

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125019/0

MEDICAL REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

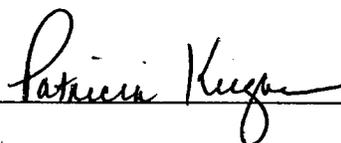
Center for Biologics Evaluation and Research

MEDICAL OFFICER REVIEW

BLA STN #: 125019/0
Date Received by CBER: November 1, 2000
Established and Proprietary Product Names: Ibritumomab tiuxetan (Zevalin™)
Applicant: IDEC Pharmaceuticals Corp.
Indication or change being requested: Treatment of patients with relapsed or refractory low grade follicular or CD20+ transformed B-cell non-Hodgkin's lymphoma and Rituximab-refractory follicular NHL
Reviewer Names and Mail Code: Philippe Bishop, M.D., HFM-573
George Mills, M.D., HFM-573
Date Review Completed: February 19, 2002

Reviewer: 
Reviewer: 

Concurrence:

Deputy Division Director: 

Division Director: 

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File STN BL 125019/0

From: Deborah Trout, OCBQ, DMPQ, HFM-675

Subject: Review of IDEC Pharmaceuticals Corp., BLA STN 125019/0, to determine its acceptability for filing.

Date: December 11, 2000

I have completed an initial review of the submission and find it acceptable for filing. My judgement was based on the verification that the following information is included in the submission:

Drug Substance

1. identification for each manufacturer and testing facility including a brief description of operations performed, responsibilities conferred by applicant;
2. general layout of each manufacturing area;
3. comprehensive list of other products;
4. contamination precautions;
5. flow charts of the manufacturing process;
6. one completed batch record;
7. drug substance stability;

Drug Product

1. identification for each manufacturer and testing facility including a brief description of operations performed, responsibilities conferred by applicant;
2. complete description of manufacturing process flow including, sterilization operations, _____, packaging;
3. container/closure system data;
4. one completed batch record;
5. _____ processing procedures (see narrative below)
6. drug product stability.

IDEC is using _____ as a contract manufacturer for conjugation,

formulation, filling, and packaging of the finished drug product.

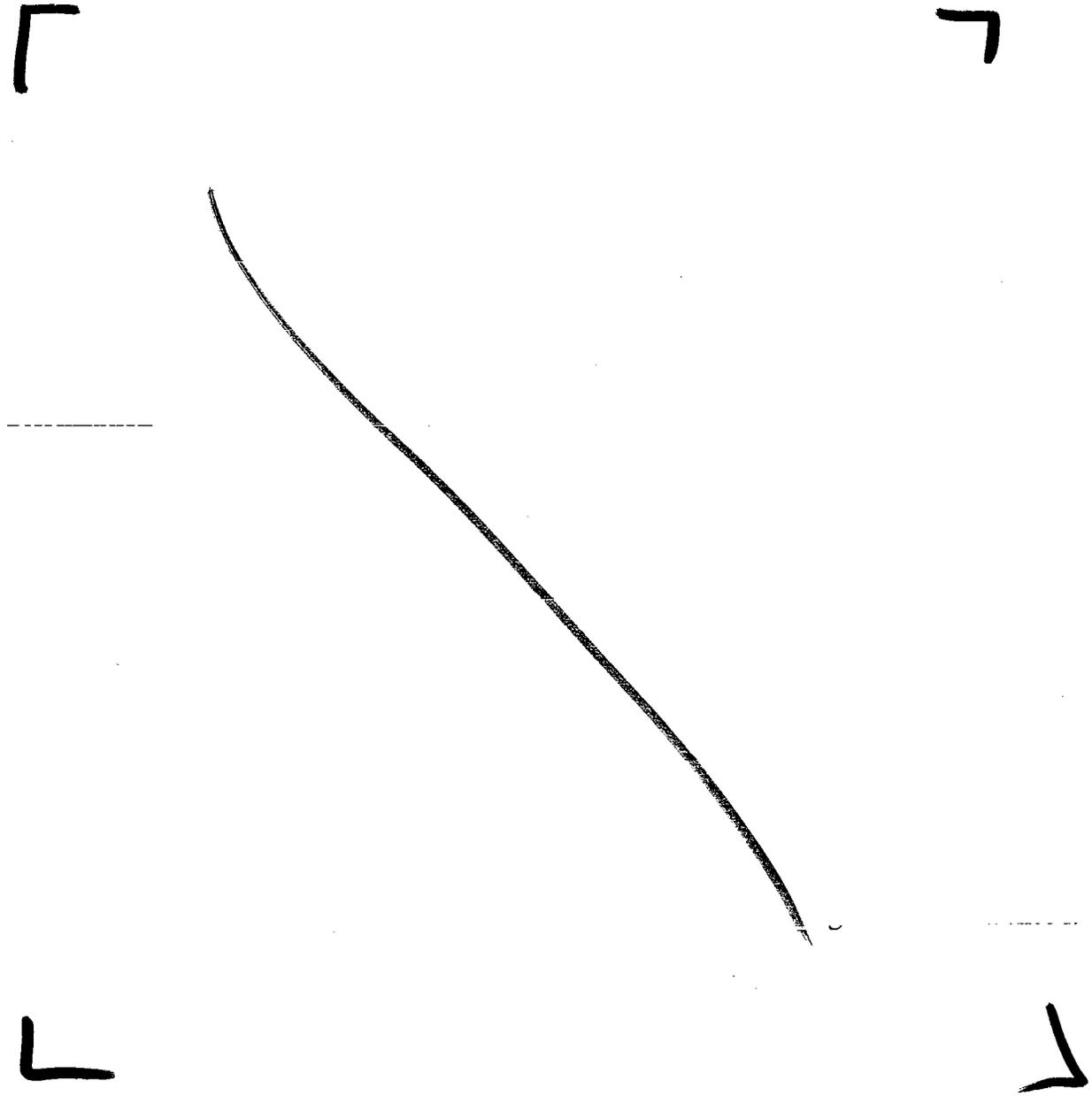
The following items, required for filing, under the "Microbiology" section of the BLA were not provided but referenced in [redacted] Drug Master File:

Contamination Precautions

Details regarding contamination precautions are provided in the [redacted] Filled Products Sections [redacted] Master File No. [redacted]

Description of Building and Facilities

Information specific to this facility is referenced to [redacted] Master File No. [redacted]



the Microbiology section, such as site maps and microbiological monitoring of the environment. Product specific information, such as the drug product container/closure system and sterilization information included in the batch record, is provided within the BLA.”

I’ve reviewed a letter from [redacted] to CBER dated 4/22/00 concerning the above telecon. The letter states “CBER representatives agreed that the MF is the appropriate place to provide proprietary information (active names and/or product names), items specific to [redacted] regarding validation, and reference to [redacted] SOPs. BLA submission should contain product specific information and the classifications of the products manufactured at [redacted]. As an example, [redacted] regarding media fills should be in the MF, whereas the actual data that supports the container closure for the specific product should be files in the BLA. There is no requirement for specific equipment validation to be listed in the BLA”.

I called Alice Wei, Senior Director, Regulatory Affairs, for IDEC Pharmaceuticals to inform her that the application will not be considered filed until the following data from their Contract Manufacturer has been received (see telecon dated November 27, 2000):

- A. Room numbers where manufacturing equipment is located.
- B. Data resulting from media fill validation using the same container closure system and filling procedure used for their product. These data should be obtained using the same filling line(s) that are used for their product. In addition, the following information should be submitted for each media fill run:
 1. [redacted]
 - 2.
 - 3.
 - 4.
 - 5.
 - 6.
 - 7.
 - 8.
 - 9.
 10. [redacted]
- C. Verification that sterilization validations referenced in the DMF are applicable to their container closure system.

I received the information requested on December 6 and December 8, 2000 via facsimile. Ms. Wei indicated that the information faxed to me was also submitted to DCC for filing in the application.

cc: Noska HFM-588
electronic cc: Lukas HFM-675
electronic cc: Shapiro HFM-561 (Chair)

**Review of Biologics License Application
for
IDEC Pharmaceutical ZEVALIN Kit**

BLA# 125019

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SPONSOR

IDEC Pharmaceuticals Corporation
3030 Callan Road, San Diego, California 92121
(858) 431-8500

PRODUCT

ZEVALIN

Kits for the Preparation of Indium-111 (In-111) Ibritumomab Tiuxetan (In-111 ZEVALIN) and Yttrium-90 (Y-90) Ibritumomab Tiuxetan (Y-90 ZEVALIN)

In-111 Ibritumomab Tiuxetan and Y-90 Ibritumomab Tiuxetan are components of the ZEVALIN therapeutic regimen (See Description).

PROPOSED INDICATION

ZEVALIN, as part of the ZEVALIN therapeutic regimen is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates. The effects of the ZEVALIN therapeutic regimen on survival are not known.

REVIEW COMMITTEE

Product/Committee Chair:

Marjorie Shapiro, Ph.D.

Clinical Reviewers:

Philippe C. Bishop, MD

George Mills, MD

Biostatisticians:

Satish C. Misra, Ph.D.

Clinical Toxicology and Pharmacology:

David Green, Ph.D.

RPM:

Mike Noska

Compliance/BIMO:

Mary Andrich

DMA/CMC:

Leon Epps

DMPQ/CMC

Kevin O'Brien

DMPQ/CMC

Deborah Trout

EXECUTIVE SUMMARY

EXECUTIVE SUMMARY

The ZEVALIN™ Kit contains the materials for final manufacture ZEVALIN therapeutic regimen. The treatment program consists of sequential administrations of unlabeled chimeric anti-CD20 antibody (rituximab) and radiolabeled murine anti-CD20 antibody (ibritumomab). Ibritumomab is the parent murine anti-CD20 antibody from which rituximab was generated.

Rituximab is administered immediately prior to the radiolabeled ibritumomab in order to saturate the CD20 receptors on normal lymphocytes in the circulation and to enhance tumor targeting by the radiolabeled antibody. The clinical development program required administration of the 111-In-Ibritumomab Tiuxetan in order to allow confirmation of tumor targeting, to allow identification and characterization of normal organ biodistribution, altered biodistribution, and to generate data to permit biodistribution risk assessment (eg: proximity and risk of injury to normal tissue adjacent to tumor site) and dosimetric assessment.

The sponsor has submitted the results obtained in 348 subjects enrolled in five clinical studies [two efficacy studies, one phase 2 and one phase 1 trial, and preliminary information on an ongoing expanded access trial].

Anti-tumor activity, as measured by durable objective tumor responses, was documented in both efficacy studies.

- 106-04 Randomized, multicenter trial of ZEVALIN therapeutic regimen vs. RITUXAN

Outcome	ZEVALIN (n=73)	RITUXAN (n=70)
ORR	73%	47%
Resp. Duration (mos)	14.2	12.1
CR	20%	9%
Time to Progr. (mos)	11.2	10.1

- 106-06- Single-arm trial of ZEVALIN therapeutic regimen in chemotherapy-refractory and RITUXAN-refractory patients
 - 58% overall response rate in follicular NHL
 - 4% CR rate in follicular NHL
 - Duration of response (responders) 7.7+ months

The toxicity profile of ZEVALIN therapeutic regimen is dominated by cytopenias, which occurred at a high frequency (55-57% Grade 3 and 4 neutropenia and thrombocytopenia) and last approximately 3-4 weeks. In exploratory analyses, extent of prior therapy, prior

fludarabine use, extent of malignant infiltration of the marrow, and pretreatment cytopenias, were all associated with greater risk of prolonged cytopenias. Severe non-hematologic toxicities occurred in less than 10% of subjects. The most serious adverse events included infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), hemorrhage while thrombocytopenic (resulting in two deaths) and myeloid malignancies and dyscrasias (3 patients with AML and 2 with MDS). The most common non-hematologic toxicities that appear to be related to ZEVALIN therapeutic regimen (as compared to incidence in the RITUXAN arm of 106-04) were gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), which occurred at grade 1-2 severity in 57% of ZEVALIN subjects vs. 34% of RITUXAN subjects. Other adverse effects that occurred at a higher rate in the ZEVALIN arm included infection, increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis.

Tumor targeting was documented in the majority of patients, although not necessarily at all known sites of disease. In those without evidence of tumor targeting, anti-tumor activity was observed. Since the numbers were small, and to show distribution to normal lymphocytes, most notably gastrointestinal uptake in lymphoid aggregates (Peyer's patches) and the spleen, as well as unexpected uptake in testes.

The anti-tumor activity observed is clinically significant but also associated with significant toxicity, which in a small proportion of subjects may be associated with serious morbidity and/or preclude the ability to deliver adequate dose intensity of salvage therapy. The benefits of this active agent are clearly acceptable in the setting of chemotherapy and RITUXAN-refractory patients, however the benefits in patients who have not failed RITUXAN may not outweigh the higher toxicity for all such subjects.

ZEVALIN therapeutic regimen has demonstrated anti-tumor activity in a heavily pretreated population. The experience in subjects with low-grade, non-follicular lymphoma and with low-grade lymphoma that has undergone transformation is very limited. The clinical behavior and level of CD20 expression in these two entities may be sufficiently different from that of low-grade follicular NHL to allow extrapolation of the clinical results. The Agency believes that the data are insufficient to determine the net benefit in these settings and that additional studies with adequate experience in these subpopulations should be undertaken.

Low grade NHLs are extremely rare in the pediatric population. In the past, the Committee has advised that studies in pediatric patients should not be required (under the Pediatric Rule) because the disease (follicular NHL) does not occur with sufficient frequency in children. The Agency seeks the Committee's advice regarding the waiver of studies in pediatric patients.

The ibritumomab antibody is a foreign protein; both this product and other murine or partially murine (chimeric) proteins generate immune responses in human subjects. Based on clinical experience with other murine proteins, the development of an immune response will alter both the safety profile and reduce the efficacy of the product, through altered biodistribution and clearance of the product.

- One subject was reported by the investigator to have altered biodistribution in the study population. However, the number of subjects studied for biodistribution (182 patients) is insufficient to rule out an altered biodistribution that may occur at rate $\leq 5\%$.
- The population studied in these trials was carefully screened, in that patients with prior exposure to murine antibodies or evidence of human anti-murine antibodies (HAMA) were excluded. As novel murine or partially murine agents enter the clinical trials and ultimately approved for marketing, it is expected that the potential for prior exposure to a murine protein and the potential of acquiring an immune response will increase. The safety and efficacy profile observed in the current ZEVALIN therapeutic regimen trials is unlikely to be applicable to a population exposed to other murine proteins. Limitation of ZEVALIN therapeutic regimen to subjects with no prior exposure to murine proteins is impractical and possibly unnecessary, however no other screening test has been adequately evaluated to identify patients at increased risk of altered biodistribution.
- An additional function of pre-treatment imaging and biodistribution studies would be to identify areas of uptake adjacent to normal tissues that may be damaged by targeted radiotherapy. In such subjects, adequate counseling regarding potential risks and, in some instances, more targeted assessment for radiation-related toxicity could be undertaken.

