CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

Statistical Review

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Product/Application: IDEC-Y2B8 -- Y-90-ZEVALIN (Zevalin) for patients with relapsed or refractory low-grade of follicular non-Hodgkin's lymphoma (NHL)

Sponsor: IDEC Pharmaceuticals Corp.

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Conclusions:

The sponsor proposed that Zevalin is indicated for the treatment of patients with relapsed or refractory low grade, follicular or CD20+ transformed B cell non-Hodgkin's lymphoma, and for the treatment of patients with Rituxan-refractory follicular lymphoma.

The effectiveness of Zevalin rests primarily on the results of two studies, Study 106-04, a randomized, multicenter active-control study and Study 106-06, an uncontrolled, supportive trial. There is a significantly higher overall response rate in the Zevalin arm as compared to the Rituxan arm in Study 106-04. The results are not supported by improvements in secondary measures of clinical benefit. Specifically, Zevalin- and Rituxan-treated patients had similar response duration (DR), time-to-disease progression (TTP), and overall survival. However, there is trend in both DR and TTP favoring Zevalin. There is also significantly reduced time to response (TTR) in favor of Zevalin.

The sizes of the efficacy studies (106-04 and 106-06) are relatively small given the total number of subjects available for study. Study 106-04 enrolled a total of 143 patients (73 to Zevalin)and may not contain a population typical of this disease from which to base generalizable conclusions regarding safety and effectiveness.

A tertiary endpoint of this study was a comparative analysis of Quality of Life (QOL), using the FACT-G questionnaire as the QOL instrument. The protocol stated that QOL will be assessed at baseline, week 4, week 8 and week 12. There were no statistical hypotheses specified in the protocol regarding QOL. The FACT-G overall score was available at baseline and 12 weeks post-treatment for 45 patients in the Zevalin arm (61.6%) and 36 patients in the Rituxan arm (51.4%). The week 8 assessment in the Rituxan arm was missing by design. Because of the amount of missing data and the lack of a pre-defined analytic plan, the results are uninterpretable and can provide no useful information in the assessment of the clinical benefit. Deficiencies include the fact that the sample size is small, there is a unacceptably large amount of missing information, the baseline values may be biased as they were obtained after treatment was administered, there was no pre-specified plan for handling missing data, dropouts, and no allowance for endpoint multiplicity adjustments.

Background

The non-Hodgkin's lymphomas (NHLs) are a diverse group of lymphoid neoplasms that collectively rank fifth in cancer incidence and sixth in cancer mortality in the United States . The incidence and prevalence of NHL has risen 150% over the past few decades. Recent projections estimated 54,900 new cases and 26,100 deaths in the year 2000. The incidence of NHL increases with age and males are affected about 1.5 times more often than females.

According to the International Working Formulation (IWF) the NHLs were categorized into three clinical prognostic groups :

- low-grade (small lymphocytic, follicular small-cleaved cell, and follicular mixed small-cleaved and large-cell). The low-grade or follicular lymphomas account for approximately 43% of the incidence of malignant B-cell lymphomas in North America and for over 65% of the prevalence.

- intermediate-grade (follicular large-cell, diffuse small-cleaved cell, diffuse mixed small and large cell, and diffuse large-cell)

- high-grade (large-cell immunoblastic, lymphoblastic, and small noncleaved cell)

Although multiple regimens are currently used in the treatment of relapsed or refractory, low-grade or follicular NHL, there is no curative agent and none of the current regimens have been shown to increase survival. In the absence of a curative therapy or survival benefit, a new agent that reduces tumor burden or conveys a prolonged treatment-free period would be valuable. A treatment that is well tolerated, that is administered in an outpatient setting, and that is associated with a good quality of life is clearly of interest.

Rituximab (Rituxan) is licensed in the United States as therapy for patients with relapsed or refractory low-grade or follicular, CD20+ B-cell NHL. Rituximab is a chimeric IgG1 kappa monoclonal antibody, with mouse variable and human constant regions. In an open-label, single-arm, pivotal trial, 166 patients received infusions of 375 mg/m^2 rituximab once weekly for four weeks. Ninety-one percent of patients (151 of 166) were evaluable for efficacy: 9 evaluable patients (6% of patients) achieved a complete response (CR), and 66 evaluable patients (44%) achieved a partial response (PR), for an ORR of 50%. Median time to progression (TTP) for responders was 13.2 months and median duration of response (DR) was 11.6 months.

Zevalin is a radiolabeled molecule composed of a murine IgG1 kappa monoclonal antibody, ibritumomab (IDEC-2B8), covalently bound to the chelator tiuxetan, which chelates the radioisotope yttrium-[90] (90 Y). Unlike unconjugated antibodies, such as rituximab, that operate through a biologic mode of action and destroy malignancies one cell at a time, radioimmunotherapy combines both biologic and radiolytic mechanisms of action.

Clinical Studies

Six clinical trials conducted between 1993 and 1999 explored Zevalin treatment in patients with B-cell NHL. Of 306 patients enrolled in these trials, 226 were treated with Zevalin, 70 were treated with Rituxan as a control therapy, and 9 received Zevalin in dosimetry studies, with or without unlabeled ibritumomab tiuxetan or rituximab a . Of the 226 patients treated with Zevalin, 211 received preinfusions with Rituxan followed by a single, weight-adjusted dose of Zevalin. The six clinical trials may be classified into the following three groups:

Dose-finding, safety, and pilot trials.

Two dose-escalation studies were conducted to optimize the biodistribution of radiolabeled Zevalin, and to determine the maximum tolerated dose (MTD) of Zevalin under conditions of optimal biodistribution. Briefly, in Study 106-01, the Zevalin dose was preceded by an infusion of the murine-derived antibody ibritumomab to facilitate the biodistribution of Zevalin. Zevalin doses were not adjusted for patient body weight. In Study 106-03, patients were preinfused with Rituxan and then received weight-adjusted doses of Zevalin in an initial Phase I, ascending-dose part of the study, and in a Phase II, pilot efficacy part of the study. The MTD was identified as 0.4 mCi/kg, based upon clinical efficacy and the reversibility of dose-limiting hematologic toxicity. The dose-limiting toxicity (DLT) was established as [redacted]

A third dose-finding study, Study 106-02, was designed to test a multiple low-dose treatment scheme for Zevalin. After enrollment of a single patient, the study was terminated for administrative reasons (investigator relocation to another institution). Study termination was not due to safety concerns.

Randomized, Active-Controlled Phase III Trial.

Study 106-04, the largest study conducted with Zevalin (143 patients), was designed to compare the efficacy and safety of the recommended Zevalin regimen with that of a control regimen of Rituxan (375 mg/m 2 once weekly for 4 weeks) in patients with relapsed or refractory low-grade or follicular or transformed NHL. Rituxan was selected as the control regimen because it is the only FDA-approved therapy for relapsed, refractory, low-grade or follicular NHL. The primary endpoint, overall response rate (ORR) was determined by a blinded, independent, third-party panel of radiologists and oncologists expert in lymphoma (Lymphoma Expert Confirmation of Response [LEXCOR]). The ORR was compared between patients treated with Zevalin versus Rituxan. Patients were followed until development of progressive disease or initiation of other antilymphoma therapy, although the study was not designed initially to demonstrate a statistically significant difference in time to progression (TTP) between the treatment groups.

Supportive Phase II or Phase III Trials in Special Populations

The sponsor conducted a Phase II study was conducted in relapsed or refractory low-grade or follicular or transformed NHL patients who had mild thrombocytopenia at baseline (Study 106-05; 30 patients) to confirm that the reduced dose of Zevalin (0.3 mCi/kg) was therapeutically active with acceptable toxicity in this specific patient population. The sponsor conducted a Phase III comparative study in relapsed follicular NHL patients who were refractory to standard treatment with Rituxan (Study 106-06; 57 patients) to confirm the safety and therapeutic activity of Zevalin. Study 106-06, conducted in patients with relapsed or refractory follicular NHL, was classified as a Phase III by the sponsor, comparative trial because patients' response rates and response durations were compared with results obtained for patients' last prior chemotherapy, and for patients' prior Rituxan treatment.

An ongoing Phase II study (Study 106-98; 55 enrolled patients as of May 31, 2000) was designed to provide treatment to patients who were ineligible for other Zevalin protocols, and to add to the overall efficacy and safety experience in this indication. This single-arm, open-label trial is ongoing; safety results from patients completing the treatment period will be included in the 120-day safety update in this BLA. Additional safety and efficacy results will be analyzed upon completion of the trial. Similarly, individual-patient, emergency-use studies, under Protocol 106-99, were performed to provide treatment for patients with relapsed or refractory B-cell NHL who were ineligible for other Zevalin protocols.

The sponsor conducted all six studies in patients with B-cell NHL. Patients were to have CD20-positive tumors, WHO status of 0 to 2, no anticancer treatment for 3 weeks prior to enrollment, and to be at least 18 years of age with an expected survival of at least 3 months.

