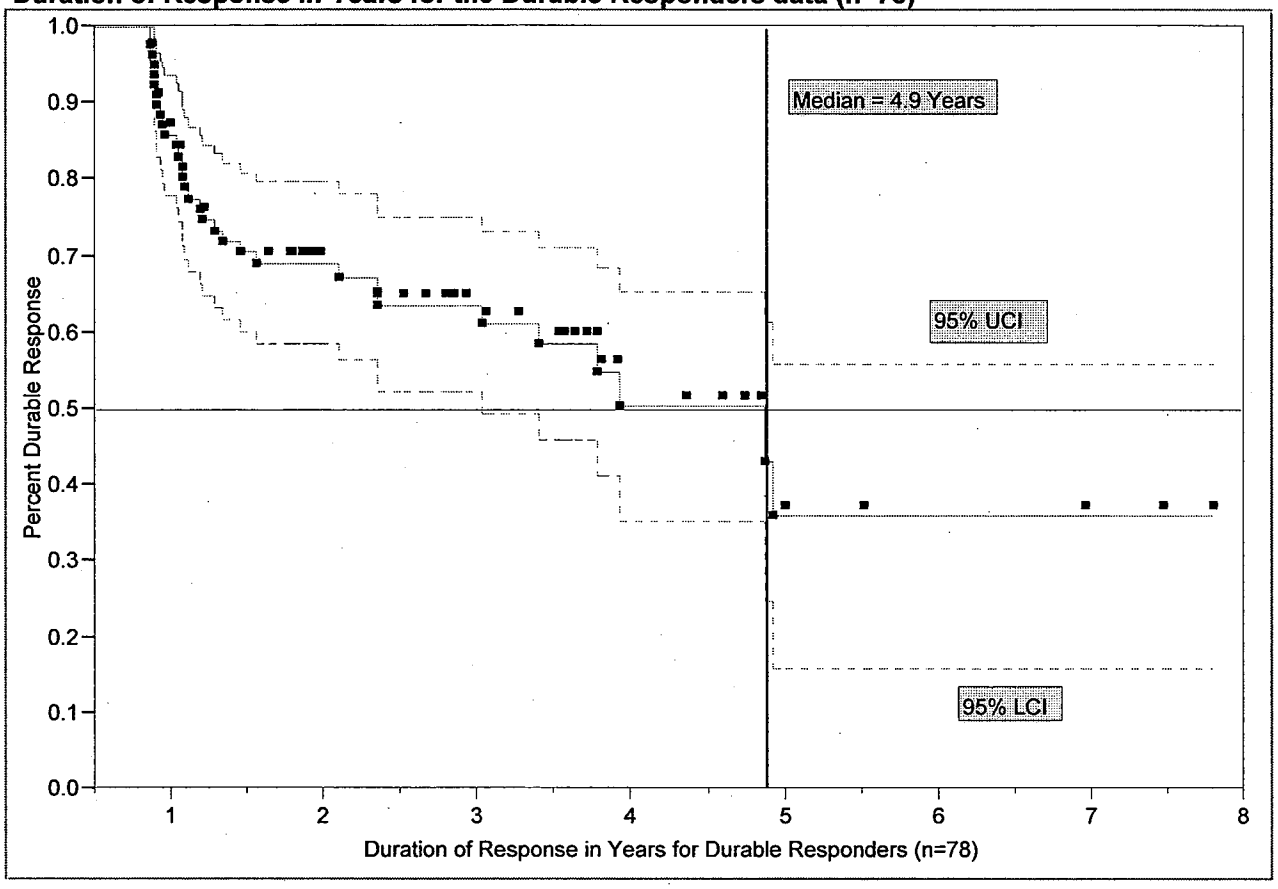
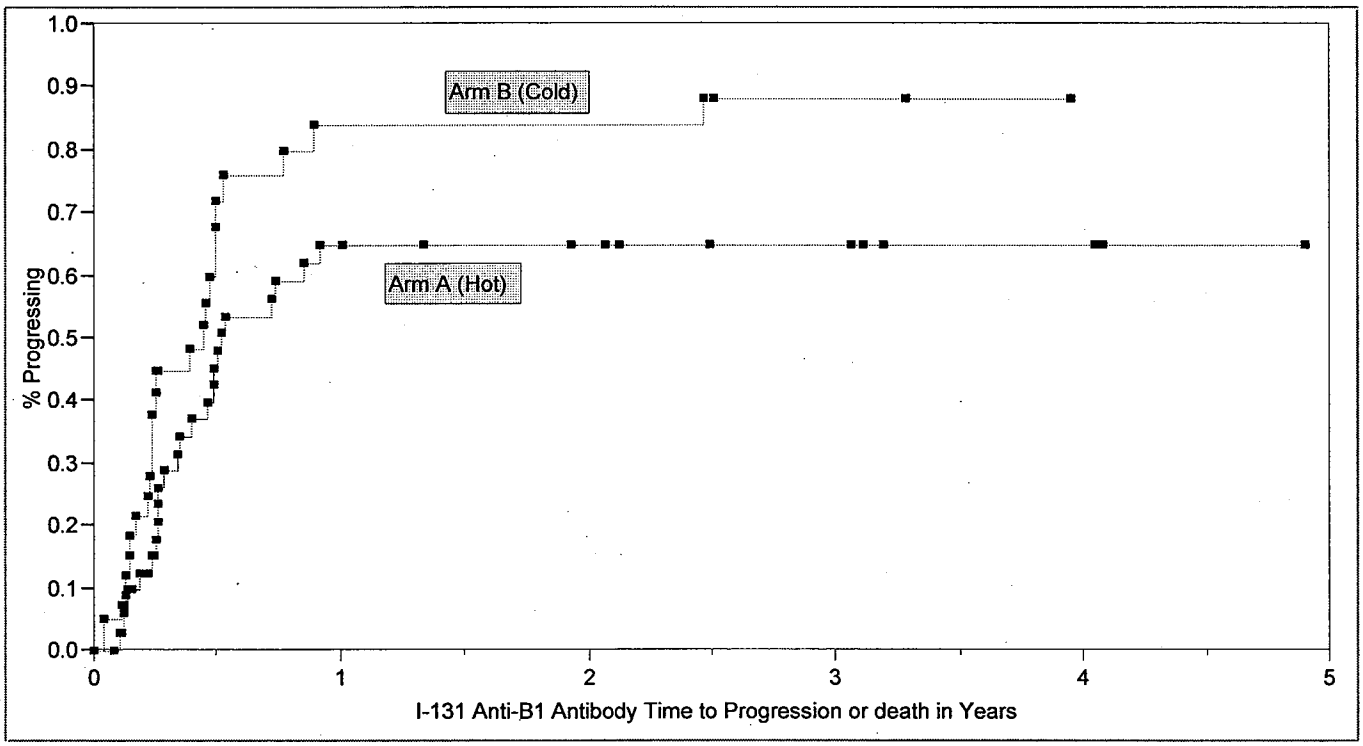
Duration (Years) of Response for the CBER derived ISE data (n=271)