The ZEVALIN therapeutic regimen was presented in a public forum on September 11, 2001 to the Oncology Drug Advisory Committee (ODAC). Safety and efficacy concerns were discussed and the Committee presented its advice to FDA. ODAC voted 13-2 recommending the ZEVALIN therapeutic regimen for approval for patients that failed existing rituximab therapy. With respect to the use of the ZEVALIN therapeutic regimen in patients that are not rituximab-refractory, that is, patients with relapsed or refractory, low grade, follicular or CD20-positive transformed, B-cell NHL, ODAC recommended that the FDA consider approval of ZEVALIN in this indication under the agency's accelerated approval regulations.

Under the accelerated approval for biological products regulations, 21 CFR 601.40-46, an approval is subject to additional adequate and well-controlled studies to verify the clinical benefit as evidenced by durable favorable outcomes and to further characterize the safety of the ZEVALIN therapeutic regimen. Consequently IDEC agreed to the following post-approval commitments:

1. To verify the clinical benefit and further assess the safety and efficacy of ZEVALIN radioimmunotherapy in patients with chemotherapy relapsed or refractory follicular NHL. Proposed is a randomized, multicenter study to establish the net clinical benefit of the ZEVALIN therapeutic regimen used in combination with RITUXAN as compared to RITUXAN therapy alone. For this study, the primary efficacy variable will be event-free survival defined as absence of disease progression, initiation of additional lymphoma therapy, or death from any cause. Uniform criteria will be used to define when additional anti-lymphoma treatment is initiated including the presence of disease-related symptoms, threatened end-organ function, cytopenias secondary to NHL, massive bulk disease, or steady disease progression over at least 6 months without meeting the definition of progressive disease.
2. To verify the clinical benefit and further assess the safety and efficacy of the ZEVALIN therapeutic regimen in patients with transformed CD20+ B-cell NHL. For this study, the primary efficacy variables will be overall response rate and duration of response. Other measures of clinical benefit will include event-free survival, time to progression, and quality of life and disease-related symptoms, including B symptoms.
3. To continue to assess patients enrolled in Study 106-04 and 106-06 for progression-free (PFS) and overall survival (OS). Patient follow-up data will be collected every 6 months, until the time to progression data has matured.
4. Continued assessment of the immunogenicity of the ZEVALIN therapeutic regimen by long term monitoring of subjects enrolled in all ZEVALIN studies under any IDEC ZEVALIN IND including the post-approval commitment studies 106-10 and 106-11. Interim data on immunogenicity will be submitted annually to the IND(s) and a final report will be submitted when all studies are completed.
5. Continued assessment of MDS and AML of the ZEVALIN therapeutic regimen by long term monitoring of subjects enrolled in all ZEVALIN studies under any IDEC ZEVALIN IND including the post-approval commitment studies 106-10 and 106-11. Interim data on MDS and AML will be submitted annually to the IND(s) and a final report will be submitted when all studies are completed.
6. If the data on immunogenicity or MDS/AML warrants a supplement to the ZEVALIN BLA, IDEC would initiate supplement to the BLA and submit a SAS compatible database.

RECOMMENDATION:

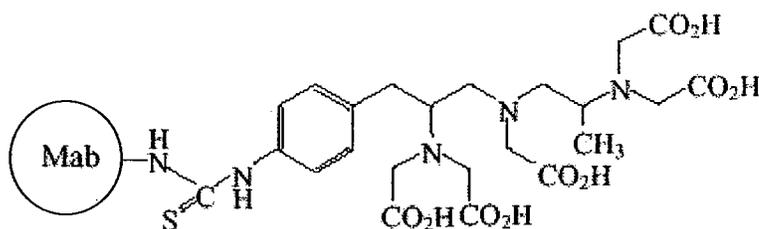
It is recommended that Ibritumomab Tiuxetan, as part of a specific therapeutic regimen, be approved for introduction into interstate commerce for the treatment of patients with

relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab (Rituxan™) refractory follicular non-Hodgkin's lymphoma. The therapeutic regimen includes Rituximab, Indium-111 Ibritumomab Tiuxetan, and Yttrium-90 Ibritumomab Tiuxetan.

GENERAL PRODUCT DESCRIPTION

GENERAL PRODUCT DESCRIPTION

ZEVALIN (Ibritumomab Tiuxetan) is the immunoconjugate prepared by a stable thiourea covalent bond between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan [[N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for ^{111}In or ^{90}Y .



(Ibritumomab tiuxetan)

Ibritumomab is produced by genetically modified Chinese hamster ovary (CHO cells) cells grown in suspension culture in a nutrient medium.

CD20 (p35 antigen)

Located on Chromosome 11q12-q13.1

Expressed on subpopulation of precursor-B cells, all B lymphocytes, follicular dendritic reticulum cells, lost with differentiation into plasma cells.

Low-grade B-cell NHL, Precursor B-Cell Neoplasm, Precursor B-Lymphoblastic Leukemia/Lymphoma (B-LBL), HCL, B-CLL (weak); B-PLL

CD20 is a tetraspanning membrane protein with possible role in regulating B cell activation and regulation of B-cell growth by forming calcium channel and allowing the influx of Ca^{++} .

PRODUCT NOMENCLATURE:

ZEVALIN Therapeutic Regimen: one infusion of 250 mg/m² rituximab immediately preceding a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of ¹¹¹In Ibritumomab Tiuxetan injected as a slow 10 minute IV push; followed seven days later by a second infusion of 250 mg/m² of rituximab prior to 0.4 mCi/kg (1.6 mg total antibody dose) of ⁹⁰Y Ibritumomab Tiuxetan slow IV 10 minutes push.

ZEVALIN Kit: components necessary for the final manufacturing of the 2 radionucleotide labeled antibodies ¹¹¹In Ibritumomab Tiuxetan and ⁹⁰Y Ibritumomab Tiuxetan.

ZEVALIN Antibody: Ibritumomab Tiuxetan

Ibritumomab Tiuxetan: drug product also known as IDEC-2B8-MX-DTPA consisting of the murine antibody (IDEC-2B8) directed against CD20 fused with the radioisotope linker (MX-DTPA).

¹¹¹In Ibritumomab Tiuxetan: (synonyms: In2B8, IDEC-In2B8, ¹¹¹In-2B8-MX-DTPA); Indium labeled murine antibody (IDEC-2B8) directed against CD20 fused with the radioisotope linker (MX-DTPA).

⁹⁰Y Ibritumomab Tiuxetan: (synonyms: Y2B8, IDEC-Y2B8, ⁹⁰Y-2B8-MX-DTPA); yttrium labeled murine antibody (IDEC-2B8) fused with the radioisotope linker (MX-DTPA).

Rituximab: (synonyms: RITUXAN™, IDEC-C2B8); genetically engineered chimeric murine/human monoclonal antibody directed against the CD20.

CLINICAL DEVELOPMENT

ZEVALIN THERAPY CLINICAL DEVELOPMENT PROGRAM

The ZEVALIN therapeutic regimen clinical development has focused on 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 non-Hodgkin's lymphoma.

There is no previous clinical experience with the ZEVALIN therapeutic regimen outside of the clinical studies provided in the license application materials.

NON-HODGKIN'S LYMPHOMAS

General

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

Epidemiology

NHL ranks fifth in cancer incidence and mortality, with a U.S. incidence of approximately 55,000 cases per year and a prevalence of approximately 300,000 cases. Of these, 65 percent are low-grade or follicular histology. The median age at diagnosis is 60 years and 85% of patients have widespread disease at initial presentation. The median survival for patients with low-grade or follicular NHL subtypes is 10 years.

Classification

Several histologic classifications of NHLs exist. Commonly used systems are the 1982 International Working Formulation (IWF)¹ and the 1994 Revised European-American (REAL) classifications². These classification systems group lymphoid neoplasms according to clinical behavior (low grade/indolent, intermediate grade/aggressive, or high grade/very aggressive). Historically, this grouping often served as a basis for choosing a first line therapy.

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

More recently, the World Health Organization (WHO) proposed a new classification system³. Unlike the IWF and REAL classifications, the WHO committee felt that grouping lymphoid neoplasms according to clinical behavior was neither necessary nor desirable⁴. The committee recognized that specific disease entities could be defined by a combination of morphology, immunology, genetic features, and clinical features. Each entity had distinct clinical behavior and outcome predictable by applicable prognostic factors (e.g.; the international Prognostic Index) and related to the type of initial therapy administered. The committee concluded that each lymphoma type needed to be treated as distinct entities. Therefore, rather than depending on clinical grouping (i.e.; low grade/indolent, etc.), the committee emphasized that clinical decisions should be based on the specific lymphoid neoplasm.

PROPOSED WHO CLASSIFICATION OF B-CELL NEOPLASMS

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

Natural History

The median age prevalence of indolent lymphoma is in the sixth decade. B-cell indolent (low-risk group) NHL is not curable with standard treatment. First line therapy is commonly associated with a high rate of clinical response followed by relapse. Subsequent remissions may occur but at a progressively lower rate and with progressively shorter durations with a median progression-free survival (PFS) frequently less than 6 months⁵ using traditional chemotherapeutic regimens. However, recent studies suggest that treatment using unconjugated monoclonal antibodies directed against CD20 antigen may yield a prolonged median PFS greater than 6 months⁶ in relapsed or refractory indolent NHL populations.

Over time, indolent NHL may transform to aggressive (intermediate risk) or very aggressive (high-risk) lymphomas that have a more aggressive clinical course. The incidence of transformation ranges from 40% to 70% and is associated with disease progression and known adverse prognostic factors⁷. In general, transformation has a poor prognosis and frequently results in a rapidly fatal outcome. However, some patients can have complete responses to salvage chemotherapy regimens and achieve durable complete remissions⁸. Overall survival following transformation is poor with an estimated median survival ranging from 7 to 22 months.

Prognostic Indicators

The most valuable and widely used prognostic indicator system for NHL is the International Prognostic Index (IPI)⁹. The IPI is a prognostic index that was developed to predict outcome in patients with aggressive NHL, based on patients' clinical characteristics before treatment. However, the IPI has been shown to apply to indolent (low-risk) lymphoma¹⁰.

INTERNATIONAL PROGNOSTIC INDEX

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

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

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

IPI Score and Clinical Outcome (Follicle Center Cell NHL)

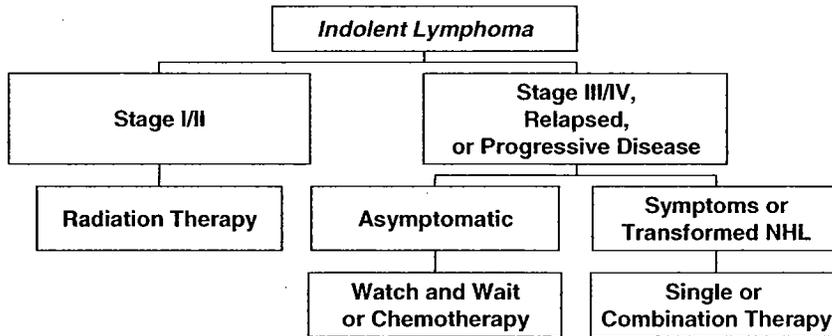
IPI	CR (%)	5-yr FFS (%)	5-yr OS (%)	Median OS (mo)
Low	92	75	85	160
Low-Int	81	64	69	108
High-Int	77	38	28	35
High	0	0	0	12

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

Therapy

FIRST LINE TREATMENT

Treatment Strategy



Localized indolent lymphoma at initial presentation is unusual and represents less than 5% of the population. Patients with early-stage indolent lymphomas are potentially curable with radiation therapy (46% to 68% 10-year DFS)^{11, 12, 13}. The addition of chemotherapy to radiotherapy as primary treatment has not convincingly prolonged remission duration or survival.

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

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

Distinguishing follicular lymphoma into those with predominantly small cells (follicle small, grade I), those with an intermediate number of small and large cells (follicle center, mixed small/large grade II), and those with more large cells (follicle center, large grade III) is difficult¹⁴. However studies that have assessed the clinical behavior of these

FDA Approved Drugs in NHL

1. BCNU
2. Blenoxane
3. Leukeran
4. Velban
5. Oncovin
6. Cytosan
7. Adriamycin
8. Methotrexate
9. Intron A
10. Rituxan

lymphomas have shown that patients with follicular large cell lymphoma have a shorter remission duration and overall survival than patients with the other subtypes. For these patients, the incorporation of an anthracycline into the initial treatment regimen appears to improve outcome¹⁵.

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

Commonly Used First Line Treatment of Indolent NHL

1. Watch and wait
2. Radiation
 - Localized
 - Low-dose total body Irradiation
3. Oral alkylating agents
4. CVP
5. CHOP
 - CHOP + Rituxan
6. Mitoxantrone
7. Second and third generation anthracycline-based regimens
8. Fludarabine
9. Cladribine
10. Transplantation
11. Interferon alpha-2b

SECOND LINE TREATMENT

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

including high-dose therapy on overall survival is still uncertain. Rituximab can induce remissions in chemoresistant patients.

RITUXAN is the only FDA approved agent indicated for use in relapsed or refractory low grade or follicular B NHL. Marketing approval was based on 3 single arm trials with a total of 242 registered participants. The ORR was 48% (6% CR and 42% PR). Notable was a time to treatment response of 50 days and duration of response of 10-12 months. The toxicity profile was acceptable and serious adverse events were uncommon (<5%).

IND CLINICAL TRIALS SUMMARY

ZEVALIN CLINICAL TRIALS SUMMARY (BB-IND# 4850)

General Overview

Five clinical trials constitute the basis for registration. Clinical trials exploring IDEC-Y2B8 treatment in patients with B-cell NHL began in 1993 and are currently ongoing under IDEC's BB-IND#4850.