The sponsor proposed that Zevalin is indicated for the treatment of patients with relapsed or refractory low grade, follicular or CD20+ transformed B cell non-Hodgkin's lymphoma, and for the treatment of patients with Rituxan-refractory follicular lymphoma.

This review is primarily based on two studies: 106-04 and 106-06.

Efficacy Variables Definitions

Protocol-defined response classifications were as follows:

Complete Response (CR): No evidence of disease for at least 28 days, as confirmed by a second assessment following the original observation of no disease. All nodes visualized on physical exam or imaging studies must have regressed to 1.5x1.5 cm or smaller.

Clinical Complete Response (CCR): A single residual mass has decreased by 75% and remains stable or decreases for at least 3 months, and all other criteria for complete response have been met.

Partial Response (PR): At least 50% decrease from baseline in the sum of the greatest perpendicular diameters (SPD) of all measured lesions is noted for at least 28 days. Additionally, no appearance of new lesions is noted.

Stable Disease (SD): Patients exhibited neither a 50% decrease nor a 50% increase in the SPD of all the measured lesions compared with baseline. In addition, no new lesions have appeared.

Progressive Disease (PD): Any single observation of a >= 50% increase in the SPD of all the measured lesions or the appearance of new lesions constitutes progressive disease.

Overall Response Rate (ORR) = CR + CCR + PR

Methods of Response Evaluation

At each visit after baseline patients were evaluated for response.

Lymphoma Expert Confirmation of Response (LEXCOR) Evaluation
An independent, third-party panel of radiologist and oncologists expert in lymphoma evaluated patient data for response. This panel was blinded to treatment arm and investigator's assessment of response. LEXCOR calculated a sum of the greatest perpendicular diameters (SPD) for each patient and assigned a response classification.

Investigator Evaluation
Investigators evaluated patients for response, duration of response, and progression of disease. For all visits up to and including the visit of progression, investigators calculated SPD, recorded clinically relevant data (any data deemed by the investigator as important for the evaluation of disease status), and assigned a response classification to each patient enrolled at their site.

International Workshop (IW) NHL evaluation
The sponsor also evaluated the responses using International Workshop NHL response criteria.

Secondary Efficacy Variables – Time to Event

Secondary efficacy variables included the following time to event variables: Time to Progression (TTP), Duration of Response (DR) and Time to Response time to response (TTR). Time to Progression (TTP) measures the time between therapy from the first infusion (treatment) to progression of disease in months. For patients whose disease did not progress, the interval from the first infusion to the last contact with no evidence of disease progression was computed (censored at this point). Duration of Response (DR) is the time from onset of response to disease progression in months, and Time to Response (TTR) is time from treatment to response (responders only) in days.

Analysis

Two Phase III clinical trials of Zevalin have been conducted by IDEC Pharmaceuticals. The first Phase III clinical trial, Study 106-04, was a standard-dose study of Zevalin treatment in patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL. The primary endpoint, overall response rate (ORR) was determined by a blinded, independent, third-party panel of radiologists and oncologists expert in lymphoma (Lymphoma Expert Confirmation of Response [LEXCOR]). The ORR for patients was compared to patients treated with Zevalin versus Rituxan. Secondary efficacy variables were Time to Progression (TTP), Duration of response (DR), Time to Response(TTR), and Quality of Life (QOL).

The second Phase III clinical trial, Study 106-06, was a nonrandomized controlled study in patients with follicular B-cell NHL who were refractory to Rituxan therapy. The primary endpoint was defined as a target ORR of 35% in follicular patients, in a sample size of 50 patients. The secondary efficacy variables were TTP, DR, TTR.

The analysis of these two phase III clinical trial is given below:

Study 106-04-Pivotal Trial

Phase III Multicenter Randomized Controlled Comparison Study (N = 143)

The sponsor conducted a Phase III prospective, randomized, controlled, multicenter study comparing treatment with Zevalin to treatment with Rituxan in 143 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or CD20+ transformed B-cell NHL. A total of 73 patients received Zevalin at 0.4 mCi/kg (14.8 MBq/kg) up to a maximum of 32 mCi (1184 MBq), and 70 patients received Rituxan given as an IV infusion at 375 mg/m^2 weekly for 4 weeks.

This study was to enroll a sample of a well-defined population by using a multicenter, two-arm, randomized, controlled clinical trial design. Strata were histology (IWF A vs. follicular vs. transformed). The Zevalin treatment group received:

- An infusion of rituxan (250 mg/m^2) immediately followed by an intravenous (IV) injection of an imaging dose of Zevalin (5 mCi).

- One week following the Rituxan and Zevalin treatments, patients meeting dosimetry requirements were to receive an infusion of Rituxan (250 mg/m^2) and an IV injection of Zevalin (0.4 mCi/kg, maximum dose 32 mCi).

The Rituxan treatment group received four infusions (once weekly for four weeks) of rituximab (375 mg/m^2).

CBER's Analyses of Efficacy Variables

No statistically significant differences in demographic and disease status variables between the two arms were noted. (see Appendix A – Tables A2 & A3)

Analyses were performed on efficacy variables for the intent-to-treat (ITT) patient population.

IDEC submitted a rolling BLA to update the original submission that included additional analyses of the additional data and additional follow-up. The original submission was dated Nov. 10, 2000. This was a fast track six month review BLA. Additional efficacy and safety updates were submitted on Jan 16, 2001as part of the rolling submission. The analyses were done on this updated submission.

Primary Analysis

The primary efficacy variable was the LEXCOR evaluation of ORR. Patients were stratified by histology at registration.

Table 1 provides the efficacy comparison of ORR and CR for ITT patient populations. The efficacy data from patients treated with Zevalin were compared with data from patients receiving Rituxan. Both Fisher's exact p-values and adjusted p-values generated by Cochran-Mantel-Haenszel test stratified by pathology report histology type are reported. The results are provided for LEXCOR, Investigator and International Workshop evaluations.

The overall response rate (ORR) using LEXCOR evaluation response criteria was 72.6 % for patients treated with Zevalin and 47.1% for patients treated with Rituxan ($p = 0.002$) and the complete response (CR) rate was 17.8% for patients treated with Zevalin and 11.4% for patients treated with Rituxan ($p=0.326$). The ORR was significantly higher for patients treated with Zevalin. The results are consistent for Investigator and International Workshop evaluations.

Table 1: Overall Response (CR+CCR+PR) Rate and Complete Response (CR) ITT Patients Phase III Comparison Study 106-04 (N = 143) – All Patients

Study 106-04 – Comparative Efficacy Study

Evaluation **ORR response**	Zevalin N = 73 N	 %	Rituxan N = 70 N	 %	Unadjusted Exact p-value	 adjusted p-value*
LEXCOR	53	72.6	33	47.1	0.002	0.002
Missing Frequency	0		1			
95% CI on % Response	(61.9, 82.4%)		(35.1, 59.5)			
Investigator	60	82.2	38	54.3	<0.001	<0.001
Missing Frequency	0		0			
95% CI on % Response	(71.5, 90.2)		(41.9, 66.3)			
International Workshop	58	79.5	39	55.7	0.004	0.002
Missing Frequency	15		31			
95% CI on % Response	(68.4, 88.0)		(43.3, 67.6)			
CR response						
LEXCOR	13	17.8	8	11.4	0.348	0.326
95% CI on % Response	(9.8, 28.5)		(5.1, 21.3)			
Investigator	22	30.1	11	15.7	0.048	0.040
95% CI on % Response	(19.9, 42.0)		(8.1, 26.4)			
International Workshop	22	30.1	11	15.7	0.048	0.040
95% CI on % Response	(19.9, 42.0)		(8.1, 26.4)			

* Adjusted p-values generated by Cochran-Mantel-Haenszel test by pathology report histology type

Secondary Efficacy Variables – Time to Event

Secondary efficacy variables included the time to event variables. Treatment comparisons based on TTP and DR were analyzed by either Kaplan-Meier product limit without stratification by histology type and/or Cox proportional hazard models with stratification by histology type. The median TTP and DR for each treatment were estimated using the Kaplan-Meier estimation method.

Table 2 provides the results of the secondary endpoints -- Time to Progression, Duration of Response and Time to Response in ITT Patients.

Kaplan-Meier estimates of median time to disease progression are 11.2 months for patients treated with Zevalin and 10.1 months for patients treated with Rituxan (log-rank p-value = 0.2755). Kaplan-Meier estimates of median response duration are 14.2 months for patients treated with Zevalin and 12.1 months for patients treated with Rituxan (log-rank p-value = 0.7184). There is no statistically significant difference between Zevalin and Rituxan in relation to TTP and DR. The Kaplan-Meier curves are given in Figures 1 to 4. There is a trend in TTP and DR favoring Zevalin. Time to Response is significantly lower for Zevalin than for Rituxan ($p<0.001$).