Duration of Response in Years for the Durable Responders data (n=78)



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



Summary

Group	N Failed	N Censored	Mean		Std Dev
A	24	18	0.58889	Biased	0.05203
B	25	11	0.70316	Biased	0.15771
Combined	49	29	0.94746	Biased	0.11963

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
A	0.5233	0.3507	.	0.2685	.
B	0.4548	0.2438	0.4986	0.2301	0.537
Combined	0.4932	0.3452	0.5425	0.2438	2.474

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	4.6361	1	0.0313
Wilcoxon	3.7119	1	0.0540

Appendix C -- 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 620 patients was 281 days (9.2 months) and ranged from 4 to 2793 days (0.1 to 91.8 months). Median follow-up ranged from 1384 days (45.5 months) in Study RIT-I-000 to 183 days (6.0 months) in the Expanded Access Study. Overall, 403 patients had over six months of follow-up, 247 patients had over one year of follow-up, and 108 patients had over two years of follow-up.

Termination Reason (TRMRSN)

Reason	1	3	4	7	8	9	10	99	Missing	Total
Number	2	1	3	5	2	345	23	4	235	620

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)

Cause	0	1	2	3	Total deaths
Number	0	146	0	40	186 (30%)

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

Cumulative HAMA Positive N = 620 (Estimated using Kaplan-Meier Curves)

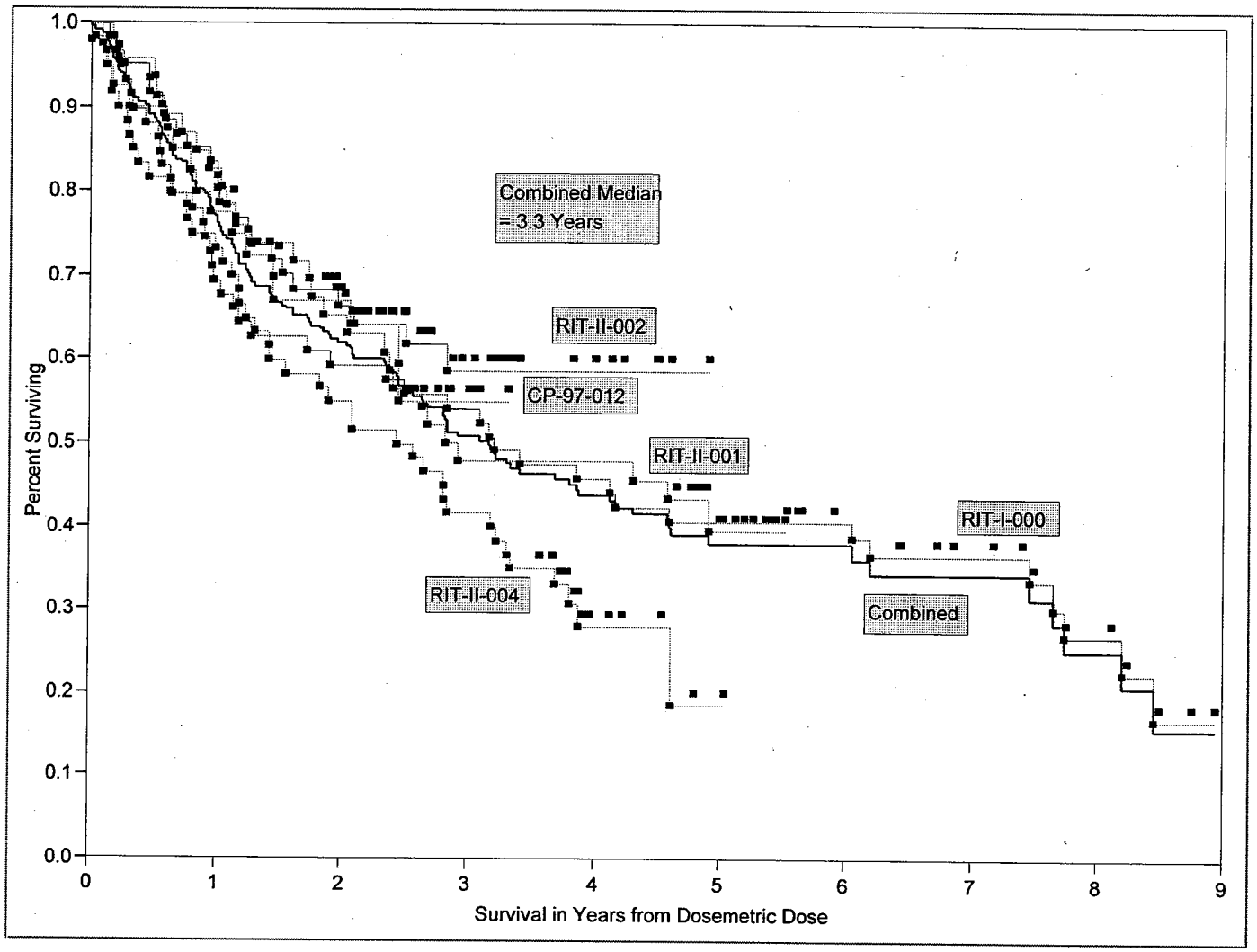
	Baseline	1 year	2 years	4 years
N	10	63	69	69
%	1.6	10.1	11	11

Survival Characteristics in Years for CBER derived ISE data for ISS Data (Based on K-M Curves)