ZEVALIN therapeutic regimen efficacy studies were conducted in 2 pivotal trials: Study 106-04 and Study 106-06. Both studies included subjects with histologically confirmed, relapsed or refractory low-grade or follicular (IWF A-D) or transformed from low-grade to intermediate-grade histology (IWF E-G) B-cell NHL, requiring treatment as determined by an increase in overall tumor size, the presence of B symptoms and/or the presence of masses that are causing ongoing clinical symptomatology.

ZEVALIN therapeutic regimen safety experience arises from 5 studies submitted in the license application: the 2 pivotal trials (106-04 and 106-06) and 3 supportive studies (106-03, 106-05, and 106-98). To date, safety data on 419 subjects has been provided for consideration. Of these, 349 were treated with IDEC-Y2B8, 70 were treated with rituximab as a control therapy. Of the 349 subjects treated with IDEC-Y2B8, 182 received 2 doses of radiolabeled Ibritumomab Tiuxetan (a Study Day 1 dose of IDEC-In2B8 followed by imaging and a Study Day 8 dose of IDEC-Y2B8).

Regulatory History

Date	Milestone
24-NOV-1992	IND Original Submission
13-JUN-1996	Trial 106-03 Initiated
30 Sep 1997	106-04 Phase 3 Meeting
24-FEB-1998	Trial 106-04 Initiated
20-MAY-1998	Trial 106-05 Initiated
7-JUL-1998	Trial 106-06 Initiated
17-NOV-1998	106-06 Phase 3 Meeting
23-MAR-1999	Pre-PLA Meeting
9-DEC-1999	Trial 106-98 Initiated
05-JUN-2000	Fast Track Designation Granted
18-JUL-2000	Pre-BLA Meeting
01-NOV-2000	Application Received
29-DEC-2000	Filing Action
03-MAY-2001	First Action-Complete Response (CR) Letter
10-JUL-2001	Complete Response To CR Letter Received
11-SEP-2001	ODAC Presentation

Eligibility Criteria Overview

	106-03	106-04	106-05	106-06	106-98
N (Total = 426)	58	143	30	57	183 (still accruing)
INCLUSION CRITERIA					
Previous treatment (tx)	≥ 1	≥ 1	≥ 1	RITUXAN failures	Open Access
IWF Histology	A - G	A - G	A - G	B - D	A-G
< 25% BM involvement	X	X	X	X	X
ANC ≥ 1,500	X	X	X	X	X
Platelet Count	≥ 100	≥ 150	100-149	≥ 150	≥ 100
EXCLUSION CRITERIA					
Prior ABMT or PBSC	X	X	X	X	X
Prior radioimmunotherapy	X	X	X	X	X
XRT to > 25% BM	X	X	X	X	X

Trial Summary Tables

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
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Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-01	Phase I Trial: Treatment of B-Cell Lymphoma with 90 Y-Labeled Pan B Monoclonal Antibody with Peripheral Stem Cell or Autologous Bone Marrow Transplantation	June 8, 1993	August 23, 1996	No	17	<p>1) Safety and tolerance of IDEC-Y2B8 in patients with B-cell lymphoma, with B-cell lymphoma, with B-cell lymphoma,</p> <p>2) MTD of IDEC-Y2B8 peripheral stem cells (PSC) or bone marrow (BM) reinfusion are used for rescue from marrow toxicity,</p> <p>3) Measure the biodistribution, pharmacokinetics, dosimetry, clearance, and tumor uptake of indium-¹¹¹I-labeled anti-CD20 monoclonal antibody (IDEC-In2B8),</p> <p>4) Compare the delivered dose to the measured effects in order to define which dosimetric measurements on individual patients help to predict toxicity and response, and</p> <p>5) Determine the frequency of development human anti-murine antibody (HAMA).</p>	<p>1) Correlation was shown between increasing hematologic toxicity and treatment doses.</p> <p>2) The dose-limiting toxicities were thrombocytopenia, leukopenia, and neutropenia.</p> <p>3) A Y2B8 dose of ≤ 0.5 mCi/kg did not require peripheral stem cell or bone marrow support.</p> <p>4) Subject 104 had confirmed positive HAMA.</p> <p>5) Subject 116 had unconfirmed positive HAMA</p> <p>6) Subject 109 initially reported to have a positive HAMA by the investigator had negative HAMA upon retesting but was removed from study due to unfavorable biodistribution (liver to whole body ratio was $> 8:1$. Please note that the liver dose was estimated to be 900cGy).</p>

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-02	A Phase I/II Clinical Trial of Yttrium-90]-Labeled IDEC-2B8 Given Every Six to Eight Weeks to Patients with B-cell Lymphoma	September 28, 1993	March 22, 1994	no	1	<p>1) Evaluate the safety of IDEC-Y2B8 given in repeated low doses to patients with relapsed or refractory NHL following conventional therapy,</p> <p>2) Determine if IDEC-In2B8 can target tumor sites,</p> <p>3) Establish the biodistribution, pharmacokinetics, dosimetric parameters, clearance, and tumor uptake of radiolabeled IDEC-2B8 antibody,</p> <p>4) Assess the percent injected dose/gram IDEC-Y2B8 in tumor by repeat biopsy,</p> <p>5) Estimate the frequency for the development of HAMA</p> <p>6) Estimate radiation dose delivered to the tumor and normal organs by dosimetry,</p> <p>7) Assess preliminary clinical activity in an early Phase II trial.</p>	<p>This study was discontinued due to administrative reasons</p> <p>Conclusions cannot be made due to limited enrollment.</p>

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-03	A Phase I/II Clinical Trial to Evaluate the Safety and Clinical Activity of IDEC-Y2B8 Administered to Patients with B-Cell Lymphoma	June 13, 1996	September 11, 1998	No	58	<p>1) Evaluate the safety and clinical activity of Y2B8 in relapsed or refractory B-cell NHL</p> <p>2) Evaluate the safety and activity of Rituximab when used in conjunction with Y2B8</p> <p>3) Study the IDEC-In2B8 targeting of tumor sites and the biodistribution, pharmacokinetics, dosimetric parameters, clearance, and tumor uptake of IDEC-In2B8 by radioimaging techniques when Rituximab is given prior to IDEC-In2B8</p> <p>4) Estimate the IDECY2B8 radiation dose delivered to normal organs and to tumors, using dosimetry.</p>	<p>1) Adverse events were primarily hematologic,</p> <p>2) Grade 4 hematologic toxicity was related to thrombocytopenia and bone marrow involvement with lymphoma at baseline.</p> <p>3) 2% of patients developed post-treatment HACA/HAMA.</p> <p>4) Dosimetric parameters were not able to predict which patients were at higher risk for hematologic toxicity.</p>

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-04	A Randomized, Phase III Multicenter, Controlled Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmunotherapy Compared to RITUXAN/Immunotherapy of Relapsed or Refractory Low-Grade or Follicular B-Cell Non-Hodgkin's Lymphoma III	February 24, 1998	July 28, 2000	Yes	143	<p>1) To compare the efficacy of ZEVALIN therapeutic regimen in relapsed or refractory, low-grade or follicular NHL with that of rituximab monotherapy</p> <p>2) To characterize the safety of ZEVALIN therapeutic regimen compared with the safety of rituximab monotherapy</p> <p>3) To estimate IDEC-Y2B8 radiation absorbed doses delivered to the tumor and to normal organs</p> <p>4) To demonstrate the clinical utility of baseline platelet counts as a surrogate predictor of IDEC-Y2B8 safety.</p>	<p>1) ZEVALIN therapeutic regimen has a superior overall response rate (73% vs. 47%, p=0.002) in patients with relapsed or refractory, low-grade, follicular B-cell NHL.</p> <p>2) ZEVALIN group time to progression (all subjects) and duration of response (responders only) were not statistically different to the rituximab group.</p> <p>3) Hematologic toxicity is common with ZEVALIN therapeutic regimen and represents a significant clinical limitation.</p> <p>4) Median duration of Grade ≥ 3 neutropenia within 90 days of ZEVALIN therapeutic regimen was 27 days for 56% of subjects.</p> <p>5) Median duration of Grade ≥ 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen was 23 days for 60% of subjects</p>

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-05	A Phase II, Open-Label, Multi-Center Trial to Evaluate the Safety and Efficacy of IDEC-Y2B8 Radioimmunotherapy of Relapsed or Refractory Low-Grade or Follicular B-Cell Non-Hodgkin's Lymphoma in Patients with Mild Thrombocytopenia	May 20, 1998	June 20, 2000	No	30	<p>1) determine the safety and efficacy of a reduced dose (0.3 mCi/kg) of IDEC-Y2B8 therapy in relapsed or refractory, low-grade, follicular, or transformed NHL subjects who have mild thrombocytopenia</p> <p>2) characterize the safety of ZEVALIN therapeutic regimen</p> <p>3) To estimate IDEC-Y2B8 radiation absorbed doses delivered to the tumor and to normal organs</p> <p>4) To demonstrate the clinical utility of baseline platelet counts as a surrogate predictor of IDEC-Y2B8 safety.</p>	<p>1) IDEC-Y2B8 given at 0.3 mCi/kg is usually tolerated in subjects with mild thrombocytopenia but may result in prolonged or refractory hematologic toxicity.</p> <p>2) ZEVALIN therapeutic regimen has clinical activity in mildly thrombocytopenic subjects</p> <p>3) Clinical selection criteria including baseline platelet count, bone marrow involvement, and individualized dosing based on patient weight resulted in acceptable toxicity profile for subjects treated with ZEVALIN therapeutic regimen..</p> <p>4) Median duration of Grade ≥ 3 neutropenia within 90 days of ZEVALIN therapeutic regimen was 29 days for 87% of subjects.</p> <p>5) Median duration of Grade ≥ 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen was 30 days for 87% of subjects.</p>

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-06	A Phase III, Open-Label, Nonrandomized Controlled, Multicenter Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmunotherapy in Patients with B-Cell Non-Hodgkin's Lymphoma Who Are Refractory to Prior Rituximab Therapy	July 7, 1998	June 30, 2000	No	57	<p>1) Determine the efficacy of ZEVVALIN therapeutic regimen in relapsed or refractory, follicular (IWF B, C, D; also defined as REAL classification Follicular center grade I, II, and III) B-cell NHL subjects whose disease was refractory to previous treatment with rituximab,</p> <p>2) Determine the overall response rate (ORR) to ZEVVALIN therapeutic regimen in follicular NHL patients, and</p> <p>3) Characterize the safety profile of ZEVVALIN Therapy</p>	<p>1) ZEVVALIN therapeutic regimen has clinical activity in patients with relapsed or refractory, follicular B-cell NHL who are also refractory to rituximab therapy.</p> <p>2) The LEXCOR protocol defined overall response rate to ZEVVALIN therapeutic regimen was 59%</p> <p>3) Time to progression for all subjects was 6.8 months</p> <p>4) Duration of response (CR and PR) to ZEVVALIN therapeutic regimen was 7.7 months</p> <p>5) Median duration of Grade ≥ 3 neutropenia within 90 days of ZEVVALIN therapeutic regimen was 22 days for 68% of subjects.</p> <p>6) Median duration of Grade ≥ 3 thrombocytopenia within 90 days of ZEVVALIN therapeutic regimen was 24 days for 75% of subjects</p>

Study	Title	Date Study Initiated	Date Study Closed	RCT	(n)	Study Objectives	Results
106-98	A Multicenter, Open-Label Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmunotherapy of Relapsed or Refractory Low-Grade or Follicular or Transformed B-Cell Non-Hodgkin's Lymphoma	December 9, 1999	ongoing	No	182	<p>1) To provide ZEVALIN therapeutic regimen to patients with relapsed or refractory low-grade or follicular or transformed B-cell NHL</p> <p>2) To add to the overall efficacy and safety experience in this indication</p> <p>3) To compare, in a selected subset of patients, the biodistribution of IDEC-Y2B8 prepared with 90Y radionuclides from two different suppliers</p>	<p>1. The study is ongoing and will be analyzed following completion</p> <p>2. The 120-day update will include safety analyses of all patients completing the 13-week treatment period, and an interim safety analysis of all patients participating in the 90Y pharmacokinetics comparison study.</p> <p>3. Median duration of Grade \geq 3 neutropenia within 90 days of ZEVALIN therapeutic regimen was 22 days for 43% of subjects</p> <p>4. Median duration of Grade \geq 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen was 28 days for 44% of subjects</p>

INSPECTIONS AND FINANCIAL DISCLOSURES

BIORESEARCH MONITORING INSPECTION RESULTS

Inspections of three clinical investigators were performed in support of the subject BLA. The inspections were conducted in with CPGM with 7348.811, the Inspection Program for Clinical Investigators.

Specific questions concerning the studies were included. Data audits were performed at the following three sites:

Site	Protocols	Investigator(s)	Form 483	Classification
Mayo Clinic	106-03 106-04	Witzig, Wiseman	No	NAI
Northwestern University	106-03 106-04	Gordon	No	NAI
Sidney Kimmel Cancer Center	106-03 106-04	Saleh	Yes	VAI

Inspectional Findings

A Form FDA 483 was issued to Dr. Saleh.
Inspection of the sites revealed the following

NORTHWESTERN UNIVERSITY / DR. GORDON

Three subjects were given doses of IDEC-Y2B8 that were higher than specified by Protocol 106-03. The doses were calculated at 0.4 mCi/kg in the Nuclear Medicine Department without taking into account the maximum dose of 32 mCi in the protocol.

SIDNEY KIMMEL CANCER CENTER / DR. SALEH

Although all subjects signed consent forms at enrollment, versions that were revised while on study were missing for 2 subjects. Another subject, who was enrolled on 6/97, did not sign an 8/97 version of the consent form until 1/99.

Inspectional Summary Statement

The results of bioresearch monitoring inspections of five clinical sites indicate that the deviations made by the clinical investigators are not substantive, with the exceptions noted, and that the submitted data can be considered reliable and accurate.

FINANCIAL DISCLOSURE

Under 21 CFR 54, an applicant is required to certify all investigators and consultants have disclosed any financial arrangements that could influence the study outcome.

Investigators and consultants were asked to provide information pertaining to:

1. Any financial arrangement between the sponsor and the individual that could influence the outcome of the study
2. Any significant payments of other sorts (eg: grants, honoraria, retainer fees, equipment, etc.) made on or after February 2, 1999
3. Any proprietary interest held in the product tested
4. Any individual, spousal, or dependent children equity interest exceeding a value of \$50,000.