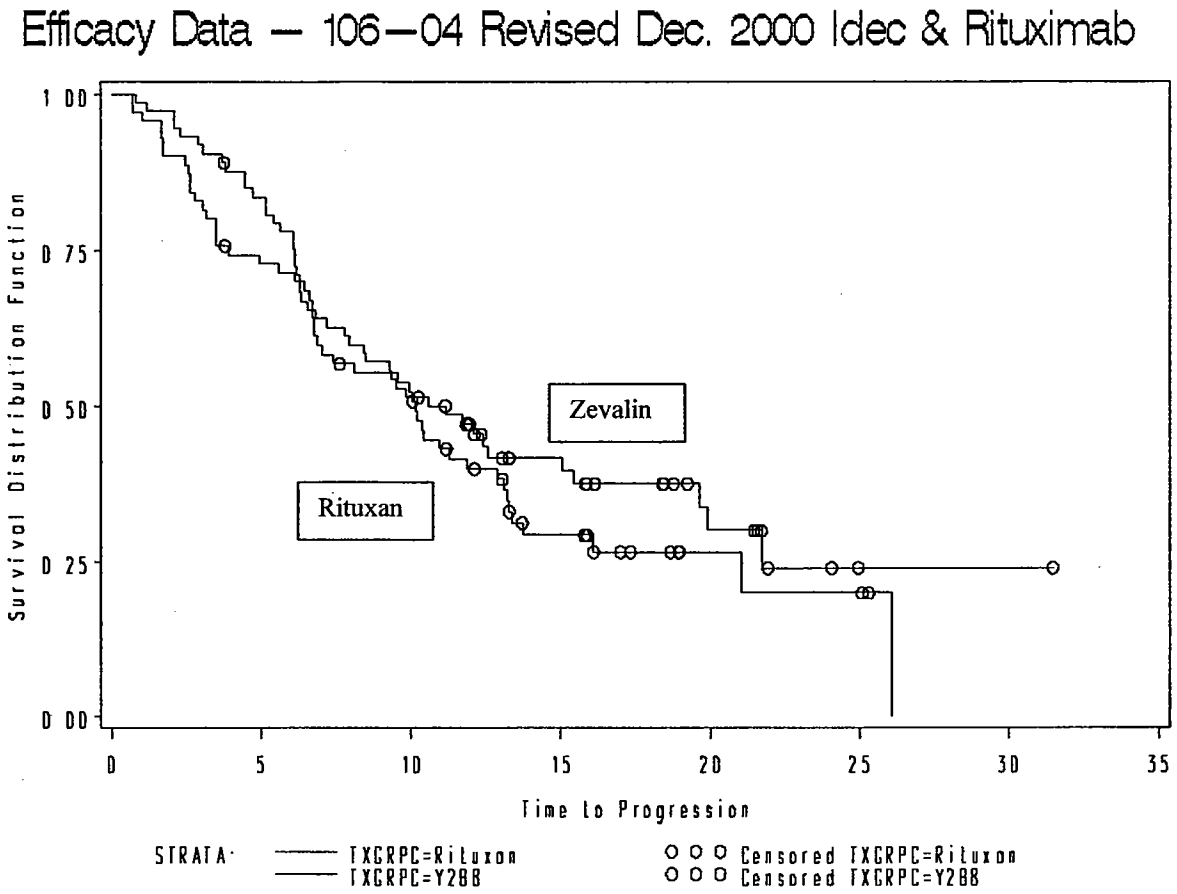
Table 2: Secondary Endpoints – Time to Progression and Duration of Response

Time to Progression, Duration of Response and Time to Response in ITT Patients Phase III Comparison Study (N = 143) – Study 106-04

Treatment	Variable	Zevalin (n = 73)	Rituxan (n = 70)	Logrank p-values
Time to Progression (months) All Patients	N Median (K-M) 95% CI Range Total (%) Censored	73 11.2 (7.8 – 15.4) (0.8 – 31.5+) 27 (37.0%)	70 10.1 (6.8 – 12.9) (0.7 – 26.1) 20 (28.6%)	0.2755
Duration of Response (months) Responders Only	N Median (K-M) 95% CI Range Total (%) Censored	53 14.2 (9.4, ..) (0.9 – 28.9+) 25 (47.2%)	33 12.1 (8.0, 24.5) (2.1 – 24.5) 14 (42.4%)	0.7184
Time to Progression (months) Responders Only	N Median (K-M) 95% CI Range Total (%) Censored	53 15.4 (10.6, ..) (2.1 – 31.5+) 25 (47.2%)	33 13.8 (10.4, 26.1) (6.1 – 26.1) 14 ((42.4%)	0.9814
Time to Response (Days) Responders Only	N Median (K-M) 95% CI Range Total (%) Censored	53 35.0 (35.0 - 36.0) (29.0 - 129) 0	33 51.0 (49.0 – 79.0) (43.0 – 140) 0	< 0.0001

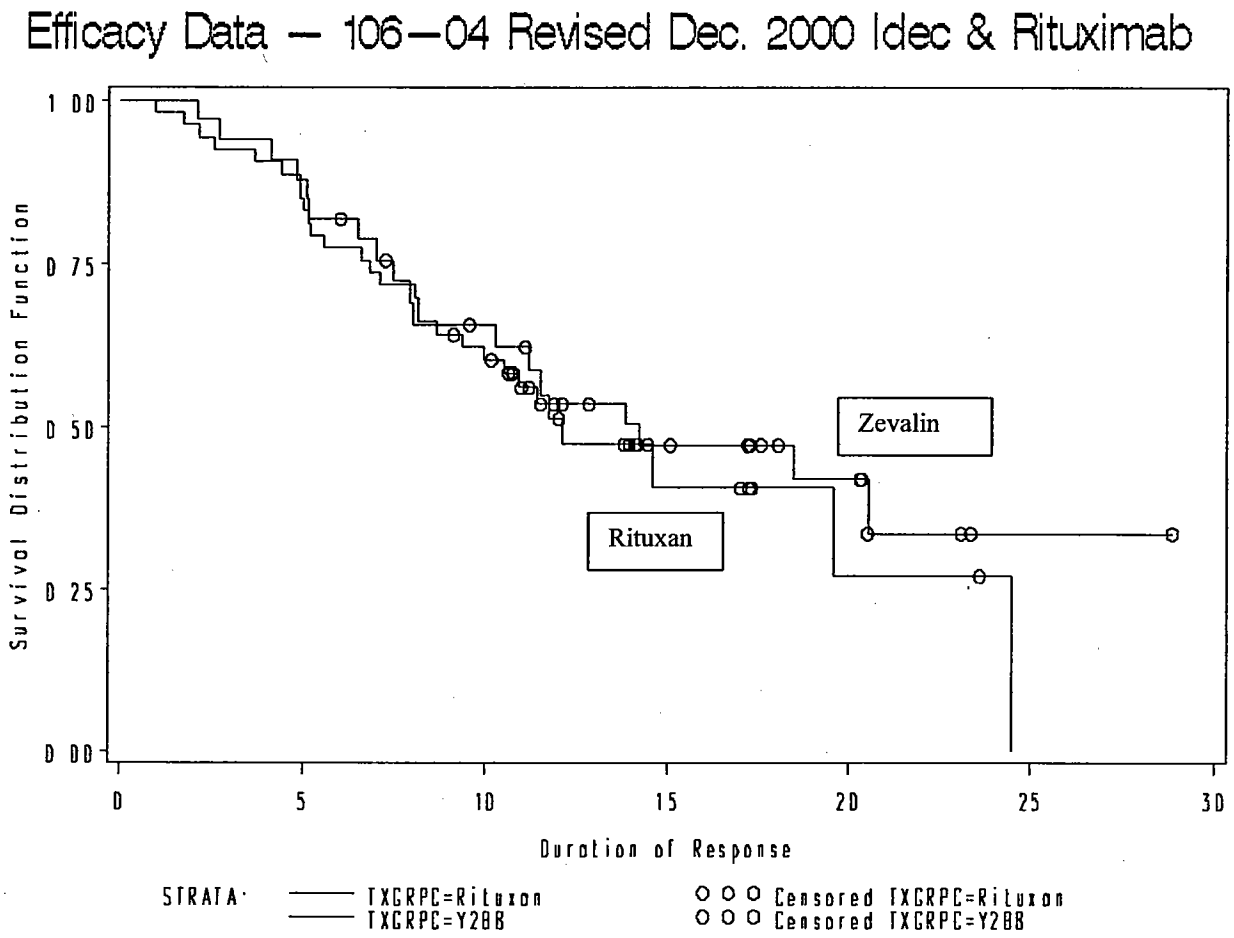
Notes:
Time to Response is time from treatment to response (responders only) in days
Duration of Response from onset of response to disease progression in months
Time to Progression from the first infusion (treatment) to disease progression in months
For patients whose disease did not progress, the interval from the first infusion to the last contact with no evidence of disease progression is computed (censored at this point).