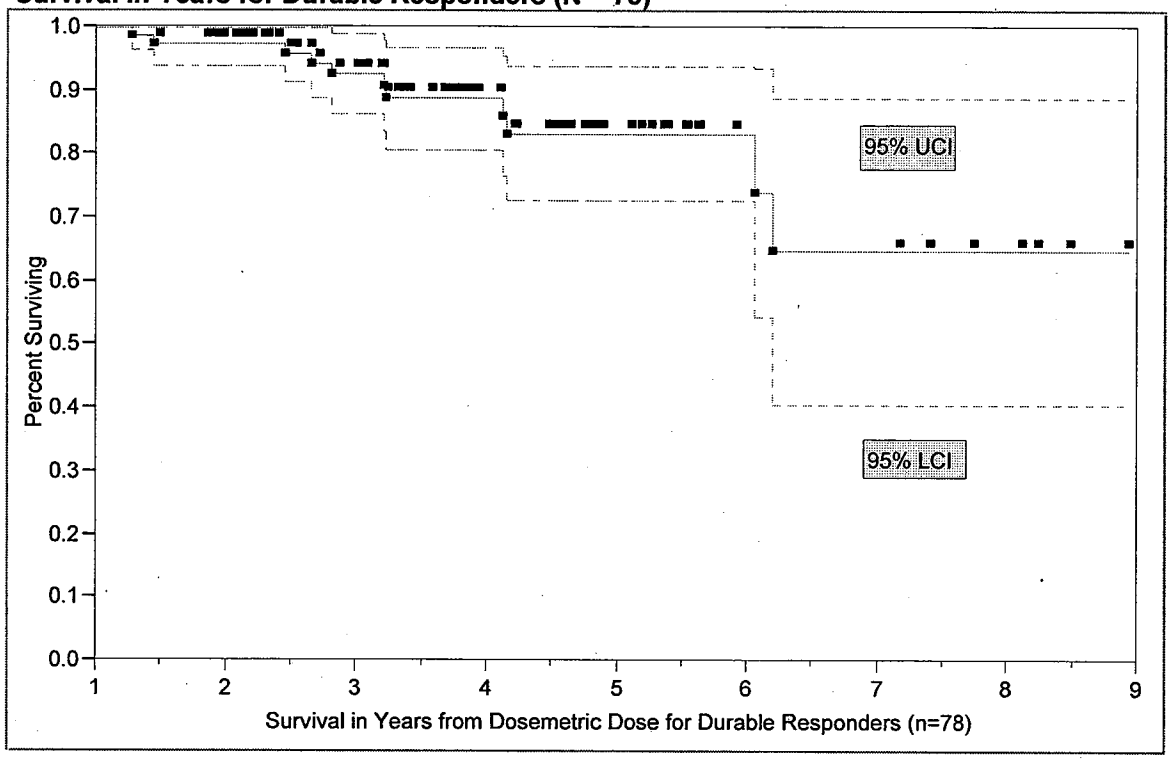
Duration (Years)	All Patients	ISE	RIT-I-000	RIT-II-001	RIT-II-002-A	RIT-II-002-B	RIT-II-002-X	RIT-II-002 (A+X)	RIT-II-004	CP-97-012	Tran Pop	Dur Res	ISE-Dur Resp
N	835	271	59	47	42	36	19	61	61	43	71	78	193
Median	4.3		3.2	2.9	...	...	...	...	2.4	...	1.9	...	1.8
95%CI	(3.4, 6.2)		(1.3, 6.2)	(1.9, ...)	(2.0. ...)	(2.9, ...)	(1.5, ...)	(2.5, ...)	(1.3, 3.3)	(2.1, ...)	(1.2, 3.8)	(6.1 , ..)	(1.3, ...)
Q1	1.2		0.9	1.3	1.0	2.0	1.5	1.3	0.8	1.1	0.6	6.1	0.8
Q3	8.5		8.2	...	...	...	...	...	4.6	...	7.7	...	4.6
Min	0.01	0.01	0.2	0.01	0.2	0.1	0.3	0.15	0.04	0.1	0.04	1.3	0.01
Max	8.95+	8.95+	8.95+	5.5+	4.9+	4.8+	4.5	4.9+	5.0+	3.3+	8.5+	8.9 5+	8.8+
# Dead	310	151	42	27	16	12	7	23	43	16	49	11	140
# Alive (censored)	520	116	17	20	26	24	12	38	17	24	22	67	49

p-value comparing ORR for A vs B for RIT-I-002 trial = 0.4822 (Log-rank Test)
Arm B includes the survival of 19 patients who crossed over to A