The sponsor collected retroactive financial disclosure information retroactive to February 2, 1999 from 34 of 36 principle investigators, 4 of 5 co-principle investigators, and 343 of 386 sub-investigators. In addition, information was collected for 12 of 13 consultants who had participated in the Lymphoma Expects Confirmation of Response assessment (LEXCOR) or dosimetry assessment. The sponsor has provided documentation that substantiates multiple attempts at getting the required information from those investigators who failed to provide financial disclosures.

The sponsor has certified that :

1. 1 former PI, 2 sub-investigators and their institutions, and 1 consultant had significant equity interest that required disclosure.
2. None of the clinical investigators or consultants held any proprietary interests in ZEVALIN

FDA Conclusion:

Study results from sites involving investigators who had disclosed significant equity interest were similar to other study sites and did not significantly impact or alter the efficacy results.

PHASE III TRIALS

PHASE I/II TRIALS

Studies 106-03, 106-05, and 106-98

Study 106-03

PROTOCOL HISTORY

Date	Milestone	Comments
22-DEC-1995	Protocol Submitted	
8-MAR-1996	Protocol Amendment #1	<ol style="list-style-type: none"> 1. Imaging study time points changed 2. PK and selected laboratory assessment specifications modified
13-JUN-1996	Trial Initiated	
14-JUN-1996	Protocol Amendment #2	<ol style="list-style-type: none"> 1. Administrative changes 2. Dosimetry and PK analysis time point modified 3. Laboratory and BM sampling time points amended 4. Optional SPECT imaging allowed 5. Response criteria definition modified 6. Y2B8 Dose specification for subjects < 50 Kg
5-JUN-1997	Protocol amendment #3	<ol style="list-style-type: none"> 1. Gamma-camera imaging requirements modified 2. Parallel analysis for group 3 to assess the need or adequacy of dosimetry is further defined 3. Lexcor panel included 4. Administrative changes
4-AUG-1997	Protocol Amendment #4	<ol style="list-style-type: none"> 1. Groups 2 and 3 patients stratified by baseline platelet counts to receive 0.3 or 0.4 mCi/kg IDEC-Y2B8 2. Efficacy analyses by histology and by dose subgroups defined 3. Accrual to Group 3 increased 4. Study drug handling clarification

STUDY DESIGN, OBJECTIVES, AND TREATMENT PLAN

This was an open-label, single-arm, multicenter, Phase I/II clinical activity and safety study of IDEC-Y2B8 in patients with advanced, refractory or relapsed NHL. Patients with low- or intermediate-grade or mantle cell NHL who had relapsed disease or had failed primary conventional therapy and required treatment were eligible to participate in this study.

The study was comprised of three groups.

- **Group 1** included subjects enrolled to determine the optimum dose of rituximab to be used as an unlabeled antibody prior to IDEC-In2B8 and IDEC-Y2B8 administration
- **Group 2** studies determine the optimum dose ⁹⁰Y as a component of IDEC-Y2B8.
- **Group 3** subjects were treated with the optimal Rituximab, IDEC-In2B8 and IDEC-Y2B8 doses determined from Group 1 and 2 safety and imaging results.

All doses of Rituximab were to be determined based on body surface area and were to be given prior to IDEC-In2B8 (5 mCi), and IDEC-Y2B8. The dose of IDEC-Y2B8 was calculated based upon the patient's weight during the Baseline evaluation. Subjects were

treated with IDEC-Y2B8 only if the dosimetry MIRDOSE projected organ exposure was <2000 rad for normal organs and <300 rad for bone marrow.

Group	N	Treatment	Objective
1	6-9 (n=3/dose level)	Day 0, 7: 100 or 250 mg/m ² Rituximab and 5 mCi IDEC-In2B8 WK 2,3,4,5: 375 mg/m ² Rituximab	Optimize Rituximab Dose
2	15-18 (n=5/dose level)	Day 0: Optimum dose of Rituximab and IDEC-In2B8 Day 7-10: Following receipt of dosimetry data: Optimum dose of Rituximab and 0.2, 0.3, or 0.4 mCi/kg IDEC-Y2B8	Optimize IDEC-Y2B8 Dose
3	20-35	Day 0: Optimum dose of Rituximab and 5 mCi IDEC-In2B8 Day 7-10: Following receipt of dosimetry data: Optimum dose of Rituximab and optimum dose (mCi/kg) IDEC-Y2B8	Phase II Recommended Dose

STUDY RESULTS

Disposition

Fifty-eight subjects were enrolled in Study 106-03

- 7 were enrolled in Group 1,
6 were treated with rituximab and IDEC-In-2B8
1 subject did not receive study drug for personal reasons.
- 51 were enrolled in Groups 2 and 3
50 participants received any dose of IDEC-Y2B8.

1 Subject enrolled at the 0.3 mCi/kg never received IDEC-Y2B8 and was treated with four infusions of Rituximab based on the on site-specific, imaged –based, bone marrow dosimetry although the estimated marrow radiation dose was acceptable on blood-derived and sacral image-derived MIRDOSE3 dosimetry performed by the central dosimetry analysis.

12 did not complete the treatment period (defined as the time between the first infusion and 12 weeks after the last infusion)

- 1 subject (0.2 mCi/kg) died because of disease progression, and

Evaluable Subjects (106-03)

Y2B8	n
0.2 mCi/kg	5
0.3 mCi/kg	15
0.4 mCi/kg	30

- 1 subject receiving 0.2 mCi/kg, 2 receiving 0.3 mCi/kg, and 8 receiving 0.4 mCi/kg IDEC-Y2B8 did not complete the treatment period due to disease progression.

Protocol Modifications

1. 1 Subject had an initial kidney dose estimated at 2187 rads that exceeded the protocol defined maximum allowable dose (2000 rad limit). However, SPECT scanning indicated that the high values were due to tumor involvement in the retroperitoneal area rather than to the overlying kidney. Based on these observations, an exception to the protocol was approved to allow administration of IDEC-Y2B8 for this subject.

Demographics (n=51 subjects included in Groups 2 and 3)	
Median age	60 years (range 24-82 years)
Sex	71% male; 29% female
Race	96% Caucasian
Median time from initial Dx	3.8 years (range 0.7-33.1 years)
Prior anthracyclines	92%
Resistant to prior therapy*	20%
Extranodal sites	
0-1	57%
>1	27%
Unknown	16%
* Resistance is defined as non-responders or progressed within 6 months	

	IWF Histology (Type)	%
	N = 51	
Low Grade	A	6
	B	27
	C	33
Intermediate Grade	D	4
	E	0
	F	6
	G	18
	Mantle	6

Activity Results

Among 51 subjects registered in groups 2 and 3, 34 (67%) had a response (13 CR + 21 PR) to ZEVALIN therapeutic regimen. Twenty-eight of 34 (82%) of subjects with low-grade NHL (IWF A, B, and C) had a response (9 CR + 19 PR) to ZEVALIN therapeutic regimen.

Subjects resistant to any prior chemotherapy had a 50% response rate, which was not statistically different from the response rate in chemo-sensitive patients.

Safety Evaluation

The dataset includes the 50 subjects who received ZEVALIN therapeutic regimen from Groups 2 and 3. All adverse events (AEs) were reported through 12 weeks following treatment with IDEC-Y2B8. AEs considered serious events and/or events related to the study treatment were to be reported through one year following the treatment period.

Adverse Events – Overall Assessment

All 50 subjects experienced at least 1 adverse event.

A total of 528 AEs were reported for all subjects. Fifty-three percent were Grade 1, 23% Grade 2, 14% Grade 3, and 10% Grade 4 by NCI CTC Grade criteria.

- Subjects were monitored for infections for one year following their first infusion
22 infections were reported in 14 subjects during the treatment period;
 - 7 subjects had Grade 1,
 - 4 had Grade 2,
 - 1 had Grade 3,
 - 2 had Grade 4 infections.
- Of the three subjects with Grade 3 and 4 infections,
 - 1 subject in the 0.4-mCi/kg dose group had Grade 3 pneumonia;
 - 1 subject in the 0.3-mCi/kg dose group had Grade 3 pneumonia concurrent with a Grade 4 bacterial infection;
 - 1 subject in the 0.4-mCi/kg dose group had Grade 4 clostridial sepsis (secondary to a gastro-splenic lymphomatous fistula.)

**Frequency of Common AEs by Subject
(n=50 subjects)**

AE (all grades)	% of subjects (n=50)
Leukopenia	88%
Thrombocytopenia	88%
Neutropenia	74%
Anemia	58%
Asthenia	34%
Chills	34%
Fever	30%
Nausea	28%

Hematologic Adverse Events

For all hematologic adverse events, duration of Grade ≥ 3 toxicity is defined as end date minus start date, where end date and start date are defined relative to the nadir lab value. A patient's end date is defined as the 1st lab test date after the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit. A patient's start date is defined as the most recent lab test date prior to the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit.

Patients not recovered from Grade ≥ 3 toxicity were censored by one of two rules. If a patient had received next anti-cancer therapy, that patient was censored to the date of the most recent lab test prior to receiving next anti-cancer therapy. If the patient had not received next anti-cancer therapy, that patient was censored to the date of the most recent lab test.

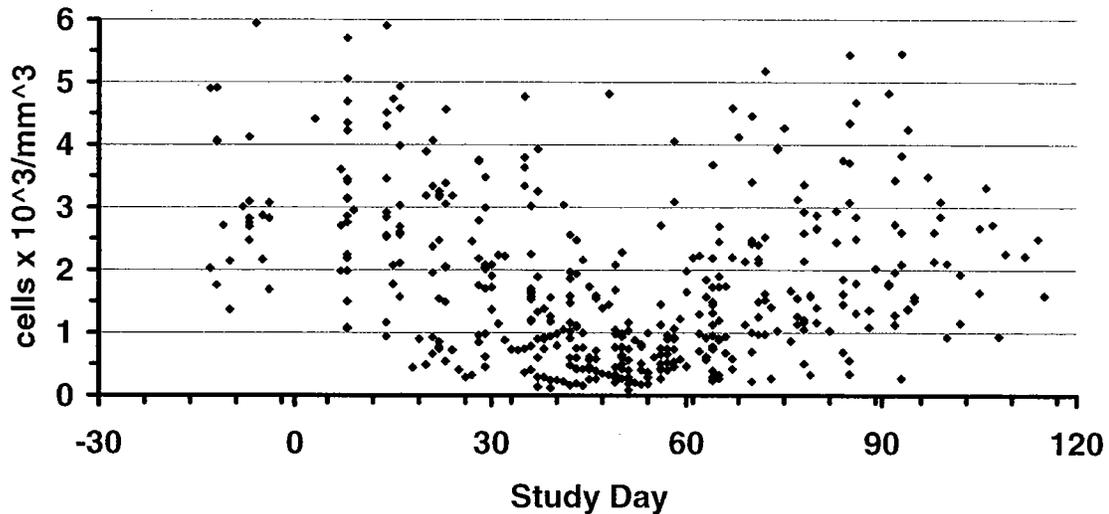
ANC

23 of 50 subjects (46 %) who received any dose of Y2B8 had Grade 3 or 4 ANC within 90 days of initial therapy.

One subject never recovered to Grade ≤ 2 ANC with 64 days of laboratory follow-up. The subject experienced progressive lymphoma on Study Day 56 and received CHOP-Bleomycin chemotherapy beginning Study Day 57. Weekly laboratory data through Study Day 64 were included in the original submission.

Median duration of grade 3-4 neutropenia was 26 days (Range 6-173 days).

**106-03 Subjects With Grade 3-4 ANC
n = 23/50 (46%)**



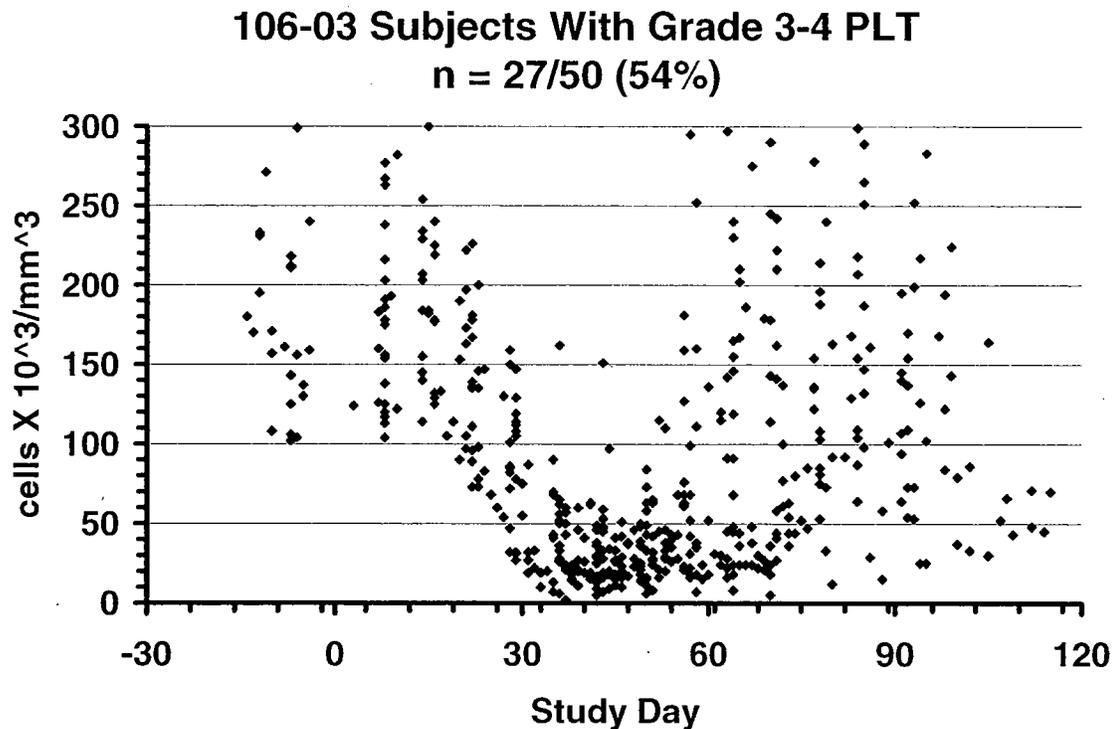
Platelets

27 of 50 subjects (54 %) who received any dose of Y2B8 had Grade 3 or 4 PLT within 90 days of initial therapy.

Two subjects did not resolve their thrombocytopenic episode:

- One subject never recovered to Grade ≤ 2 PLT with 33 days of laboratory follow-up. The subject expired on Study Day 36 with progressive disease.
- One Subject never recovered to Grade ≤ 2 PLT with 37 days of laboratory follow-up. The patient experienced progressive lymphoma on Study Day 32 and received etoposide/dexamethasone chemotherapy beginning Study Day 32. Laboratory data through Study Day 37 were included in the original submission.