Figure 1: Time to Progression – Months (all patients) -- % progression free



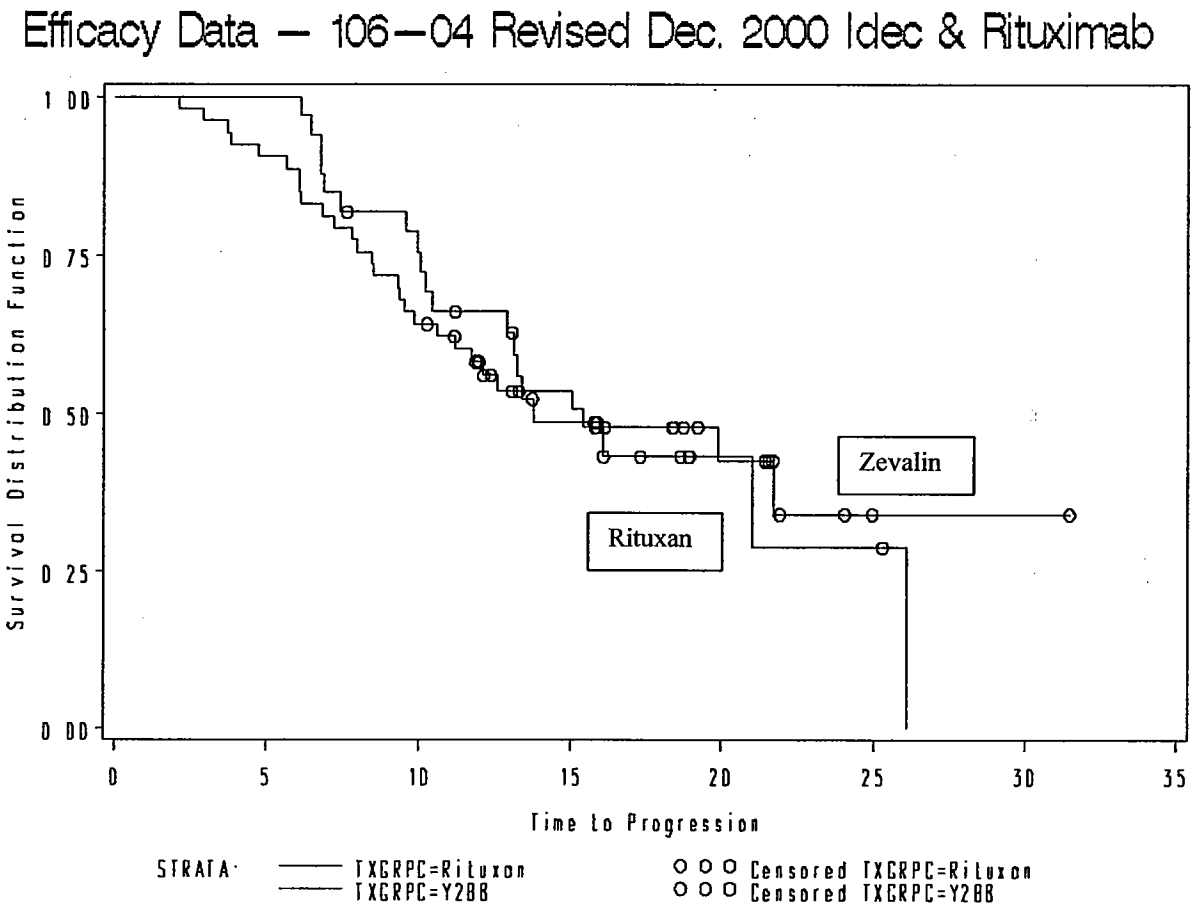
Time to Progression from the first infusion (treatment) to disease progression in months, all patients, Log-rank p-value = 0.2755

Figure 2 : Duration of Response – Months (responders) -- % progression free



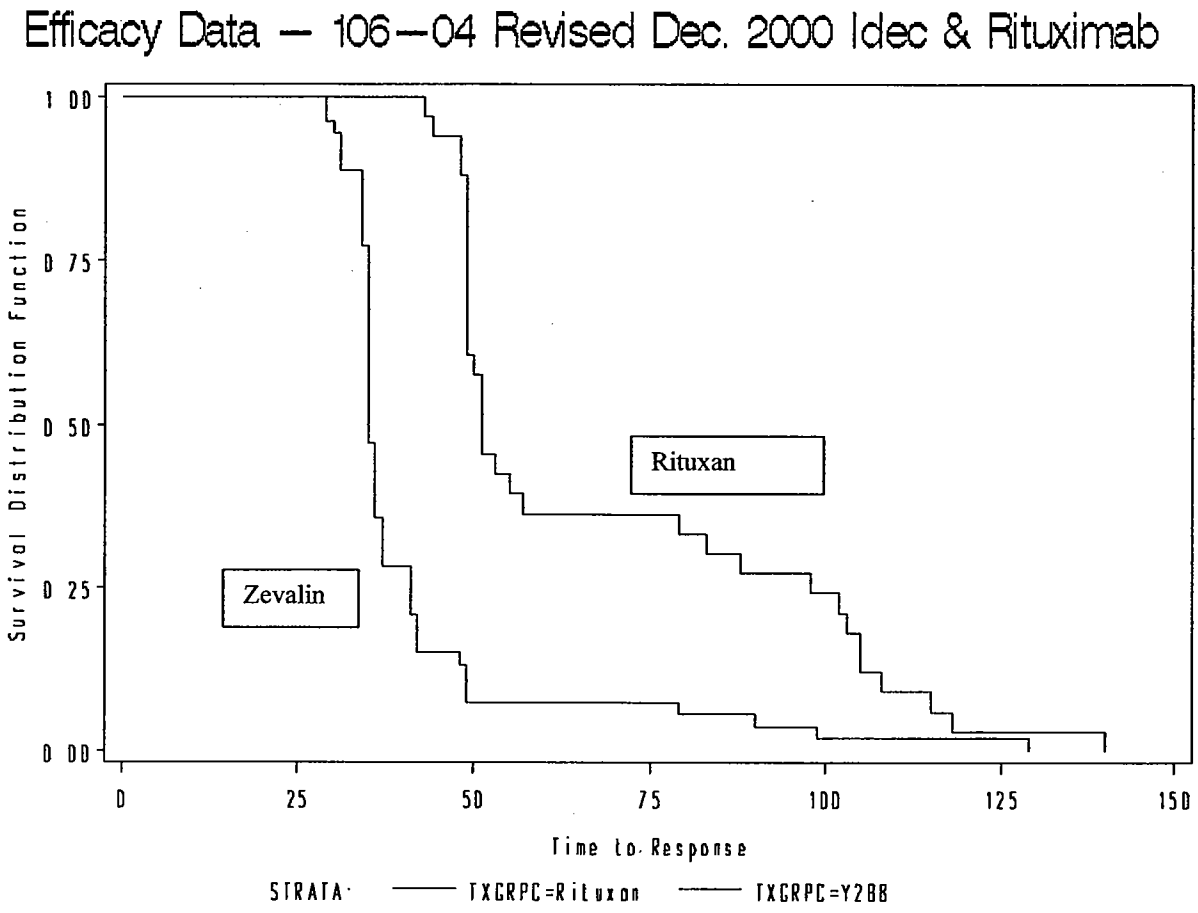
Duration of Response from onset of response to disease progression in months,
Log-rank p-value = 0.7184

Figure 3 : Time to Progression – Months (responders only) -- % progression free



Time to Progression from the first infusion (treatment) to disease progression in months, responders only, Log-rank p-value = 0.9814

Figure 4: Time to Response – Days (Responders only) -- % progression free



Time from treatment to response (responders only) in days, Log-rank p-value < 0.0001

Exploratory Analysis:

An exploratory analysis (Table 3 and Figures 5A to 5E) was performed to find where the trend in favor of Zevalin was arising. The trend in favor of Zevalin for time to progression (less rapid time to progression) is in the CR+CCR category and the trend is against in all other categories (PR, SD and PD). The patients who achieved CR+CCR had longer time to progression and longer duration of response tending towards significance. The follow-up data is not mature enough to detect significance. An unusually high number of censored observations, especially in the Zevalin arm show that they have not yet progressed during the follow-up period (given in Appendix A).

The patients with partial response, stable disease, and progressive disease had a shorter time to progression in the Zevalin arm as compared to the Rituxan arm (though not significant).

The censoring patterns are similar in the two treatment arms (Appendix A – Table A1).