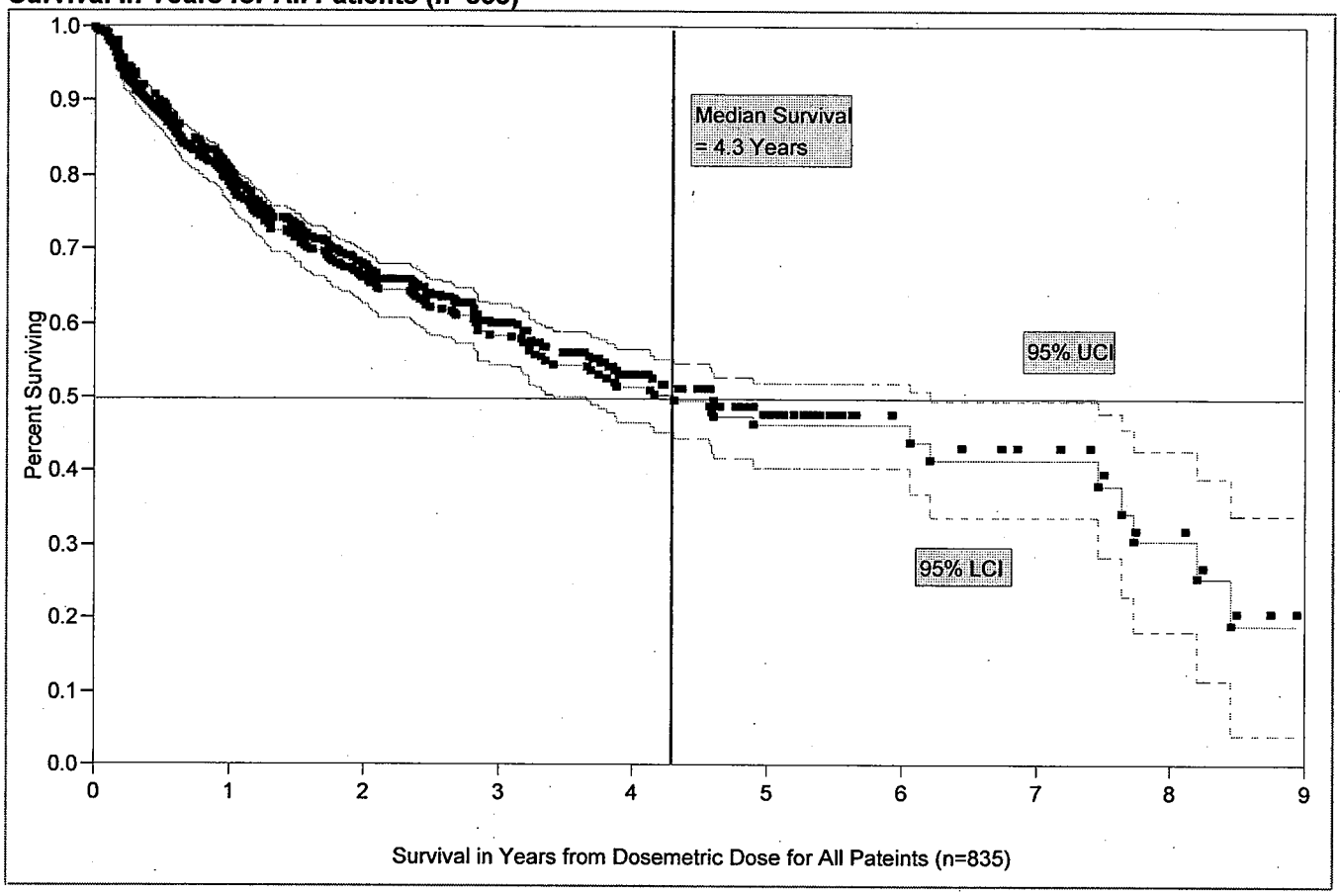
Survival in Years for CBER derived ISE population (n=271)



Survival in Years for Durable Responders (N = 78)



Survival in Years for All Patients (n=835)



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Appendix D -- Derived Dataset for 004 trial – MIRROR Assessed

Efficacy Data --Confirmed response-Chemo&I-131 Bexxar therapeutic regimen
0=NA 1=PD 2=SD 3=PR 4=CCR 5=CR Censored = 1, Not Censored = 0
M=Mirror, LQ= Last Qualifying Chemo, C=Confirmed, RES = Response
AB1= Bexxar therapeutic regimen, DUR = Duration (Days), delta = difference in duration