Median duration of grade 3-4 thrombocytopenia was 29 days (Range 1-67 days).



Baseline Bone Marrow Involvement and Hematologic Toxicity

An exploratory analysis was conducted to determine whether a relationship existed between degree of bone marrow involvement and hematologic toxicity following treatment with IDEC-Y2B8.

Patients were sorted into groups based on bone marrow involvement:

1. 0% bone marrow involvement: N = 25
2. 0.1% to 5.0% bone marrow involvement: N = 4
3. 5.1% to < 20% bone marrow involvement: N = 11
4. ≥ 20% bone marrow involvement: N = 6

The prevalence of hematologic toxicity was then determined. The incidence of platelet nadir of < 25,000 cells/ μ L was greater with increasing bone marrow involvement (8%; 25%; 46%; 100%). The incidence of Grade 4 neutropenia was greater with increasing bone marrow involvement (4%; 25%; 46%; 100%). The incidence of Grade 4 anemia did not appear to vary with increasing bone marrow involvement (0%; 25%; 0%; 50%).

Human Anti-Chimeric Antibody (HACA) Response:

46 subjects were assayed at Baseline and at follow up for HACA/HAMA response

- 1 developed positive HAMA and HACA titers post-treatment
This subject had no detectable HACA or HAMA titer on Study Days -19 and 42, but on Study Day 64, the subject had a HACA titer of 1232 ng/mL and a HAMA

titer of 13.6 µg/mL. On Study Day 92, the subject had a HACA titer of 1058 ng/mL and a HAMA of 13.6 µg/mL.

- I had a positive HACA at baseline and negative value post ZEVALIN therapeutic regimen. This Subject was tested on Study Day -13 and had a positive HACA titer of 121 ng/mL. The subject was tested again on Study Days 36, 64, 92, 206, and 303, and no HACA titer was detected on any of those days.

Deaths within Study Day 100

3 subjects died before study day 100:

1. Subject 106-03-003-203 entered Study 106-03 on _____ and received 0.2 mCi/kg dose Y2B8 on _____. On _____ Study Day 23, the subject was admitted to the hospital for further evaluation and treatment of profound weakness, abdominal pain, nausea, vomiting, and dehydration. Abdominal CT scan confirmed significant disease progression in the abdomen. The subject continued to deteriorate and end of life palliative care was instituted. The subject expired on _____ (Study Day 36). The official cause of death was listed as a cardiopulmonary arrest secondary to progressive malignant lymphoma. No autopsy was performed.
2. Subject 106-03-008-318 entered Study 106-03 on _____ and received 0.4 mCi / kg dose IDEC-Y2B8 on _____. On _____ (Study Day 36), a staging CT that revealed worsening of large right retroperitoneal lymphadenopathy with involvement of the right crus of the diaphragm and a mass involving the aorto-caval region displacing the right kidney laterally, surrounding and encasing the inferior vena cava. The mass encased the aorta and crossed the midline to the left. As a result of this disease progression, the subject discontinued the study on Study Day 36. During the procedure, a pulmonary embolus of the left descending pulmonary artery was discovered and this resulted in hospitalized and heparin and warfarin therapy. The subject was discharged on _____ (Study Day 45). The subject continued to deteriorate and began receiving hospice care at home in early October. He expired on _____ (Study Day 86). No autopsy was performed.
3. Subject 106-03-002-104 was enrolled in Group 1 of Study 106-03 and therefore did not receive ZEVALIN. The patient died on Study Day 17 of progressive lymphoma. Laboratory data for Study Days 7 and 14 were included in the original submission.

Conclusions

1. Based on Group 1 data, the 250 mg/m² Rituximab dose was chosen to be given prior to IDEC-In2B8 and IDEC-Y2B8 in Groups 2 and 3 for the following reasons:
 - No difference in tumor or normal organ dosimetry was seen between the first and second images in both dosing groups;
 - There is potential for enhanced clinical response from the higher dose of Rituximab.

2. The most frequently reported adverse events were hematologic and constitutional symptoms. Within 90 days of ZEVALIN therapeutic regimen, a median of 26 days duration was observed for Grade ≥ 3 neutropenia in 46% of subjects and a median of 29 days duration was observed for Grade ≥ 3 thrombocytopenia in 54% of subjects.
3. Grade 4 hematologic toxicity was related to thrombocytopenia and bone marrow involvement with lymphoma at baseline and dosimetric parameters were not able to predict which patients were at higher risk for hematologic toxicity.
4. 2% (1/51) of patients developed post-treatment HACA/HAMA.

Study 106-05**PROTOCOL HISTORY**

Date	Milestone	Comments
12-MAY-1998	Protocol Submitted	
20-MAY-1998	Trial Initiated	
06-AUG-1998	Protocol Amendment	3 subjects previously enrolled 1. Revision of the study design 2. Number of participating sites increased 3. Changes to the inclusion criteria, 4. Clarification of dosimetry measurements, 5. Administrative changes
26-FEB-1999	Protocol Amendment	1. Binding assay requirements removed

STUDY DESIGN, OBJECTIVES, AND TREATMENT PLAN

This was an open-label, single-arm, multicenter, Phase II study of 0.3 mCi/kg of IDEC-Y2B8 in mildly thrombocytopenic patients with advanced, relapsed or refractory, low-grade, follicular, or transformed B-cell NHL who failed primary conventional chemotherapy. Subjects had to have platelet levels >100,000 and < 150,000.

The principle objective was to determine the safety and activity of a reduced dose (0.3 mCi/kg) of IDEC-Y2B8 therapy in the setting of mild thrombocytopenia and to determine if baseline platelet count provides adequate information for choosing a safe and effective dose of IDEC-Y2B8, in this defined patient population.

Rituximab (250 mg/m²) was to be given prior to IDEC-In2B8 (5 mCi), and IDEC-Y2B8.

Dosimetry studies were performed

PATIENT POPULATIONS /STUDY RESULTS

30 subjects were enrolled in Study 106-05 and all received both rituximab infusions and the IDEC-In2B8 and IDEC-Y2B8 injections.

Protocol Violations:

- 2 subjects had bone marrow involvement > 25% at baseline, based on a review of bone marrow pathology (106-05-005-013 and 106-05-017-014)
- Subject 106-05-017-014 received In2B8 1 day after rituximab infusion.
- 2 subjects (106-05-002-011 and 106-05-009-009) received Y2B8 more than 7 days after In2B8.
- 2 subjects (106-05-017-005 and 106-05-017-014) received doses of Y2B8 that were greater than ± 10% of the intended dose. The total dose administered to both was at the limit of the protocol defined maximum dose of 32 mCi.

- Subject 106-05-011-017 received a total Y2B8 dose of 34.2 that was greater than the protocol-defined maximum dose of 32 mCi.
- Subject 106-05-006-015 was under dosed with Y2B8 and received 0.26 mCi/Kg actual dose (16.46 mCi total dose)

Demographics

Demographics (N=30 subjects)	
Median age	61 years
Range	22-85 years
Sex	60% male; 40% female
Race	97% Caucasian
Resistant to prior therapy	63.3%
Extranodal sites	
0-1	80%
>1	20%
IPI Risk Group	
Low	33%
Low-Intermediate	33%
High-Intermediate	20%
High	7%
Unknown	7%
Histology	
IWF A	7%
Follicular	83%
Transformed	10%
Bone Marrow Involvement	
0%	33%
5-20%	40%
> 20%	27%

Activity Results

The assessment of ZEVALIN therapeutic regimen activity analysis includes all 30 subjects enrolled in the study. For these subjects, the overall response rate (ORR) as assessed by the principle investigator was 67% (10 CR + 10 PR). TTP was 9.3+ months (n=30). Duration of response was 11.8+ months (range 3.6-17.4+ months with 45% of subjects censored).

Safety Evaluation

The safety analysis includes all 30 subjects enrolled in the study. All AEs regardless of the relationship to the study drug occurring during the treatment period (first treatment of the study drug until 12 weeks following IDEC-Y2B8 administration) were recorded on an

appropriate source document at the clinical site and on the applicable case report form (CRF). Following this time, AEs were to be recorded on the CRF if the investigator attributed the event to the study drug(s). AEs occurring after the initiation of other anticancer therapy were not to be followed, unless the therapy was initiated and the AE occurred within 30 days following the last study drug infusion or the investigator feels the event was related to the study drug.

Non-Hematologic Adverse Events

29 of 30 subjects (97% of study participants) experienced a total of 295 non-hematologic Grade ≥ 1 non-hematologic AEs. Sixty-six percent of non-hematologic AEs were Grade 1, 29% Grade 2, 4% Grade 3, and 1 % Grade 4 by NCI CTC Grade criteria.

Clinically significant AEs included the following:

- 3 subjects had Grade 1 AEs associated with a sensation of swelling of the throat and tongue (classified as angioedema) (106-05-002-011, 106-05-006-018, 106-05-017-029)
- 1 subject had Grade 1 edema of the face (106-05-017-021)
- 4 subjects had respiratory system AEs classified as bronchospasm (3 Grade 1 and 1 Grade 2) occurring on a treatment day (106-05-001-019, 106-005-006-015, 106-05-017-005, 106-05-017-029)
- 1 subject was diagnosed with AML (106-05-002-011) on Study Day 281. The patient developed progressive pancytopenia and rare blasts in the peripheral blood approximately one month after ZEVALIN therapeutic regimen. Bilateral bone marrow aspirates and biopsies were performed approximately three months following rituximab treatment, which showed a marrow with 70% cellularity, decreased megakaryocytes, and extensive infiltration by immature myeloblasts. There was also paratrabecular infiltration by lymphoma cells. The peripheral blood smear showed a normocytic, normochromic anemia, leukopenia with neutropenia, markedly decreased platelets, and rare blasts. Cytogenetic studies on the bone marrow revealed a t(9;11), typically associated with AML-M5. The final diagnosis was acute myelogenous leukemia (AML), consistent with therapy-related AML. It was the opinion of the investigator and the sponsor that the AML could be related to prior exposure to alkylator therapy, as evidenced by the mild thrombocytopenia prior to study entry. Nevertheless, a relationship to ZEVALIN therapeutic regimen could not be ruled out.

Non-Hematologic AEs Summary Table

Frequency of Non-Hematologic AEs
by Subject (n=30 subjects)

AE (all grades)	% of subjects
Asthenia	57
Nausea	40
Chills	37
Fever	33
Vomiting	30
Headache	27
Increased Cough	23
Pruritus	23
Abdominal Pain	20
Irritation Throat	17
Dizziness	17
Dyspnea	17
Myalgia	13
Peripheral Edema	10
Angioedema	10
Infection	7

Hematologic Adverse Events

For all hematologic adverse events, duration of Grade ≥ 3 toxicity is defined as end date minus start date, where end date and start date are defined relative to the nadir lab value. A patient's end date is defined as the 1st lab test date after the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit. A patient's start date is defined as the most recent lab test date prior to the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit.

Patients not recovered from Grade ≥ 3 toxicity were censored by one of two rules. If a patient had received next anti-cancer therapy, that patient was censored to the date of the most recent lab test prior to receiving next anti-cancer therapy. If the patient had not received next anti-cancer therapy, that patient was censored to the date of the most recent lab test.

Baseline Bone Marrow Involvement and Hematologic Toxicity

An exploratory analysis was conducted to determine whether a relationship existed between degree of bone marrow involvement and hematologic toxicity following treatment with IDEC-Y2B8.

Patients were sorted into groups based on bone marrow involvement:

5. 0% bone marrow involvement: N = 10
6. 0.1% to 5.0% bone marrow involvement: N = 0
7. 5.1% to < 20% bone marrow involvement: N = 12
8. 20% bone marrow involvement: N = 8

The prevalence of hematologic toxicity was then determined. The incidence of Grade 4 platelet nadir was greater with increasing bone marrow involvement (10%; 0%; 38%). The incidence of Grade 4 neutropenia was greater with increasing bone marrow involvement (10%; 33%; 63%). The incidence of Grade 4 anemia did not appear to vary with increasing bone marrow involvement (10%; 0%; 0%).

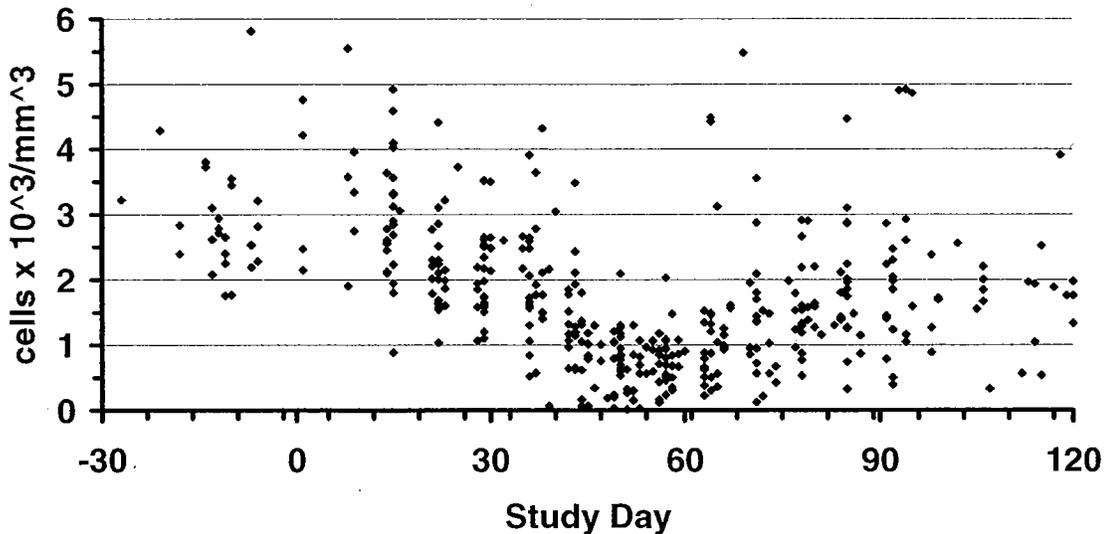
ANC

26 of 30 subjects (87 %) who received any dose of Y2B8 had Grade 3 or 4 ANC within 90 days of initial therapy.