Table 3: Secondary Endpoints – Time to Progression – Subset Analyses

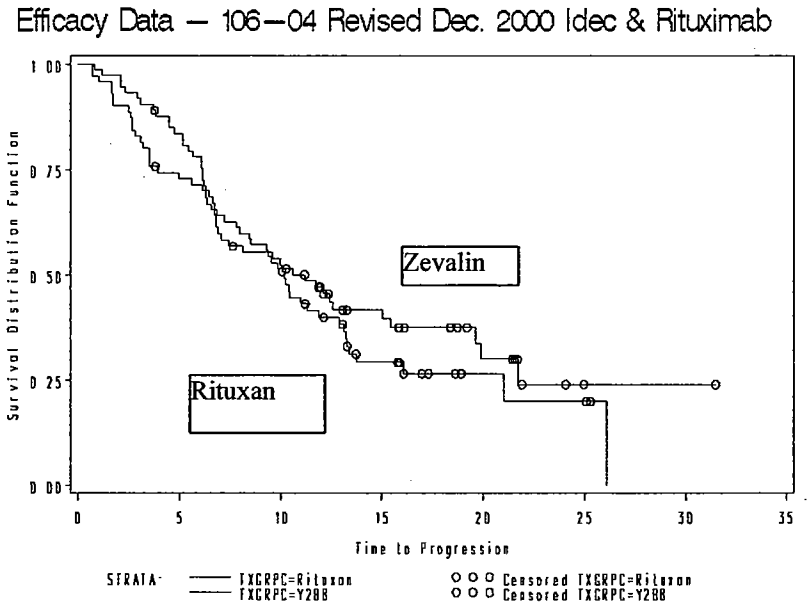
Time to Progression in ITT Patients

Phase III Comparison Study (N = 143) – Study 106-04

Treatment	Variable	Zevalin (n = 73)	Rituxan (n = 70)	Logrank p-values
Time to Progression (months) All Patients	N Median (K-M) 95% CI Range Total (%) Censored	73 11.2 (7.8 – 15.4) (0.8 – 31.5+) 27 (37.0%)	70 10.1 (6.8 – 12.9) (0.7 – 26.1) 20 (28.6%)	0.2755
Time to Progression (months) Complete Response CR+CCR	N Median (K-M) 95% CI Range Total (%) Censored	15 Not reached (15.4, ..) (8.4 – 31.5+) 11 (73.3 %)	11 13.4 (10.1, --) (6.8 – 25.3+) 5 (45.5 %)	0.1441
Time to Progression (months) Partial Response PR	N Median (K-M) 95% CI Range Total Censored	38 11.2 (9.3, 19.9) (2.1 – 21.7) 14 (36.8%)	22 16.1 (10.4, 26.1) (6.1 – 26.1) 9 ((40.9%)	0.1873
Time to Progression (months) Stable Disease SD	N Median (K-M) 95% CI Range Total (%) Censored	19 6.1 (4.5 – 6.3) (1.7 – 19.6) 2 (10.5 %)	30 6.6 (3.5 – 10.1) (1.0 – 25.1) 5 (16.7 %)	0.4546
Time to Progression (months) Progressive Disease PD	N Median (K-M) 95% CI Range Total (%) Censored	1 0.8 (--, --) (0.8 , --) 0 (0%)	6 1.7 (0.7 – 3.0) (0.7, 3.5) 0 (0%)	0.3940

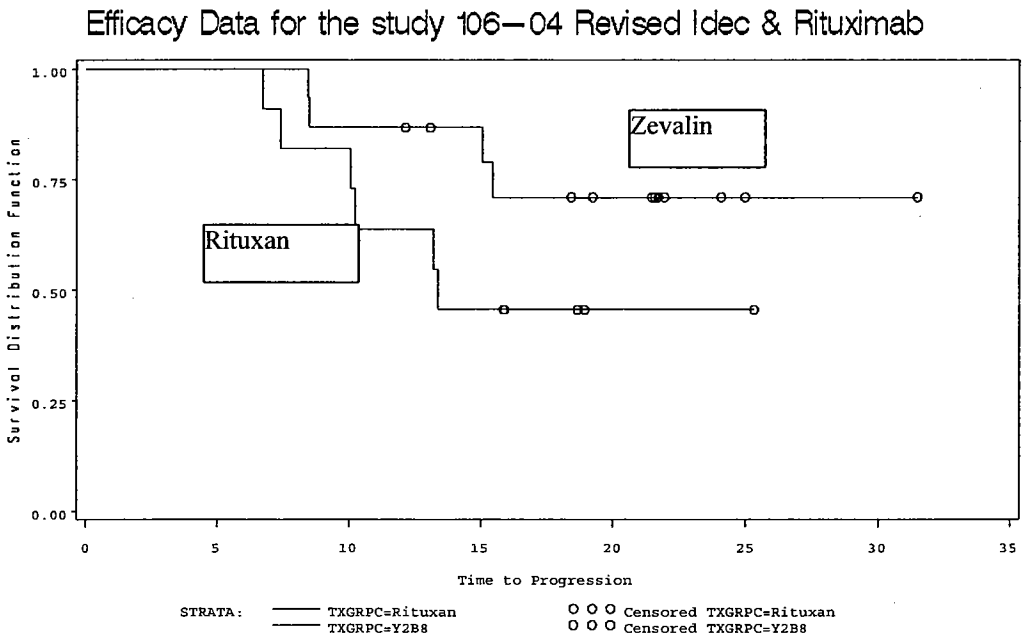
Notes: Time to Progression from the first infusion (treatment) to disease progression in months
For patients whose disease did not progress, the interval from the first infusion to the last contact with no evidence of disease progression is computed (censored at this point).

Figure 5A: Time to Progression – Months (all patients) -- % progression free



Time to Progression from the first infusion (treatment) to disease progression in months, all patients, Log-rank p-value = 0.2755

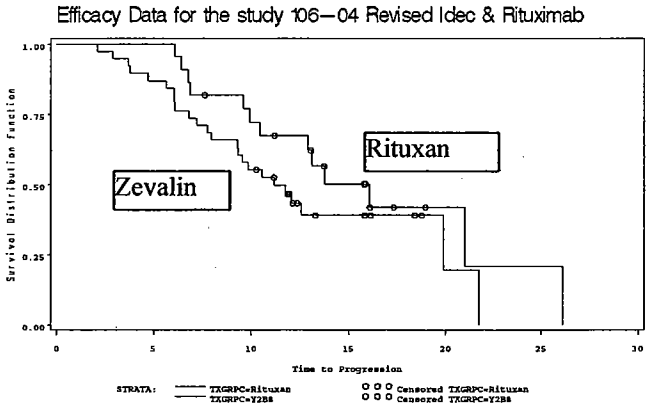
Figure 5B: Time to Progression – Months (CR+CCR patients) -- % progression free



Time to Progression from the first infusion (treatment) to disease progression in months, CR+CCR patients, Log-rank p-value = 0.1441

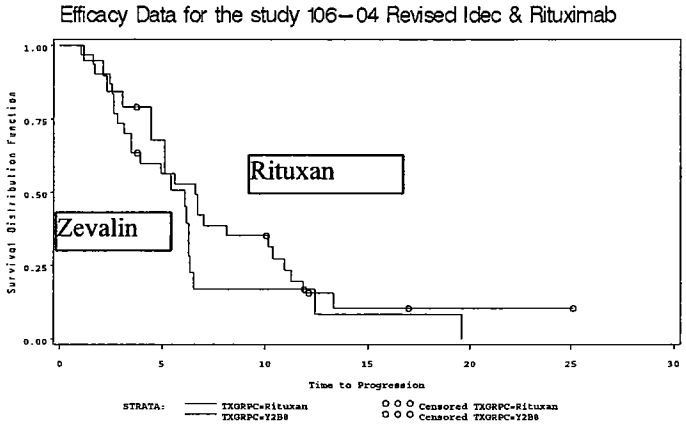
Figure 5C: Time to Progression – Months (PR patients) -- % progression free

Time to Progression from the first infusion (treatment) to disease progression in months



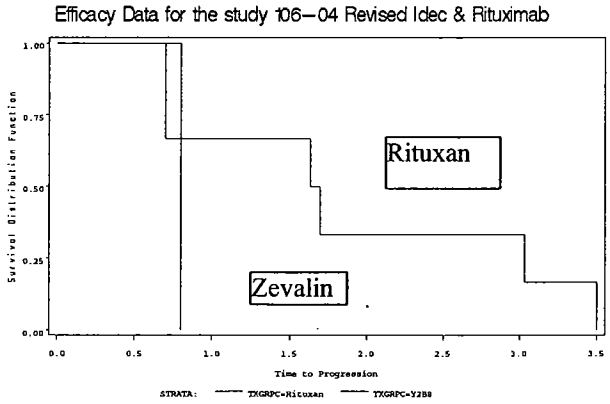
PR patients **Log-rank p-value = 0.1873**

Figure 5D: Time to Progression – Months (SD patients) -- % progression free



SD patients **Log-rank p-value = 0.4546**

Figure 5E: Time to Progression – Months (PD patients) -- % progression free



PD patients **Log-rank p-value = 0.3940**

Phase III Rituxan - Refractory Study 106-06 – Estimation Study

This Phase III, nonrandomized, controlled, open-label, multicenter study was designed to investigate the efficacy and safety of a single course of Zevalin (0.4 mCi/kg, maximum 32 mCi) in 54 follicular NHL patients who were refractory to Rituxan or responded and then progressed. The primary efficacy endpoint was the ORR (to exceed 35% protocol-defined target), as determined by the LEXCOR panel blinded to investigator assignment of response. The secondary efficacy endpoints were DR, TTP, & TTR

In this advanced-disease (74% of patients with lesions $\geq$ 5 cm), heavily-pretreated (median of 4 prior therapies) patient population, the ORR to Zevalin therapy was 59.3% (95% Confidence Interval ranging from 45% to 72.4%, Table 4) with a CR rate of 3.7% (95% Confidence Interval ranging from 0.5% to 12.8%, Table 4). The ORR for the patient's previous Rituxan therapy was 31.5%. The difference in ORR between the current Zevalin therapy and the patient's prior Rituxan therapy was statistically significant ($p = 0.002$). The ORR to Zevalin is similar to that of the patient's previous chemotherapy (66.7%), an improvement from the expected decrease in response rate with successive therapy that is found in the literature.