Obs	PATID	GRADE	MLQCRES	MLQCDUR	ABICRES	ABICDUR	delta	result
1	004-015-002 48F L00-	L	1	.	.	.	0	Equival
2	004-013-003 43M T65C	T	1	.	1	.	0	Equival
3	004-013-005 63M T75L	T	1	.	1	.	0	Equival
4	004-013-006 38F L75L	L	1	.	1	.	0	Equival
5	004-013-010 53M L75L	L	1	.	1	.	0	Equival
6	004-013-016 47F T65L	T	1	.	1	.	0	Equival
7	004-013-017 65M T65L	T	1	.	1	.	0	Equival
8	004-014-002 58F T75C	T	1	.	1	.	0	Equival
9	004-014-006 48M L75L	L	1	.	1	.	0	Equival
10	004-015-003 59M T75C	T	1	.	1	.	0	Equival
11	004-015-005 59M T00L	T	1	.	1	.	0	Equival
12	004-015-006 71F T75L	T	1	.	1	.	0	Equival
13	004-016-002 80M T65C	T	1	.	1	.	0	Equival
14	004-016-004 55M L75L	L	1	.	1	.	0	Equival
15	004-016-005 44F L75L	L	1	.	1	.	0	Equival
16	004-016-006 68M T65L	T	1	.	1	.	0	Equival
17	004-016-010 75M L65L	L	1	.	1	.	0	Equival
18	004-016-011 75F T75L	T	1	.	1	.	0	Equival
19	004-016-014 67F T75L	T	1	.	1	.	0	Equival
20	004-018-001 39F T00C	T	1	.	1	.	0	Equival
21	004-020-002 50M T75C	T	1	.	1	.	0	Equival
22	004-020-004 61M L75C	L	1	.	1	.	0	Equival
23	004-020-006 60M L75L	L	1	.	1	.	0	Equival
24	004-029-001 72M T65L	T	1	.	1	.	0	Equival
25	004-029-002 62M L75L	L	1	.	1	.	0	Equival
26	004-014-003 72M T75C	T	1	.	2	.	0	Equival
27	004-021-001 51M I75C	L	1	.	2	.	0	Equival
28	004-014-007 59F T65L	T	2	.	1	.	0	Equival
29	004-020-003 64M L75C	L	2	.	2	.	0	Equival
30	004-013-011 60F L65L	L	1	.	3	47	47	FavorBex
31	004-016-012 72F L65L	L	1	.	3	79	79	FavorBex
32	004-015-001 57F L65C	L	1	.	3	85	85	FavorBex
33	004-021-003 51M L75L	L	1	.	3	86	86	FavorBex
34	004-013-013 55F L75L	L	1	.	3	90	90	FavorBex
35	004-013-001 69M L65C	L	1	.	3	93	93	FavorBex
36	004-020-001 52F L75C	L	1	.	3	93	93	FavorBex
37	004-013-014 57M L75L	L	1	.	3	108	108	FavorBex
38	004-016-009 68M T75L	T	1	.	3	211	211	FavorBex
39	004-016-007 61M T75L	T	1	.	3	267	267	FavorBex
40	004-014-008 69M L75L	L	1	.	3	330	330	FavorBex
41	004-020-008 71M L65L	L	1	.	3	380	380	FavorBex
42	004-020-007 45M L75L	L	1	.	3	392	392	FavorBex
43	004-016-013 68M L75L	L	1	.	3	394	394	FavorBex
44	004-014-009 56M L65L	L	1	.	3	473	473	FavorBex

45	004-013-007	55M	L75L	L	1	.	4	274	274	FavorBex
46	004-013-008	82F	L65L	L	1	.	4	1395	1395	FavorBex
47	004-014-005	54M	L75L	L	1	.	5	294	294	FavorBex
48	004-021-002	51M	L65L	L	1	.	5	1291	1291	FavorBex
49	004-013-009	61M	L75L	L	1	.	5	1329	1329	FavorBex
50	004-029-003	39M	L75L	L	1	.	5	1358	1358	FavorBex
51	004-016-001	52M	L75C	L	1	.	5	1382	1382	FavorBex
52	004-014-001	44F	T75C	T	2	.	4	717	717	FavorBex
53	004-020-005	66M	L88L	L	2	.	4	1436	1436	FavorBex
54	004-016-003	44F	L75C	L	2	.	5	1306	1306	FavorBex
55	004-016-008	72F	T75L	T	3	124	4	366	242	FavorBex
56	004-013-015	58F	T75L	T	3	163	5	1196	1033	FavorBex
57	004-013-002	69F	L75C	L	3	92	1	.	92	FavorChe
58	004-013-012	66F	L75L	L	3	89	1	.	-89	FavorChe
59	004-015-004	60M	L75C	L	3	124	2	.	-124	FavorChe
60	004-014-004	53M	L65C	L	3	169	3	84	-85	FavorChe
61	004-013-004	66F	T75C	T	5	146	1	.	-146	FavorChe