Median duration of grade 3-4 neutropenia was 29 days (Range 3-78 days)

**Appears This Way
On Original**

**106-05 Subjects With Grade 3-4 ANC
n = 26/30 (87%)**



Platelets

26 of 30 subjects (87 %) who received any dose of Y2B8 had Grade 3 or 4 thrombocytopenia within 90 days of initial therapy.

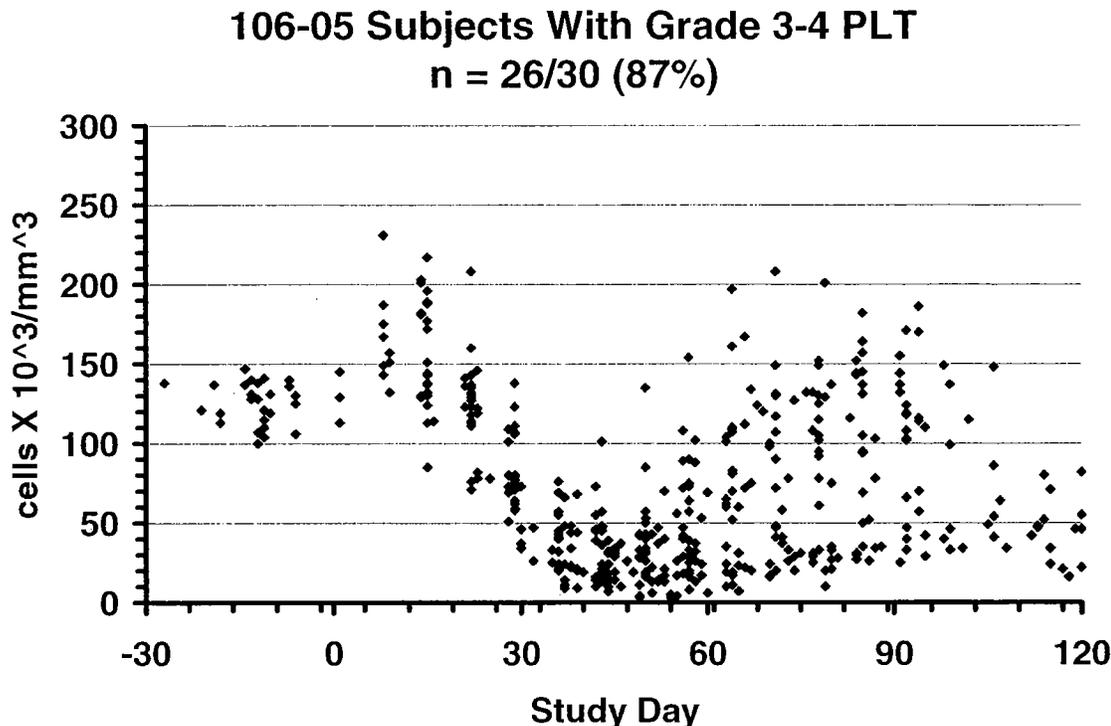
SAEs and not evidence of platelet recovery:

- Subject 106-05-001-010 never recovered to Grade ≤ 2 PLT with 139 days of laboratory follow-up. This subject received additional therapy for disease progression beginning on Study Day 132.
- Subject 106-05-005-013 is a 67-year-old female with B-cell NHL (IWF-A) who was hospitalized with thrombocytopenia (Grade 4), on Study Day 37. Laboratory tests revealed the following: WBC 1000 cells/mm³, platelets 9000 cells/mm³, and Hgb 9.5 g/dL. She received platelet and RBC transfusions, and was discharged on Study Day 38. The patient was readmitted on Study Day 54 with low laboratory values: platelets 3,000 cells/mm³, WBC 2100 cells/mm³, and Hgb 9.6 g/dL, and was discharged the next day. The patient required platelet and RBC transfusions over a one-month period; G-CSF, and epoetin over a two-month period; and oprelvekin (IL-11) for two weeks due to prolonged myelosuppression. At baseline, bone marrow biopsy revealed diffuse infiltration by small monoclonal B-cells; however, the percent bone marrow involvement was reported to be less than 25%, making the patient eligible for the study. Because of the prolonged thrombocytopenia and the description of diffuse infiltration of monoclonal B-cells on the biopsy report, the original bone marrow biopsy was reviewed once again. On repeat microscopic differential count of the baseline bone marrow aspirate, 37% of the cellular elements were considered malignant lymphocytes. According to protocol the subject would have been ineligible for the study. The extended

thrombocytopenia was classified as probably related to treatment by the PI and/or sponsor.

- Patient 106-05-002-011 is a 78-year-old female with follicular NHL who was admitted to the hospital with bruising, thrombocytopenia (Grade 4), leukopenia (Grade 3), and anemia (Grade 2) on Study Day 54. Laboratory tests revealed the following: WBC 1400 cells/mm³, platelets 17,000 cells/mm³, and Hgb 8.6 g/dL. The patient received platelet and RBC transfusions and was discharged the next day. On Study Day 67, the patient's laboratory tests showed improvement: WBC 8000 cells/mm³, platelets 59,000 cells/mm³, and Hgb 14.4 g/dL. The events were classified as probably related to the study treatment.
- Patient 106-05-002-023 is a 45-year-old female with NHL who had a history of hemolytic anemia. She was admitted to the hospital with thrombocytopenia (Grade 3) on Study Day 46. Laboratory tests prior to admission on Study Day 44 revealed the following: WBC 2400 cells/mm³, platelets 10,000 cells/mm³, and Hgb 7.0 g/dL. She received platelet and RBC transfusions and was discharged the next day. Discharge laboratory test results on Study Day 47 were the following: WBC 1300 cells/mm³, platelets 26,000 cells/mm³, and Hgb 7.1 g/dL. Follow-up results on Study Day 50 were the following: WBC 1700 cells/mm³, platelets 19,000 cells/mm³, Hgb 9.4 g/dL, and ANC 1200 cells/mm³. The event was classified as probably related to the study drug. The patient was readmitted on Study Day 70 for abdominal pain (Grade 3) and thigh pain. Laboratory tests on admission revealed the following: WBC 700 cells/mm³, platelets 17,000 cells/mm³, Hgb 7.9 g/dL. She was found to be neutropenic and to have hemolytic anemia (Grade 3) and was treated with IV antibiotics. The patient experienced a vancomycin allergic reaction (Grade 2). The patient began prednisone therapy, which she continued after discharge on Study Day 74. The neutropenia was classified as possibly related to the study treatment.

Median duration of grade 3-4 thrombocytopenia was 30 days (Range 14-106+ days)



Human Anti-Chimeric Antibody (HACA) Response:

All 30 patients were tested and no patient developed a detectable HACA/HAMA level following treatment.

Deaths within Study Day 100

No deaths were reported to have occurred within Study Day 100.

Conclusions

1. A Y2B8 dose of 0.3 mCi/kg Y2B8 administered to mildly thrombocytopenic low-grade, follicular, or transformed B-cell NHL population is feasible but resulted in prolonged or refractory Grade ≥ 3 neutropenia and/or thrombocytopenia in the majority of study participants.
2. Most frequently reported adverse events were hematologic. A median of 29 and 30 days duration was observed for Grade ≥ 3 neutropenia and thrombocytopenia in 87% of subjects within 90 days of ZEVALIN therapeutic regimen.
3. No HAMA/HACA reactions were observed.
4. One case of MDS was observed

Study 106-98**PROTOCOL HISTORY**

Date	Milestone	Comments
September 1, 1999	Protocol Submitted	
November 10, 1999	Amendment #1	<ol style="list-style-type: none"> 1. To allow the treatment of mildly thrombocytopenic patients (baseline platelet counts from 100,000/mm³ to 149,000/mm³) with reduced-dose IDEC-Y2B8 (0.3 mCi/kg). 2. To add the REAL classification of NHL 3. To note that in Phase I/II trials that maximum allowable dosimetry estimated absorbed radiation doses to the spleen could be greater than 2000cGy for patients with splenic involvement by NHL 4. To amend the schedule for Evaluation of Response and recommend that it be performed every 3 months for the first year 5. To correct the criteria for complete response from "no decrease in performance status" to "no worsening in performance status"
December 9, 1999	Protocol initiated	
February 25, 2000	Amendment #2	<ol style="list-style-type: none"> 1. To obtain pharmacokinetic samples from selected patients at predetermined sites on 35 subjects. In mid 2000, IDEC began using an additional supplier of ⁹⁰Yttrium for the preparation of the IDEC-Y2B8.
March 6, 2001	Amendment #3	<ol style="list-style-type: none"> 1. Indium Imaging reinstated

STUDY DESIGN, OBJECTIVES, AND TREATMENT PLAN

This study is a single arm open access trial that is currently on going.

The study is designed with the following objectives:

1. To provide treatment to patients with relapsed or refractory low-grade or follicular or Transformed B-cell NHL who were ineligible for other IDEC-Y2B8 protocols
2. To add to the overall efficacy and safety experience in this indication
3. To compare, in a selected subset of patients, the biodistribution of IDEC-Y2B8 prepared with ⁹⁰Y radionuclides from two different suppliers

Candidates must have histologically confirmed, relapsed or refractory low-grade or follicular or transformed B-cell NHL requiring treatment; subjects refractory to rituximab and those ineligible for other IDEC-Y2B8 protocols are included. Proof of CD20+ B cells is required in IWF A or transformed NHL patients.

The majority of subjects accrued to date have received the following regimen:

- An initial IV infusion of 250 mg/m RITUXAN followed 1 week later by
- An IV infusion of 250 mg/m² RITUXAN and an IV injection of IDEC-Y2B8.

A minority of subjects received:

- An initial IV infusion of 250 mg/m RITUXAN and an IV injection of IDEC-In2B8, followed 1 week later by
- An IV infusion of 250 mg/m² RITUXAN and an IV injection of IDEC-Y2B8.

Subjects with baseline platelet counts 100,000 – 149,000 cells/mm³ received 0.3 mCi ⁹⁰Y/kg, and those with ≥ 150,000 cells/mm³ received 0.4 mCi ⁹⁰Y/kg. The exact dose is based on body weight at baseline (maximum dose was not to exceed 32 mCi of ⁹⁰Y).

STUDY RESULTS

The primary data derived from this study pertains to the safety of ZEVALIN therapeutic regimen in relapsed or refractory low-grade or follicular or transformed B-cell NHL.

A total of 182 subjects from study 106-98 were included in the ZEVALIN BLA. This figure represents the total number of subjects at all points of follow-up, who were enrolled on study 106-98 at the time the database snapshot was taken.

Of these 182 subjects:

- 138 subjects had passed the 13 weeks follow-up time point at which time, investigators were required to submit all adverse event data. For the purpose of the BLA, 13 weeks of follow-up was defined as having received the Day 1 infusion on or before September 30, 2000.
- Additional safety information on 10 subjects who had not yet completed 13 weeks of clinical follow-up was provided. Information pertaining to these 10 subjects may be incomplete. FDA included these subjects in the overall safety analysis. The sponsor omitted these subjects from their overall safety analysis.
- A total of 148 subjects is included in FDA's non-hematologic adverse event safety analysis;
- 182 subjects were included in FDA's hematologic adverse event safety analysis.

Safety Evaluation

AEs were recorded using the NCI Clinical Cooperative Groups toxicity criteria and the Cancer Treatment Evaluation Program. Laboratory tests were conducted at each clinical site at monthly intervals for 3 months.

Non-Hematologic Adverse Events

124 of 148 subjects (84%) experienced non-hematologic AEs. 601 non-hematologic adverse events were reported over for the entire period of follow-up. Fifty-seven percent of AEs were Grade 1, 29% Grade 2, 11% Grade 3 and 3% Grade 4 by NCI CTC Grade Criteria.

Subjects with clinically significant AEs.

- 2 subjects had AEs associated with a sensation of swelling of the throat and tongue classified as angioedema (1 Grade 1 and 1 Grade 2) (106-98-002-115, 106-98-064-179)

- 4 subjects had Grade 1 respiratory system AEs classified as bronchospasm occurring on a treatment day (106-98-001-132, 106-98-001-140, 106-98-004-106, 106-98-023-010)
- 1 subject had carcinoma of the skin (106-98-038-026)
- 1 subject had Grade 3 colitis (106-98-019-077)
- 6 had diarrhea (2 Grade 1; 3 Grade 2; 1 Grade 3) (106-98-017-030, 106-98-019-025, 106-98-019-097, 106-98-023-010, 106-98-033-007, 106-98-062-124)
- 1 had Grade 2 bloody diarrhea that was also documented pre-study (106-98-017-068)
- 3 had Grade 2 herpes zoster (106-98-013-009, 106-98-019-022, 106-98-019-028)
- 3 had myasthenia (1 Grade 1; 1 Grade 2; and 1 Grade 3) (106-98-007-005, 106-98-019-025, 106-98-019-028)
- 2 had Grade 3 sepsis (106-98-019-049, 106-98-019-077)
- Subject 106-98- -016 was hospitalized with Grade 2 axillary lymph node necrosis 64 days post-IDEC-Y2B8 treatment. The event was considered by the investigator and sponsor as unrelated to study treatment and secondary to disease progression.

**Frequency of Common
Non-Hematologic AEs by Subject
(n=148 subjects)**

AE (all grades)	% of subjects
Asthenia	32
Nausea	20
Chills	16
Dyspnea	14
Abdominal Pain	9

**Frequency of Notable
Non-Hematologic AEs by Subjects
(n=148 subjects)**

AE	%
Rash	7
Dizziness	6
Fever	6
Increased Cough	5
Irritation Throat	5
Abdominal Enlargement	5
Febrile neutropenia	5
Vomiting	4
Allergic reaction	4
Myalgia	4
Angioedema	3

Hematologic Adverse Events

For all hematologic adverse events, duration of Grade ≥ 3 toxicity is defined as end date minus start date, where end date and start date are defined relative to the nadir lab value. A patient's end date is defined as the 1st lab test date after the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit. A patient's start date is defined as the most recent lab test date prior to the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit.

Patients not recovered from Grade ≥ 3 toxicity were censored by one of two rules. If a patient had received next anti-cancer therapy, that patient was censored to the date of the most recent lab test prior to receiving next anti-cancer therapy. If the patient had not received next anti-cancer therapy, that patient was censored to the date of the most recent lab test.

ANC

79 of 182 subjects (43%) who received any dose of Y2B8 had Grade 3 or 4 ANC within 90 days of initial therapy.