Table 4 also provide ORR and CR for phase III comparison study 106-04 and estimation study 106-06 for follicular patients.

Table 5, Figures 6 and 7 show that the Kaplan-Meier estimate of median time to progression in Rituxan-refractory patients was 6.8 months (95% CI [6.1, 9.3]), and median DR in Rituxan-refractory patients was 7.7 months (95% CI [5.5, 9.1]). The sponsor states that the median DR for the previous Rituxan therapy was 4 months (95% CI [3.0, 6.0]) for these patients and $p < 0.001$ when compared with Zevalin therapy and a median DR is 6.5 months (95% CI [4.0, 10.0]) for prior chemotherapy ($p = 0.355$). The results are given in Table 5 and Figures 6 and 7.

Table 5 also provides TP and DR for phase III comparison study 106-04 and estimation study 106-06 by histology type.

Table 4: Overall Response (CR+CCR+PR) Rate and Complete Response (CR) ITT Patients Phase III Comparison Study 106-04 (N = 113) and Estimation Study 104-06 (N = 54) – Follicular Patients

	Study 106-04 – Comparative Efficacy Study				Study 104-06 Estimation
Evaluation	Zevalin		Rituxan		Zevalin
Best ORR response	N = 55		N = 58	Exact	N = 54
	N %		N %	p-value	N %
LEXCOR	42	76.4	27	46.6	0.002	32	59.3
Missing Frequency	0		1			0	
95% CI on % Response	(63.0, 86.8%)		(33.3, 60.1)			(45.0, 72.4)	
Investigator	48	87.3	33	56.9	<0.001	34	63.0
Missing Frequency	0		0			0	
95% CI on % Response	(75.5, 94.7)		(43.2, 69.8)			(48.7, 75.7)	
International Workshop	47	85.5	32	55.2	<0.001	40	74.1
Missing Frequency	8		26			14	
95% CI on % Response	(73.3, 93.5)		(41.5, 68.3)			(60.4, 85.0)	
Best CR response							
LEXCOR	11	20.0	5	8.6	0.107	2	3.7
95% CI on % Response	(10.4, 33.0)		(2.9, 19.0)			(0.5, 12.8)	
Investigator	22	40.0	11	19.0	0.022	10	18.5
95% CI on % Response	(27.0, 54.1)		(9.9, 31.4)			(9.3, 31.4)	
International Workshop	19	34.5	8	13.8	0.015	8	14.8
95% CI on % Response	(22.2, 48.6)		(6.2, 25.4)			(6.6, 27.1)	

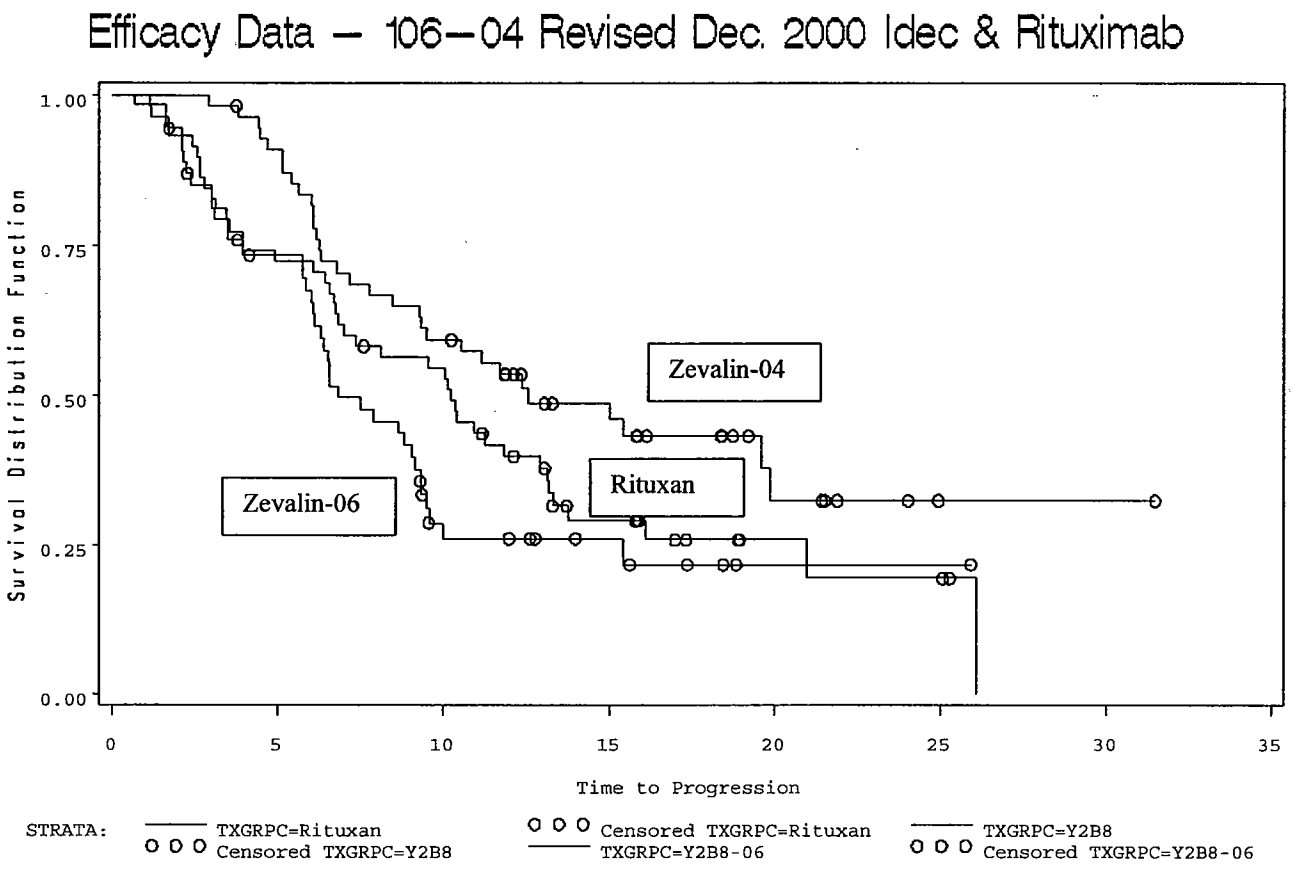
Table 5: Secondary Endpoints – Time to Progression and Duration of Response by Histology Type

Time to Progression and Duration of Response in ITT Patients by Histology Type Phase III Comparison Study 106-04 (N = 143) and Estimation Study 106-06 (N = 54)

Study		Study 106-04 -- Comparison Study			Study 106-06 Estimation Study
Treatment	Variable	Zevalin (n = 73)	Rituxan (n = 70)	Logrank p-values	Zevalin (n=54)
Time to Progression (months) Histology Type - **Follicular Patients**	N Median (K-M) 95% CI Range Total (%) Censored	55 12.6 (9.3, 19.9) (2.9, 31.5+) 24 43.6%	58 10.2 (6.9,13.1) (0.7, 26.1) 16 27.6%	0.0616	54 6.8 (6.1, 9.3) (1.1, 25.9+) 16 29.6%
Duration of Response (months) Histology Type – **Follicular Patients** Responders Only	N Median (K-M) 95% CI Range Total (%) Censored	42 18.5 (10.0, ..) (1.7, 28.9+) 22 52.4%	27 12.1 (7.9, 24.5) (2.7, 24.5) 11 40.7%	0.3708	32 7.7 (5.5, 9.1) (2.3, 24.9+) 10 31.3%
Time to Progression (months) Histology Type - **A**	N Median (K-M) 95% CI Range Total (%) Censored	9 8.4 (6.3,12.1) (2.1,21.7) 1 11.1%	8 8.3 (1.7, ..) (1.0,16.1+) 3 37.5%	0.7672	
Duration of Response (months) Histology Type - **A** Responders Only	N Median (K-M) 95% CI Range Total (%) Censored	6 9.8 (7.1, 20.5) (5.0, 20.5) 1 16.7%	3 .. (8.0, ..) (8.0, 14.5+) 2 66.7%	0.4198	
Time to Progression (months) Histology Type - **Transformed**	N Median (K-M) 95% CI Range Total (%) Censored	9 3.1 (2.1, 8.0) (0.8, 21.7+) 2 22.2%	4 10.1 (0.7, ..) (0.7,18.7+) 1 25.0%	0.5759	
Duration of Response (months) (Histology Type - **Transformed** Responders Only	N Median (K-M) 95% CI Range Total (%) Censored	5 6.8 (0.9, ..) (0.9, 20.3) 2 40.0%	3 11.7 (2.1, ..) (2.1, 17.0+) 1 33.3%	0.8503	

Notes:
Time from treatment to response (responders only) in days
Duration of Response from onset of response to disease progression in months
Time to Progression from the first infusion (treatment) to disease progression in months
For patients whose disease did not progress, the interval from the first infusion to the last contact with no evidence of disease progression is computed (censored at this point).