result	Frequency	Cumulative Frequency
Equival	29	29
FavorBex	27	56
FavorChe	5	61

The UNIVARIATE Procedure

Tests for Location: Mu0=0

Test		-Statistic-	-----p Value------	
Student's t	t	4.158408	Pr > |t|	0.0001
Sign	M	11	Pr >= |M|	0.0001
Signed Rank	S	221.5	Pr >= |S|	<.0001

Appendix E -- Derived Dataset for 004 trial
LQC-Investigator Assessed- I-131MIRROR Assessed

Obs	PATID	GRADE	LQRESP	LQDUR	AB1CRES	AB1CDUR	delta	result
1	004-015-002 48F L00-	L	1	.	.	.	0	Equival
2	004-013-002 69F L75C	L	1	.	1	.	0	Equival
3	004-013-005 63M T75L	T	1	.	1	.	0	Equival
4	004-013-006 38F L75L	L	1	.	1	.	0	Equival
5	004-013-012 66F L75L	L	1	.	1	.	0	Equival
6	004-014-002 58F T75C	T	1	.	1	.	0	Equival
7	004-014-007 59F T65L	T	1	.	1	.	0	Equival
8	004-015-003 59M T75C	T	1	.	1	.	0	Equival
9	004-015-005 59M T00L	T	1	.	1	.	0	Equival
10	004-015-006 71F T75L	T	1	.	1	.	0	Equival
11	004-016-002 80M T65C	T	1	.	1	.	0	Equival
12	004-016-004 55M L75L	L	1	.	1	.	0	Equival
13	004-029-001 72M T65L	T	1	.	1	.	0	Equival
14	004-029-002 62M L75L	L	1	.	1	.	0	Equival
15	004-014-003 72M T75C	T	1	.	2	.	0	Equival
16	004-021-001 51M I75C	L	1	.	2	.	0	Equival
17	004-013-003 43M T65C	T	2	.	1	.	0	Equival
18	004-013-010 53M L75L	L	2	.	1	.	0	Equival
19	004-013-017 65M T65L	T	2	.	1	.	0	Equival
20	004-014-006 48M L75L	L	2	.	1	.	0	Equival
21	004-016-005 44F L75L	L	2	.	1	.	0	Equival
22	004-016-010 75M L65L	L	2	.	1	.	0	Equival
23	004-016-011 75F T75L	T	2	.	1	.	0	Equival
24	004-020-004 61M L75C	L	2	.	1	.	0	Equival
25	004-020-003 64M L75C	L	2	.	2	.	0	Equival
26	004-016-012 72F L65L	L	3	72	3	79	7	Equival
27	004-013-013 55F L75L	L	1	.	3	90	90	FavorBex
28	004-020-001 52F L75C	L	1	.	3	93	93	FavorBex
29	004-016-009 68M T75L	T	1	.	3	211	211	FavorBex
30	004-021-002 51M L65L	L	1	.	5	1291	1291	FavorBex
31	004-029-003 39M L75L	L	1	.	5	1358	1358	FavorBex
32	004-014-004 53M L65C	L	2	.	3	84	84	FavorBex
33	004-015-001 57F L65C	L	2	.	3	85	85	FavorBex
34	004-021-003 51M L75L	L	2	.	3	86	86	FavorBex
35	004-013-001 69M L65C	L	2	.	3	93	93	FavorBex
36	004-013-014 57M L75L	L	2	.	3	108	108	FavorBex
37	004-016-007 61M T75L	T	2	.	3	267	267	FavorBex
38	004-014-008 69M L75L	L	2	.	3	330	330	FavorBex
39	004-020-008 71M L65L	L	2	.	3	380	380	FavorBex
40	004-020-007 45M L75L	L	2	.	3	392	392	FavorBex
41	004-016-013 68M L75L	L	2	.	3	394	394	FavorBex
42	004-013-007 55M L75L	L	2	.	4	274	274	FavorBex
43	004-014-001 44F T75C	T	2	.	4	717	717	FavorBex
44	004-020-005 66M L88L	L	2	.	4	1436	1436	FavorBex
45	004-016-001 52M L75C	L	2	.	5	1382	1382	FavorBex
46	004-014-009 56M L65L	L	3	82	3	473	391	FavorBex
47	004-016-008 72F T75L	T	3	133	4	366	233	FavorBex
48	004-013-008 82F L65L	L	3	105	4	1395	1290	FavorBex
49	004-014-005 54M L75L	L	3	51	5	294	243	FavorBex
50	004-016-003 44F L75C	L	3	172	5	1306	1134	FavorBex
51	004-013-009 61M L75L	L	3	139	5	1329	1190	FavorBex