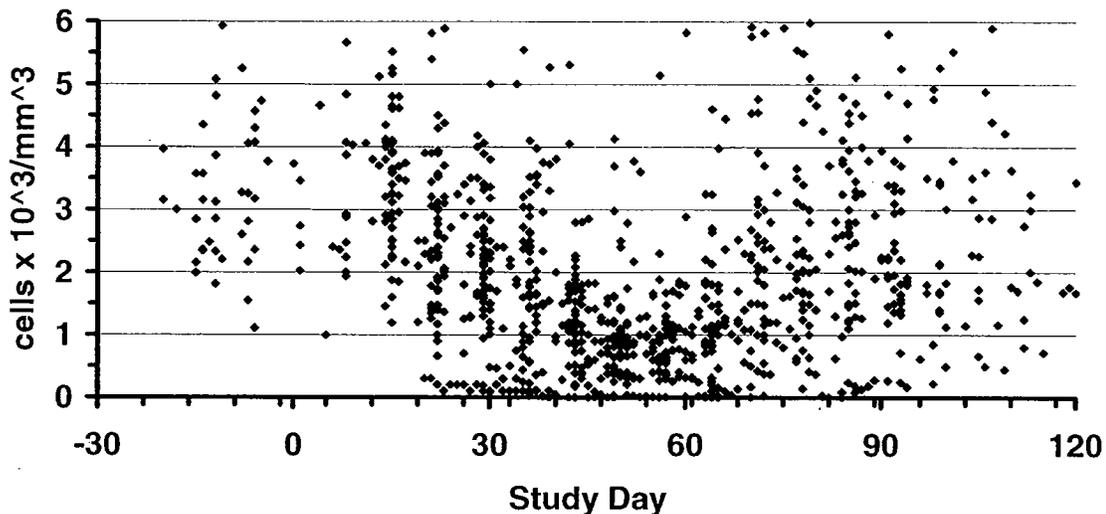
4 Subjects failed to have documented neutropenic recovery.

- Subject 106-98-001-131 never recovered ANC with 36 days of follow-up. On Study Day 20, a clinical evaluation determined that the subject had progressive disease. Radiation therapy was instituted on Study Day 21. The subject died on Study Day 48.
- Subject 106-98-002-057 never recovered ANC with 175 days of follow-up

- Subject 106-98-019-083 never recovered ANC with 22 days of follow-up. The subject died of progressive disease on Study Day 37.
- Subject 106-03-041-063 never recovered ANC with 100 days of follow-up. The subject had progressive disease and went on hospice care. No additional data were provided.

Median duration of grade 3-4 neutropenia was 22 days (Range 1-176+ days)

106-98 Subjects With Grade 3-4 ANC
n = 79/182 (43%)



Platelets

80 of 182 subjects (44%) who received any dose of Y2B8 had Grade 3 or 4 thrombocytopenia within 90 days of initial therapy

12 subjects failed to have documented platelet recovery.

- Subject 106-98-001-131 never recovered PLT with 41 days of follow-up. This subject had progressive disease on Study Day 20, began radiation therapy on Study Day 21 and died of NHL on Study Day 48.
- Subject 106-98-002-057 never recovered PLT with 210 days of follow-up
- Subject 106-98-003-135 never recovered PLT with 33 days of follow-up. This subject was reported to have had disease progression on Study Day 26 and to have died on Study Day 35.
- Subject 106-98-011-073 never recovered PLT with 34 days of follow-up. Progressive disease was documented on study day 35. Additional chemotherapy was initiated on Study Day 48.

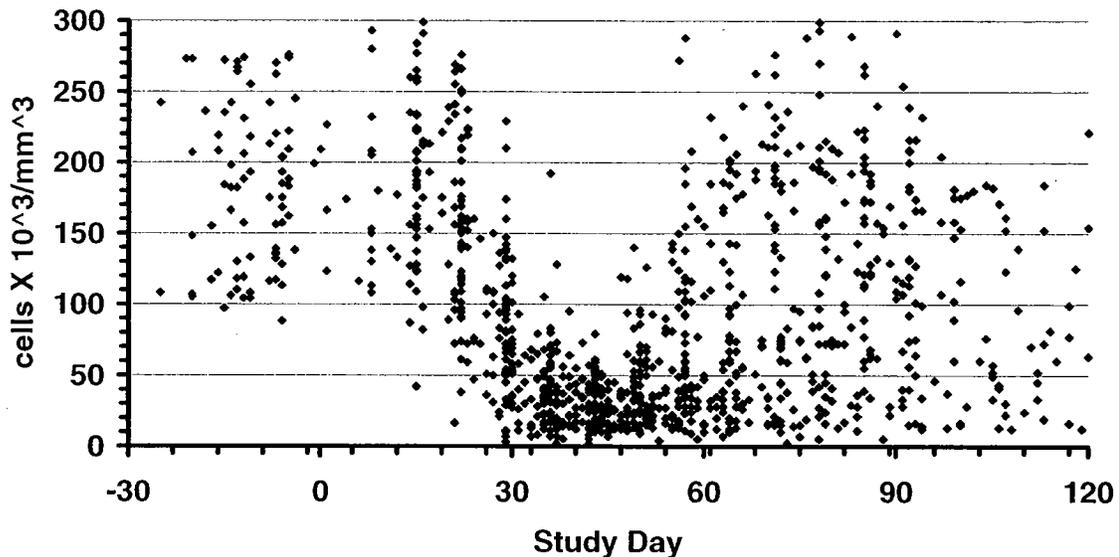
- Subject 106-98-017-068 never recovered PLT with 57 days of follow-up. This subject had documented disease progression on Study Day 37. Additional therapy was initiated on Day 44.
- Subject 106-98-018-120 never recovered PLT with 41 days of follow-up. Progressive disease was documented on Study Day 41 and radiation therapy begun on Study Day 44. The subject expired on Study Day 101.
- Subject 106-98-019-049 never recovered PLT with 234 days of follow-up. This subject had a baseline hypocellular bone marrow and history of failed prior stem cell collection.
- Subject 106-98-019-083 never recovered PLT with 37 days of follow-up. The subject expired on Study Day 37.
- Subject 106-98-019-088 never recovered PLT with 44 days of follow-up. The subject expired on Study Day 74.
- Subject 106-98-022-040 never recovered PLT with 112 days of follow-up. The subject had progressive disease documented on Study Day 58 and additional chemotherapy was initiated on Study Day 66. The subject died of NHL on Study day 119.
- Subject 106-98-027-067 never recovered PLT with 42 days of follow-up. The subject had progressive disease on Study Day 32 and died on Study Day 44.
- Subject 106-98-041-063 never recovered PLT with 106 days of follow-up. The subject had progressive disease on Study Day 100 and subsequently received palliative care. No additional laboratory data was available.

Subjects with clinically significant AEs:

- 4 subjects had hemochezia (1 Grade 2 and 3 Grade 3) (106-98-001-050, 106-98-002-029, 106-98-019-076, 106-98-041-084)
- 1 subjects had intracranial bleed (106-98-019-028)
- 1 subjects had Grade 1 heme per rectum (106-98-001-114)
- 4 subjects had Grade 1 epitaxis (106-98-017-030, 106-98-019-028, 106-98-041-063, 106-98-062-124)
- 2 subjects had Grade 1 vaginal bleeding (106-98-017-162, 106-98-019-028)
- 1 subjects had Grade 3 hematemesis (106-98-019-076)
- 2 subjects had hematuria (1 Grade 1 and 1 Grade 2) (106-98-002-080, 106-98-004-106)
- 4 subjects had melena (2 Grade 1 and 2 Grade 3) (106-98-004-106, 106-98-019-076, 106-98-019-077, 106-98-019-078)

Median duration of grade 3-4 thrombocytopenia was 28 days (Range 1-182+ days)

106-98 Subjects With Grade 3-4 PLT
n = 80/182 (44%)



Deaths within Study Day 100

106-98-003-089 (day 74)

Subject 106-98-003-089 is a 62-year-old Hispanic male with a history of idiopathic pulmonary fibrosis for which he was taking prednisone, furosemide, zolpidem, potassium chloride, hydrocodone, lisinopril, and escalating doses of azathioprine. The patient was diagnosed with IWF D NHL in _____ and had previously received CHOP and etoposide/cyclophosphamide/procarbazine/prednisone. He received IDEC-Y2B8 (0.3 mCi/kg) on _____. On Day 74 he was admitted to the hospital with respiratory failure, placed on a respirator, and died. The event (respiratory failure) was considered related to the patient's underlying disease by the investigator and sponsor. There were no comments pertaining to whether or not an autopsy was obtained.

106-98-003-121 (day 84)

Subject 106-98-003-121 is a 72-year-old Caucasian male with a history of chronic obstructive pulmonary disease (COPD), congestive heart failure, and coronary artery disease (CAD). He was diagnosed with IWF A NHL in _____ and received IDEC-Y2B8 (0.3 mCi/kg) on _____ (Study Day 8). The patient was taking metoprolol, lisinopril, prazosin, paroxetine, aspirin, lasix, fentanyl, oxycodone, and simvastatin for heart condition and died in his sleep on Study Day 85. Unresolved AEs at time of death were Grade 1 asthenia and chronic pain; the cause of death was cardiac arrest secondary to CAD. This event was considered not related to study treatment. There were no comments pertaining to whether or not an autopsy was obtained.

106-98-041-084 (day 13)

Subject 106-98-041-084 is a 65-year-old Caucasian female with a history of COPD, hypercalcemia, and a 50-pack year history of smoking. She was diagnosed with IWF B in _____ and previously received fludarabine, DHAD, CNOP, solumedrol, and rituximab before being treated with IDEC-Y2B8 (0.3 mCi/kg) in _____. She received the rituximab infusion on 1. _____ (Study Day 1) and was admitted to the hospital with dyspnea, and pulmonary edema, and hypercalcemia. Her condition improved with treatment, and she received the second rituximab infusion and IDEC-Y2B8 injection in the hospital as scheduled on Study Day 8 and was discharged. At the time of the second infusion, patient was using oxygen via nasal canula at 10 L. Patient was readmitted to the hospital on Study Day 11 _____ with gastrointestinal bleed that resolved. She received prophylactic IV ranitidine. Chest X-ray revealed severe lymphomatous involvement; basic panel was BUN of 51 mg/dL, creatinine of 1.6 mg/dL, calcium of 12.5 mg/dL, bicarbonate of 19 mmol/L; WBC count was 4000 cells/mm³, platelets were 77,000 cells/mm³, and hemoglobin was 8.6 g/dL. Patient was given saline diuresis to lower calcium. Her pulmonary status worsened, and she received oxygen, progressing from 15 L to 100% nonrebreather oxygen. Patient developed recurrent fevers and received ceftriaxone and morphine. Patient became comatose on Study Day 12 _____ and died of respiratory failure on Study Day 13 _____. Cause of death was listed as respiratory failure secondary to recurrent B-cell lymphoma. This event was considered not related to study treatment, but related to the patient's pre-existing pulmonary condition and underlying disease. There were no comments pertaining to whether or not an autopsy was obtained.

Conclusions

1. Study continues to be open to accrual and definitive conclusions cannot be made at this time.
2. Safety data extends the overall ZEVALIN therapeutic regimen experience.
3. Most frequently reported adverse events were hematologic.
 - Grade ≥ 3 neutropenia was observed in 43% of subjects with a median duration of 22 days.
 - Grade ≥ 3 thrombocytopenia was observed in 44% of subjects with a median duration of 28 days.

PHASE III STUDIES

PHASE III STUDIES

Studies 106-04 and 106-06

The effectiveness of ZEVALIN rests primarily on the results of two Phase III studies: Study 106-04, a randomized, multicenter active-control study and Study 106-06, an uncontrolled, supportive trial.

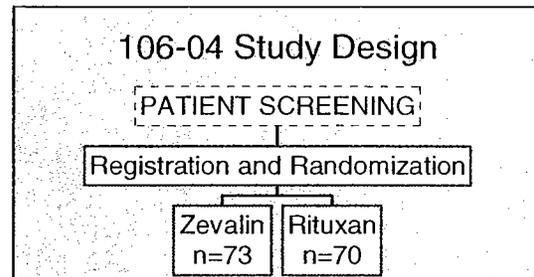
Study 106-04

PROTOCOL HISTORY

Date	Milestone	Comments
December 8, 1997	Protocol Submitted	
February 24, 1998	Protocol initiated	
March 13, 1998.	Amendment #1	<ol style="list-style-type: none"> 1. Inclusion of an interim analysis. 2. Dosimetry no longer be necessary for a defined low-risk population. 3. To include an analysis for bcl-2 from peripheral blood, if positive at baseline, at Months 6, 9, and 12. 4. To define the exclusion criteria of concurrent systemic corticosteroid therapy. 5. To clarify that the inclusion criteria total lymphocyte count < 5,000/mm³ is applicable to only those patients with small lymphocytic lymphoma - Working Class Formulation Type A. 6. To omit the requirement for a baseline HACA analysis. 7. To clarify that patient will remain on study following disease progression for follow up of the patient's first anti-cancer therapy following study treatment and survival status. 8. To clarify that the number of participating clinical sites will be approximately 30.
June 2, 1998.	Amendment #2	<ol style="list-style-type: none"> 1. To include patients whose tumor histology has transformed. 2. To add a third stratification subgroup for transformed patients.
October 9, 1998.	Amendment #3	<ol style="list-style-type: none"> 1. To revise the bidimensional lesion measurement requirement to allow patients with measurable disease between 2 - 3 cm to be enrolled. 2. To allow screening evaluations to be done within the time specified prior to the date of patient registration instead of prior to the initial study treatment. 3. To require the LEXCOR to review all patients, not just responders, enrolled in the study. 4. To include a bcl-2 analysis at two additional time points, if positive at baseline. 5. To revise Appendix K to clarify dosimetry procedures and include a section describing the role and the activities of the Central Data Processing center at the Mayo Clinic.
February 26, 1999.	Amendment #4	<ol style="list-style-type: none"> 1. To remove the binding assay requirement (radiolabeling immunoreactivity QC) from ongoing IDEC-Y2B8 clinical trials.

STUDY DESIGN, OBJECTIVES, AND TREATMENT PLAN

This Phase III, prospective, two-arm, randomized, controlled, open-labeled, multicenter study was designed to compare ZEVALIN therapeutic regimen with rituximab in subjects with relapsed or refractory low-grade or follicular NHL (IWF types A, follicular, or transformed).



