

Long-term responders

In the ----- submission to the FDA, the sponsor identified 75 long-term responders from the five clinical studies. In the ----- 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 -----, 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/---/92, 5/---/92 and 5/---/92 before receiving the therapeutic dose of the labeled antibody on 6/---/92. He was noted to have a CCR until disease progression after 477 days. However, a CT scan done on 6/---/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 ----- 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 ----- 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 ----- to tumor response evaluations at appropriate intervals and further amended on ----- 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 cm² were considered to be measurable disease. Lesions with products of perpendicular diameters between 1.0 cm² and 4.0 cm², 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 cm².

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	52	53
Range	(23-82)	(23-82)

Gender		
Male/Female	46/32	41/27
% Male	59 %	60%
Histology Grade at study entry		
Low N (%)	61 (78 %)	54 (79%)
Transformed N (%)	17 (22%)	14 (21%)
Tumor grade at the study entry		
Low N(%)	65 (83%)	58 (85%)
Intermediate N (%)	13 (17%)	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	26/77 (34%)	19/67 (28%)
2	32/77 (42%)	30/67 (45%)
3	16/77 (21%)	15/67 (22%)
4-5	3/77 (4%)	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.

Response to last qualifying chemotherapy (investigator) CR	22 (11%)	25 (32%)	24 (32%)	21 (31%)	3 (38%)
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Baseline Entry Variable	Patients without long-term responses (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=78	n=76	n=68	n=8
Tumor grade at the study entry					
Low	123 (64%)	65 (83%)	65 (86%)	58 (85%)	7 (88%)
Intermediate	65 (34%)	13 (17%)	11 (14%)	10 (15%)	1 (13%)
High	5 (3%)				

CCR PR	4 (2%) 61 (32%)	2 (3%) 26 (33%)	2 (3%) 26 (34%)	2 (3%) 25 (37%)	1 (13%)
Duration of response to last qualifying chemotherapy (yrs)					
Median	0.4	0.6	0.6	0.6	0.8
95% CI	(0.3, 0.5)	(0.5, 0.9)	(0.5, 0.9)	(0.5, 0.9)	(0.1, ...)
Q1	0.2	0.4	0.4	0.4	0.3
Q3	0.7	1.0	1.0	1.0	2.0
Min	0.1	0	0	0	0.1
Max	3.0	4.5	4.5	4.5	2.0
Number of prior chemotherapies					
Median	3	3	3	3	3
Q1	2	2	2	2	2
Q3	5	4	4	4	4
Min	1	1	1	1	1
Max	13	8	8	6	8

Last qualifying chemotherapy end day to study day (yrs)					
Median	0.4	1.1	1.1	1.0	1.2
95% CI	(0.4, 0.6)	(0.8, 1.2)	(0.9, 1.2)	(0.8, 1.2)	(0.3, 1.8)
Q1	0.2	0.5	0.5	0.5	0.5
Q3	1.0	1.6	1.6	1.6	1.8
Min	0	0.1	0.1	0.1	0.3
Max	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 $p = 0.3338$)].

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

Efficacy Outcome	Patients without long-term responses (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=78	n=76	n=68	n=8
Response					
CR (%)	13 (7%)	30 (38%)	30 (39%)	30 (44%)	
CCR (%)	2 (1%)	30 (38%)	28 (37%)	24 (35%)	4 (50%)
PR (%)	49 (25%)	18 (23%)	18 (24%)	14 (21%)	4 (50%)
ORR (%)	64 (33%)	78	76	68	8
Response Duration (yrs)					
Median	0.4	4.9	4.9	4.9	1.5
95% CI	(0.3, 0.6)	(3.0, ---)	(3.0, ---)	(3.4, ---)	(0.9, ---)
Q1	0.3	1.2	1.3	1.6	1.0
Q3	0.7	---	---	---	---
Min	(0.1+	0.9	0.9	0.9	0.9
Max	1.4	7.8+	7.8+	7.0+	7.8+

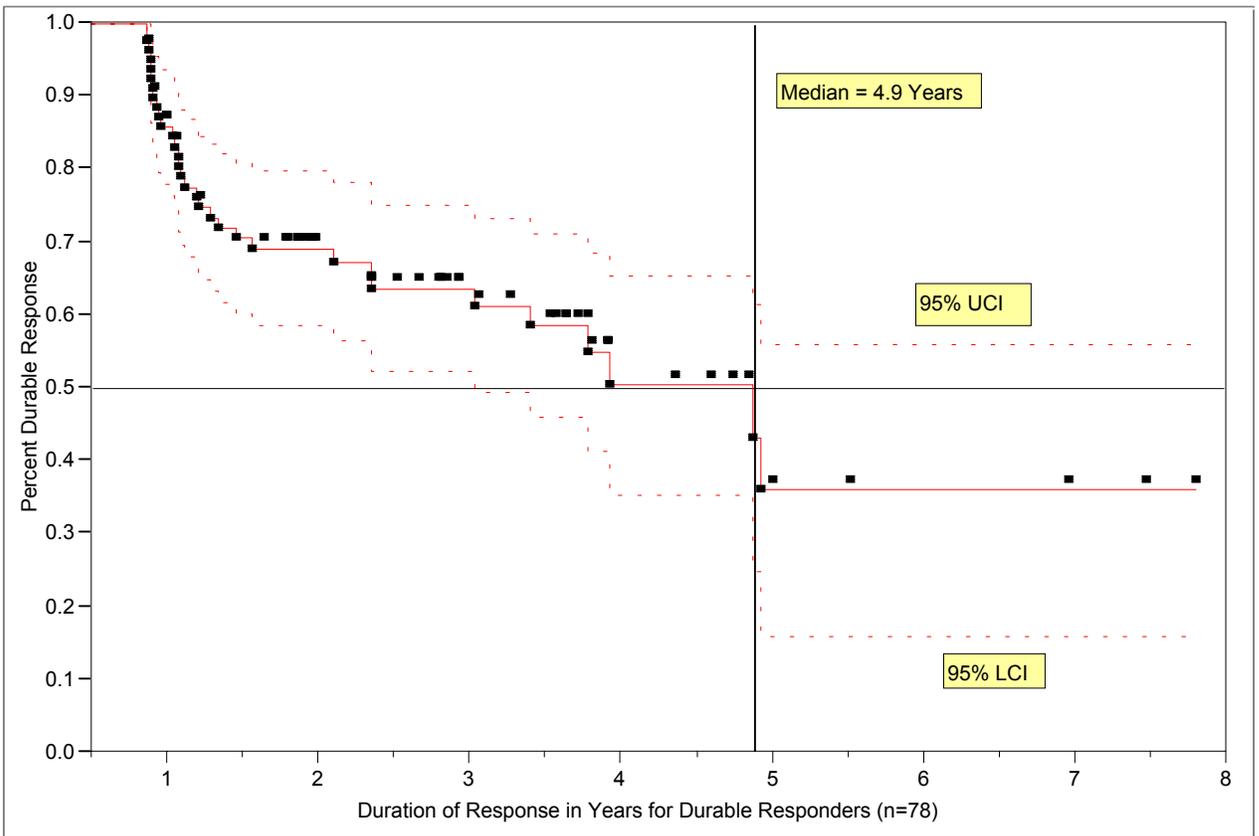
5. Assessment of the efficacy outcomes in long-term responders vs. transient or non-responding patients.

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 studies. The 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 tositumomab 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 ----- 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. The FDA review team agreed with the sponsor on one case. While the FDA would like to afford the sponsor the benefit of the doubt, copies of the sponsor's response, which also contain the gist of FDA queries is provided as an appendix.