Figure 6: Time to Progression – Months (Follicular histology type patients) – % progression free



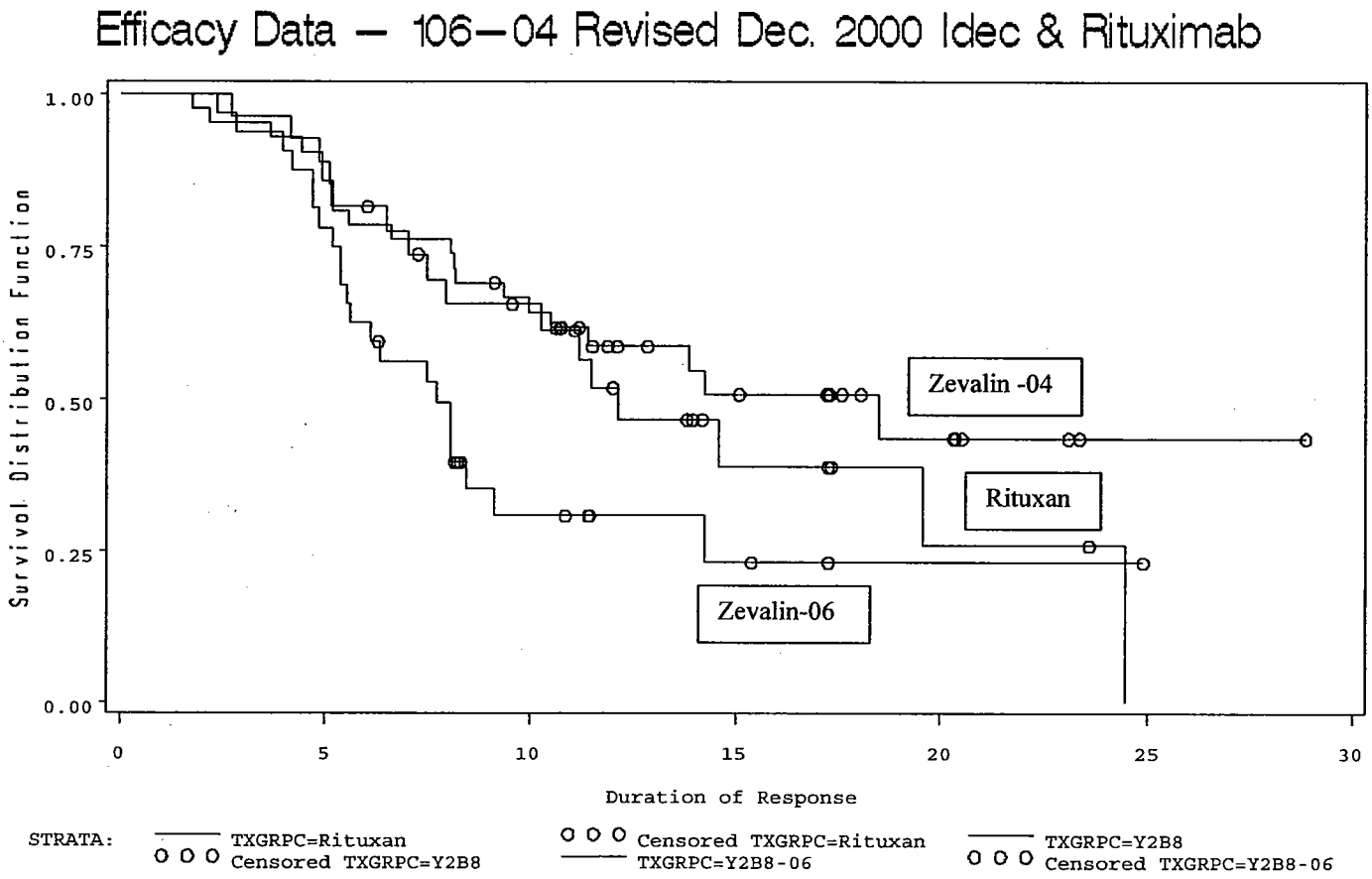
Time to Progression from the first infusion (treatment) to disease progression in months, Follicular histology patients

Log-rank p-value = 0.0616 – for comparing Zevalin to Rituxan in 106-04 randomized study

Log-rank p-value = 0.0116 – for comparing all three curves

Conclusion: Even though patients on 104-06 study progressed faster than patients on Rituxan or patients on 104-04 study, these patients were Rituxan refractory and there is an evidence of clinical activity on these patients.

Figure 7: Duration of Response – Months (responders - Follicular histology type patients) - - % progression free



Duration of Response from onset of response to disease progression in months, Follicular histology patients

Log-rank p-value = 0.3708 – for comparing Zevalin to Rituxan in 106-04 randomized study

Log-rank p-value = 0.0315 – for comparing all three curves

Conclusion: Even though patients on 104-06 had shorter duration of response than patients on Rituxan or patients on 104-04 study, these patients were Rituxan refractory and there is an evidence of clinical activity on these patients..

Agreement Rate between LEXCOR and Investigators 106-04 Pivotal Trial and 106-06 Estimation Study:

Table 6 provides Agreement Rate between LEXCOR and Investigators in the 106-04 Pivotal Trial and 106-06 Estimation Study. There is no significant difference in the dis-concordance rates between the two readers in the overall response rates. However, there is a significant difference in the CR discordance rates between the two readers for IDEC (both studies), but not for Rituxan.

Table 6: Agreement Rate between Lexcor and Investigators 106-04 Pivotal Trial and 106-06 Estimation Study

LEXCOR							
Overall Response (CR + CCR + PR)							
Investigator		Zevalin-106-04		Rituxan-106-04		Zevalin-106-06	
		Yes	No	Yes	No	Yes	No
	Yes	50	10	31	7	28	6
	No	3	10	2	30	4	16
	Total	53	20	33	37	32	22
	Concordance Rate	82.2%		87.1%		81.5%	
	p-value-McNemar	0.0923		0.1797		0.7539	
	Complete Response						
	Yes	12	14	7	7	1	9
	No	1	46	1	55	1	43
	Total	13	60	8	62	2	52
	Concordance Rate	79.5%		88.6%		81.5%	
	p-value-McNemar	0.0010		0.0703		0.0215	

There is no significant difference in the discordance rates between the two readers in the overall response rates. However, There is a significant difference in the CR discordance rates between the two readers for IDEC (both studies), but not for Rituxan.

The robustness of the efficacy (response rate) results vary according to the evaluator. The observed differences between the clinical site investigators and the independent LEXCOR group in interpretation of complete response (CR) rates raise questions regarding the robustness of Zevalin's clinical benefit.

Tertiary Endpoint -- Quality of Life: FACT-G Analysis

Quality of Life was a tertiary endpoint in the protocol.

Functional Assessment of Cancer Therapy-General (FACT-G) analyses of two separate patient populations (ITT patients and patients classified as responders) were performed. The paired t-test was performed within treatment comparisons for each patient population between the total score at baseline and total score at 12-weeks post-treatment and between the total score at baseline and the onset of response. The general linear model, with the total scores at 12-weeks post-treatment as the dependent variable, evaluated treatment differences, where total score at baseline and prognostic factors were included as covariates.

The FACT-G survey is a validated instrument that captures the major areas of a patient's evaluation of cancer's impact on his or her life. Domains included in the self-administered questionnaire are: physical, social/family, relationship with doctor, emotional, and functional well-being. Scores indicate the level of impact that cancer has on a patient's quality of life; an increase in score equates to an increase in QOL.