52	004-013-015	58F	T75L	T	4	163	5	1196	1033 FavorBex
53	004-020-006	60M	L75L	L	3	176	1	.	-176 FavorChe
54	004-013-004	66F	T75C	T	3	110	1	.	-110 FavorChe
55	004-016-014	67F	T75L	T	3	105	1	.	-105 FavorChe
56	004-018-001	39F	T00C	T	3	83	1	.	-83 FavorChe
57	004-020-002	50M	T75C	T	3	76	1	.	-76 FavorChe
58	004-013-016	47F	T65L	T	3	53	1	.	-53 FavorChe
59	004-015-004	60M	L75C	L	3	64	2	.	-64 FavorChe
60	004-013-011	60F	L65L	L	3	144	3	47	-97 FavorChe
61	004-016-006	68M	T65L	T	5	210	1	.	-210 FavorChe

The FREQ Procedure

result	Frequency	Cumulative Frequency
Equival	26	26
FavorBex	26	52
FavorChe	9	61

Tests for Location: Mu0=0

Test		-Statistic-		-----p Value------
Student's t	t	3.966275	Pr > |t|	0.0002
Sign	M	9	Pr >= |M|	0.0039
Signed Rank	S	246	Pr >= |S|	<.0001

Manufacturer	T1/2ϑ, hr	AUC, %ID hr/ml	Cmax, %ID/ml	Vdss, L
Coulter, N=10	66.4 (25)	1.28 (0.33)	0.018 (0.004)	7.4 (1.8)
Lonza, N=10	63.1 (13.7)	1.4 4 (0.38)	0.0021 (0.005)	6.7 (2.2)

Table of pharmacokinetic endpoints from study RIT-II-003 for Coulter and Lonza. Mean (SD).

Study	T1/2ϑ, hr	AUC, %ID hr/ml	Cmax, %ID/ml	Vdss, L
RIT-I-000, N = 22 - 23	84.7 (65.5)	1.73 (0.70)	0.021 (0.004)	6.7 (2.2)

Table of pharmacokinetic endpoints from study RIT-I-000 using Coulter material to compare to the pharmacokinetic values from Coulter material used in study RIT-II-003.

Manufacturer	T1/2ϑ, hr	AUC120, %ID hr/ml	Cmax, %ID/ml	Vdss, L
Lonza/CYTOGEN, N =26	63.5 (11.8)	1.01 (0.27)	0.02 (0.005)	6.9 (2)
BI Pharma, N = 24	65.4 (17.7)	1.07 (0.25)	0.02 (0.005)	6.4 (1.4)

Table of pharmacokinetic endpoints from RIT-II-003 for Lonza/CYTOGEN and BI Pharma. Mean (SD)

The pharmacokinetic comparability of Lonza/CYTOGEN versus BI Pharma manufactured material was assessed with and without adjustment for covariates that were selected from patients factors with significant influence on the pharmacokinetics of anti-B1 antibody. Based on area under the curve measurement and Cmax and comparison was made between the two sources of manufacture with adjustments for patient spleen size, patient weight, and tumor burden. After adjustment, the area under the curve differed by –2.4% with a 90% confidence interval (CI) of –11.5% to 7.9% and for Cmax by –7.9% with a 90% CI of –14.1% to –1.2%. Without adjustments for covariates, the difference was 6.2% with a 90% CI of –6% to 19.9% whereas the difference in Cmax was –2.4% with a 90% CI of –12.4% to 8.8%. As these differences are less than 20%, the materials are considered to be pharmacokinetically comparable.

Martin D. Green 6/25/03

Martin D. Green, Ph.D.