The FACT-G overall score was available at baseline and 12 weeks post-treatment for 45 ITT Zevalin patients (61.6%) and 36 ITT Rituxan patients (51.4%). The baseline mean overall FACT-G score was 86.9 in Zevalin patients and 90.7 in Rituxan patients. The mean overall FACT-G score at 12 weeks post-treatment was improved: 93.3 in Zevalin patients and 93.4 in Rituxan patients. The change in score from baseline to 12 weeks post-treatment was statistically significant in the Zevalin treatment group ($p = 0.001$), but not in the Rituxan treatment group ($p = 0.185$). The results are given in Table 7 and summarizes the FACT-G scores for paired t-test:

The protocol stated that QOL would be assessed at baseline, week 4, week 8 and week 12. There were no statistical hypotheses specified in the protocol regarding QOL . The week 8 assessment in the Ritxan arm was missing by design. There are inconsistencies in QOL data, e.g., modest sample size to begin with, sample size not based on detecting any differences, missing information, informative dropouts, protocol not followed, biased baseline values as they were obtained after treatment was administered, no allowance for endpoint multiplicity adjustments, etc. Therefore, this QOL data is not statistically robust to draw meaningful inferences.

Therefore, we can not infer anything from these data.

Table 7: Summary of the FACT-G scores for paired t-test:

	Zevalin	Rituxan
Overall N	73	70
Completed the FACT-G Survey at the Baseline & 12 weeks post-treatment	45 (61.6%)	36 (51.4%)
Mean FACT-G Score at the Baseline	86.9	90.7
Post treatment (Week 12) Mean Score	93.9	93.4
Change from baseline	6.4	2.7
95% Confidence interval on difference	(3.0, 9.8)	(-1.2, 6.6)
p-value	0.001	0.185

Appendix A

Table A1: Censoring Pattern- Study 106-04

Efficacy Data for the study 106-04 Revised Zevalin & Rituxan

Obs	Treatment Group	Lexcor Response	Time to Response	CENSOR (1=Yes)
1	Rituxan	SD	3.8000	1
2	Rituxan	PR	7.6333	1
3	Rituxan	SD	10.0667	1
4	Rituxan	PR	11.2000	1
5	Rituxan	SD	12.1333	1
6	Rituxan	PR	13.0667	1
7	Rituxan	.	13.3000	1
8	Rituxan	PR	13.7333	1
9	Rituxan	PR	15.8000	1
10	Rituxan	CR	15.8667	1
11	Rituxan	PR	15.8667	1
12	Rituxan	CR	15.9000	1
13	Rituxan	PR	16.1000	1
14	Rituxan	SD	17.0000	1
15	Rituxan	PR	17.3333	1
16	Rituxan	CR	18.6667	1
17	Rituxan	CCR	18.9333	1
18	Rituxan	PR	18.9667	1
19	Rituxan	SD	25.1000	1
20	Rituxan	CR	25.3000	1
21	Zevalin	SD	3.7667	1
22	Zevalin	PR	10.2667	1
23	Zevalin	PR	11.1667	1
24	Zevalin	PR	11.8667	1
25	Zevalin	SD	11.9000	1
26	Zevalin	PR	11.9667	1
27	Zevalin	PR	12.1333	1
28	Zevalin	CR	12.1333	1
29	Zevalin	PR	12.3667	1
30	Zevalin	PR	12.3667	1
31	Zevalin	CR	13.0667	1
32	Zevalin	PR	13.3000	1
33	Zevalin	PR	15.8333	1
34	Zevalin	PR	15.8667	1
35	Zevalin	PR	16.1333	1
36	Zevalin	PR	18.4000	1
37	Zevalin	CR	18.4333	1
38	Zevalin	PR	18.4333	1
39	Zevalin	PR	18.7667	1
40	Zevalin	CR	19.2333	1
41	Zevalin	CR	21.4667	1
42	Zevalin	CR	21.5667	1
43	Zevalin	CR	21.7000	1
44	Zevalin	CR	21.9333	1
45	Zevalin	CCR	24.0667	1
46	Zevalin	CR	24.9667	1
47	Zevalin	CR	31.5000	1

Table A2:
Summary of Demographic Data for ITT Patients
Phase III Comparison Study
(N = 143)

	Zevalin N = 73	Rituxan N=70	p-value
Age (years)			
N	**73**	**70**	
Median	**60.0**	**57.0**	**0.394**
Range	(29.0-80.0)	(36.0-78.0)	
Gender [N (%)]			
Female	38 (52.1 %)	35 (50.0 %)	**0.868**
Male	35 (47.9 %)	35 (50.0 %)	
Ethnicity [N (%)]			**0.610**
Caucasian	68 (93.2 %)	63 (90.0%)	
African-American	2 (2.7 %)	3 (4.3%)	
Hispanic	2 (2.7 %)	2 (2.9%)	
Asian	1 (1.4%)	0 (0.0%)	
Other	0 (0.0%)	2 (2.9%)	
American/Indian	0 (0.0%)	1 (1.4%)	
Portuguese	0 (0.0%)	1 (1.4%)	
Weight Group [N (%)]			**0.709**
< 80 kg	45 (61.6%)	41 (58.6%)	
>= 80 kg	28 (38.4%)	29 (41.4%)	

N = number of patients
*p-values generated from Cochran-Mantel-Haenszel test for ordinal variables, Fisher's exact two-tailed test for categorical variables, and t-test for continuous variables.

Table A3:
Summary of Disease Status for ITT Patients -- Phase III Comparison Study (N = 143)

	Zevalin (N=73) N %	Rituxan (N=70) N %	p-value
Disease Stage at Study Entry			
I/II	8 (11.0)	6 (8.6)	0.780
III/IV	65 (89.0)	64 (91.4)	
Stratified Histology Type			
A	9 (12.3)	8 (11.4)	1.000
Follicular	57 (78.1)	56 (80.0)	
Transformed	7 (9.6)	6 (8.6)	
Pathology Report Histology Type			
A	9 (12.3)	8 (11.4)	0.391
Follicular	55 (75.3)	58 (82.9)	
Transformed	9 (12.3)	4 (5.7)	
Bone Marrow Involvement			
0%	42 (57.5)	46 (65.7)	0.456
0.1 - 5%	3 (4.1)	5 (7.1)	
5 - 20%	20 (27.4)	15 (21.4)	
>= 20%	8 (11.0)	4 (5.7)	
Splenomegaly			
Yes	7 (9.6)	3 (4.3)	0.327
No	66 (0.4)	67 (95.7)	
Extranodal Disease			
0, 1	60 (82.2)	61 (87.1)	0.490
>=2	13 (17.8)	9 (12.9)	
Bulky Disease			
< 5 cm	40 (54.8)	39 (55.7)	0.672
5 - < 7 cm	18 (24.7)	13 (18.6)	
7 - < 10 cm	9 (12.3)	13 (18.6)	
>= 10 cm	6 (8.2)	5 (7.1)	
WHO Performance Status			
0, 1	72 (98.6)	68 (97.1)	0.614
>=2	1 (1.4)	2 (2.9)	
Baseline LDH			
Normal or Low	57 (78.1)	54 (77.1)	0.653
High	14 (19.2)	10 (14.3)	
Unknown	2 (2.7)	6 (8.6)	
Baseline PB B-Cell Counts (x10 3 cells/mm 3)			
None	3 (4.1)	2 (2.9)	0.844
Low (< 32)	15 (20.5)	13 (18.6)	
Normal/High (>=32)	52 (71.2)	54 (77.1)	
Unknown	3 (4.1)	1 (1.4)	
***bcl*-2 (PB)**			
Positive	30 (41.1)	33 (47.1)	0.493
Negative	39 (53.4)	33 (47.1)	
Unknown	4 (5.5)	4 (5.7)	

***bcl*-2 (BM)**			
Positive	27 (37.0)	30 (42.9)	0.357
Negative	34 (46.6)	26 (37.1)	
Unknown	12 (16.4)	14 (20.0)	
Number of Prior Regimens			
N	73	70	0.803
Median	2.0	2.0	
Range	(1.00-6.00)	(1.00-5.00)	
Number of Prior Regimens by Category			
1	34 (46.6)	29 (41.4)	0.668
2 - 3	31 (42.5)	35 (50.0)	
>=4	8 (11.0)	6 (8.6)	
Type of Prior Regimen			
Alkylator +/- Prednisone	21 (28.8)	19 (27.1)	N/A
Purine Analogs	7 (9.6)	15 (21.4)	
Steroids	14 (19.2)	15 (21.4)	
CVP or COP	27 (37.0)	19 (27.1)	
CHOP	30 (41.1)	34 (48.6)	
Other Aggressive	18 (24.7)	30 (42.9)	
Prior Radiotherapy			
Yes	21 (28.8)	15 (21.4)	0.341
No	52 (71.2)	55 (78.6)	
IPI Risk Group			
Low	25 (34.2)	32 (45.7)	0.188
Low/Intermediate	38 (52.1)	23 (32.9)	
Intermediate/High	5 (6.8)	7 (10.0)	
High	3 (4.1)	2 (2.9)	
Unknown	2 (2.7)	6 (8.6)	

N = number of patients
N/A = not available
p-values generated by Cochran-Mantel-Haenszel test for ordinal variables, Fisher's exact two-tailed test for categorical variables, and Wilcoxon rank sum test for continuous variables. Unknown group is excluded from p-value calculation
None = level below the detectable limit