Objectives:

1. To compare the efficacy of ZEVALIN therapeutic regimen (rituximab infusion followed by ^{121}In labeled murine antibody 2B8 and a second rituximab infusion followed by ^{90}Y labeled murine antibody 2B8) in relapsed or refractory, low-grade or follicular NHL with that of rituximab alone.
 - The protocol defined overall response rate (ORR) as determined by an independent panel of radiology and oncology experts in lymphoma (LEXCOR) who were blinded to the treatment received and the Investigator's assessment of response is the primary efficacy variable. The sample size was chosen to yield at least 80% power given an 0.05 alpha level and a 25% higher overall response rate in the IDEC-Y2B8 group. Patients were stratified by histology and randomly assigned to either the IDEC-Y2B8 or rituximab group.
 - Duration of response and time to progression are secondary efficacy variables. (NOTE: The study was not designed or powered to demonstrate a difference in TTP and DR for ZEVALIN therapeutic regimen compared with rituximab treatment (FDA agreement, September 30, 1997). Instead the protocol statistical section prospectively defined the TTP and DR objectives stating "the target median TTP for ZEVALIN therapeutic regimen group will be at least similar to that of the rituximab group.")
 - Additional analyses include complete, clinical complete and partial response rate, time to next anti-cancer treatment, and quality of life
2. To characterize the safety of IDEC-Y2B8 and IDEC-In2B8 when administered in conjunction with rituximab (ZEVALIN therapeutic regimen) compared with the safety of rituximab alone.
3. To study dosimetry of IDEC-In2B8 preceded by rituximab as a predictor of IDEC-Y2B8 radiation dose delivered to the tumor and to normal organs.
4. To eliminate the necessity for dosimetry by demonstrating that baseline platelet counts provide adequate information for predicting safety of IDEC-Y2B8 administration in this defined population.

Inclusion Criteria

1. Histologically confirmed, relapsed or refractory low-grade or follicular (IWF A-D)
or

2. Transformed from low-grade to intermediate-grade histology (IWF E-G) B-cell NHL requiring treatment (\uparrow tumor size, B symptoms, and/or symptomatic masses)
3. Bi-dimensionally measurable disease
4. CD20+ B-cell population in LN or BM
5. $< 25\%$ BM involvement
6. No anti-cancer therapy for three weeks (six weeks if nitrosourea or Mitomycin C) prior to study initiation, and fully recovered from all toxicities associated with prior surgery, radiation treatments, chemotherapy, or immunotherapy.
7. Age ≥ 18 years
8. Expected survival ≥ 3 months
9. Pre-study WHO performance status of 0, 1, or 2
10. Acceptable hematologic status within two weeks prior to initial treatment, including:
 - Absolute neutrophil count $\geq 1,500/\text{mm}^3$.
 - Total lymphocyte count $\leq 5,000/\text{mm}^3$ for patients with small lymphocytic lymphoma (Working Class Formulation Type A)
 - Platelet counts $\geq 150,000/\text{mm}^3$.

Exclusion Criteria

11. Histologies falling outside of the designated Working Formulation, e.g., mantle cell/zone and subjects with chronic lymphocytic leukemia (CLL)
12. Prior myeloablative therapies with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell (PBSC) rescue
13. Prior radioimmunotherapy
14. Presence of CNS lymphoma
15. Presence of HAMA
16. Prior anti-CD20 therapy, including IDEC-Y2B8 and rituximab
17. HIV or AIDS-related lymphoma
18. Abnormal liver function: total bilirubin > 2.0 mg/dL
1. Abnormal renal function: serum creatinine > 2.0 mg/dL
2. Prior external beam radiation therapy to $> 25\%$ of active bone marrow (involved field or regional)
19. Use of G-CSF or GM-CSF therapy within two weeks prior to treatment
20. Serious nonmalignant disease or infection
21. Major surgery, other than diagnostic surgery, within four weeks
22. Another primary malignancy (other than squamous or basal cell carcinoma of the skin or in situ carcinoma of the cervix) for which the patient has not been disease-free for at least five years
23. Concurrent systemic corticosteroid therapy: (1) ≥ 40 mg prednisone as a single dose (or equivalent) or (2) ≤ 40 mg prednisone (or equivalent) for more than six doses (to allow for pre-medication of CT allergy dye and treatment of possible first rituximab infusion reactions)

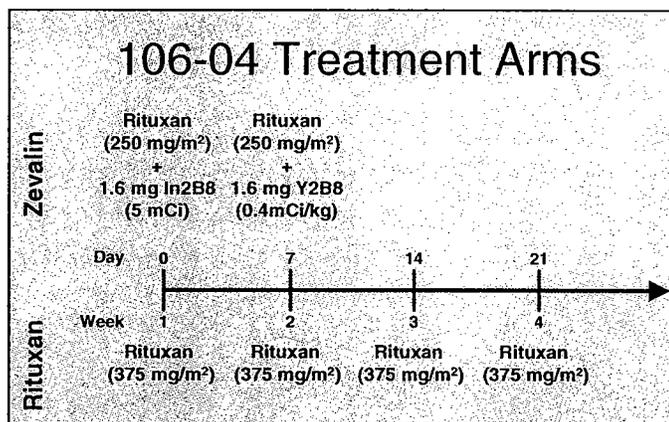
Treatment Plan***ZEVALIN Therapeutic Regimen Arm***

Subjects randomized to the ZEVALIN therapeutic regimen treatment group received one infusion of 250 mg/m² rituximab prior to a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of IDEC-In2B8, which was injected as a slow IV push over 10 minutes. Dosimetry and biodistribution studies were then performed prior to administering a second infusion of 250 mg/m² of rituximab followed by 0.4 mCi/kg (1.6 mg total antibody dose) of IDEC-Y2B8 slow IV push over 10 minutes the following week.

For subjects whose body weight exceeded 80 kg, a maximum dose of 32 mCi of ⁹⁰Y was to be administered.

Rituximab Arm

Subjects randomized to the rituximab group received an infusion of 375 mg/m² rituximab once weekly times four.

**RESULTS**

The ITT dataset for safety and for efficacy included all 143 patients enrolled.

ZEVALIN Group: 73 subjects who received two infusions of 250 mg/m² rituximab, one injection of 5.0 mCi of IDEC-In2B8, and one injection of 0.4 mCi/kg IDEC-Y2B8.

Rituximab Group: 70 subjects who received a course of rituximab, which consisted of four infusions of 375mg/m² rituximab (once weekly x 4).

Protocol Violations***ZEVALIN Therapeutic Regimen Group***

1. Subject 106-04-023-277 was permitted to continue prescribed oral Prednisone 10 mg daily, a stable regimen which began approximately two years prior to enrollment.
2. Subject 106-04-018-312 refused follow up after Week 4 visit and the patient was taken off the study. Weekly laboratory data through Study Day 63 were included in the original submission. Additional laboratory data for Study Day 171, the day prior to initiation of subsequent anticancer therapy (chlorambucil and prednisone), were obtained and documented hematologic recovery.

3. Administration of yttrium treatment was delayed beyond one week in 11 subjects. (106-04-001-202, 106-04-001-204, 106-04-001-210, 106-04-001-230, 106-04-001-259, 106-04-002-101, 106-04-002-238, 106-04-012-261, 106-04-011-226, 106-04-011-239, 033-258) because of yttrium delivery delay (N = 8) or need to repeat radioincorporation (N = 5). For Patients 106-04-033-258 and 106-04-001-259, repeat radioincorporation and delivery delay occurred.

Rituximab Group

1. ANC in Patient 106-04-012-260 was below the 1500 cells/mm³ minimum (1265 cells/mm³).
2. In Patient 106-04-006-107, five infusions of rituximab were administered because the first infusion was interrupted for alleviation of infusion-related events.
3. CT scans for confirmation of response were done < 28 days for Subjects 106-04-007-256 (21 days) and 106-04-011-269 (27 days)
4. Subject 106-04-026-214's full sets of CT scans for confirmation of response were not performed at Week 8, Week 12, or Month 6. A full set was done at Month 9.

Study Population & Disease Characteristics

Differences between the ZEVALIN and Rituximab group were not significant.

	Y2B8 (N = 73) %	RITUXAN (N = 70) %
Stratified Histology Type		
A	12	11
Follicular	78	80
Transformed	10	9
Disease Stage at Study Entry		
I/II	11	9
III/IV	89	91
Tumor bulk		
< 5 cm	55	55
5 - < 7 cm	25	19
7 - < 10 cm	12	19
≥ 10 cm	8	7
Extranodal Disease (# sites)		
0, 1	82	87
≥ 2	18	13

	Y2B8 (N = 73) %	RITUXAN (N = 70) %
Stratified Histology Type		
Bone Marrow Involvement		
0%	58	66
0.1 - 5%	4	7
5 - 20%	27	21
≥ 20%	11	6
Splénomegaly		
Yes	10	4
No	90	96

Risk Assessment

Prognostic indicators and risk assessment were not different for the study groups.

IPI Risk Group

	Y2B8 (N = 73) %	RITUXAN (N = 70) %
Low	34	46
Low/Intermediate	52	33
Intermediate/High	7	10
High	4	3
Unknown	3	8

Prior Therapy

No differences in the number or type of prior therapy were seen between the two study groups.

Number of Prior Regimens

	Y2B8 N	RITUXAN N
Median	2	2
Range	1-6	1-5

	Y2B8 (N = 73) %	RITUXAN (N = 70) %
Type of Prior Regimen		
Alkylator +/- Prednisone	29	27
Purine Analogs	10	21
Steroids	19	21
CVP or COP	37	27
CHOP	41	49
Other Aggressive	25	43
Prior Radiotherapy		
Yes	29	21
No	71	79

Subject Disposition

	Y2B8 N = 73		RITUXAN N = 70	
	N	(%)	N	(%)
Disposition				
On-Going Patient	27	(37)	23	(33)
Off Study Patient	46	(63)	47	(67)
Complete Treatment Period	38	(83)	34	(72)
Not Complete Treatment Period	8	(17)	13	(28)
Reason For Off Study				
Progressed	45	(98)	42	(89)
Death	0	(0)	1	(2)
Other Therapy	1	(2)	4	(9)

Primary Efficacy Analysis

The primary efficacy variable for study 106-04 is the protocol defined overall response rate as determined by an independent review panel (LEXCOR). Subjects were stratified by histology at registration. Per agreement with FDA, the Cochran-Mantel-Haenszel test by pathology report histology type would be used to assess ORR. In addition, ZEVALIN therapeutic regimen needed to show superior ORR with similar or longer DR to the rituximab control group to be considered successful.

An interim analysis was to be performed when efficacy data for the first 90 patients became available. The purpose of the interim analysis was to confirm that the primary

analysis had a minimum of 80% power given an alpha level of 0.05. Power calculations were based on baseline assumptions of a 50% ORR for the rituximab treatment arm and 75% to 80% ORR for the ZEVALIN treatment arm. If, based on interim results, the study was declared underpowered, the sample size could be adjusted. Otherwise, a minimum of 140 patients was to be enrolled in the study to provide enough patients for safety assessment. The two-stage group sequential stopping rules based on the O'Brien-Flemming method was to be used. The levels of significance for the interim and final analysis were to be 0.005 and 0.048, respectively.

Overall Response (ITT – All Subjects)

(CR+CCR+PR) Rate and Complete Response (CR)

	IDEC-Y2B8 (N=73) %	Rituximab (N=70) %	Unadjusted exact p-value	Adjusted p-value *
ORR				
LEXCOR (PDRC) [#] 95% CI	73 (62, 82)	47 (35, 60)	0.002	0.002
LEXCOR (IWRC) [§] 95% CI	80 (68, 88)	56 (43, 68)	0.004	0.002
Investigator 95% CI	82 (72, 90)	54 (42, 66)	<0.001	<0.001
CR rate				
LEXCOR (PDRC) [#] 95% CI	18 (10, 29)	11 (5, 21)	0.348	0.326
LEXCOR (IWRC) [§] 95% CI	30 (20, 42)	16 (8, 26)	0.048	0.040
Investigator 95% CI	36 (25, 48)	20 (11, 33)	0.042	0.033

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

[#] PDRC: Protocol Defined Response Criteria

[§] IWRC: International Workshop Response Criteria

Exploratory Analyses of the Primary Endpoint.
LEXCOR Response Assessment by Histology

Response	Histology Type	ZEVALIN Therapy	Rituximab
		(N=73) Resp/Total (%)	(n=70) Resp/Total (%)
ORR	A	6/9 (67)	3/8 (38)
	Follicular	42/55 (76)	27/58 (47)
	Transformed	5/9 (56)	3/4 (75)
CR	A	1/9 (11)	1/8 (13)
	Follicular	11/55 (20)	5/58 (9)
	Transformed	1/9 (11)	2/4 (50)

Overall Response (Follicular Patients)

Overall Response Rate and Complete Response (CR)

	IDEA-Y2B8 (N=55) %	Rituximab (N=58) %	Unadjusted exact p-value
ORR			
LEXCOR	76	47	0.002
95% CI	(63, 87)	(33, 60)	
Investigator	87	57	<0.001
95% CI	(76, 95)	(43, 70)	
CR rate			
LEXCOR	20	9	0.107
95% CI	(10, 33)	(3, 19)	
Investigator	40	19	0.022
95% CI	(27, 54)	(10, 31)	

Agreement Rate Between LEXCOR and Investigators

There is no significant discordance between the two groups in the determination of overall response rates. However, there is a significant discordance in determination of CR rate to ZEVALIN by investigators as compared to LEXCOR. This was not observed for CR rate to RITUXAN.

Overall Response (CR + CCR + PR)

		LEXCOR			
INVESTIGATOR		Y2B8		RITUXAN	
		Yes	No	Yes	No
	Yes	50	10	31	7
No	3	10	2	30	
Concordance Rate		82%		87%	

Complete Response

		LEXCOR			
INVESTIGATOR		Y2B8		RITUXAN	
		Yes	No	Yes	No
	Yes	12	14	7	7
No	1	46	1	55	
Concordance Rate		80%		89%	

Secondary Endpoints

Secondary efficacy variables supporting the primary analysis were prospectively defined and included duration of response and time to progression.

However, the study was not designed or powered to demonstrate a difference in TTP for ZEVALIN therapeutic regimen compared with rituximab. Instead the protocol statistical section prospectively defined a TTP and DR objective using a Logrank test, stating that "The target median TTP and response duration time for IDEC-Y2B8 group will be either equivalent or better than that of the RITUXAN group. Based on the current clinical experience, a median TTP of 7.5 months was expected for all patients in the rituximab group.

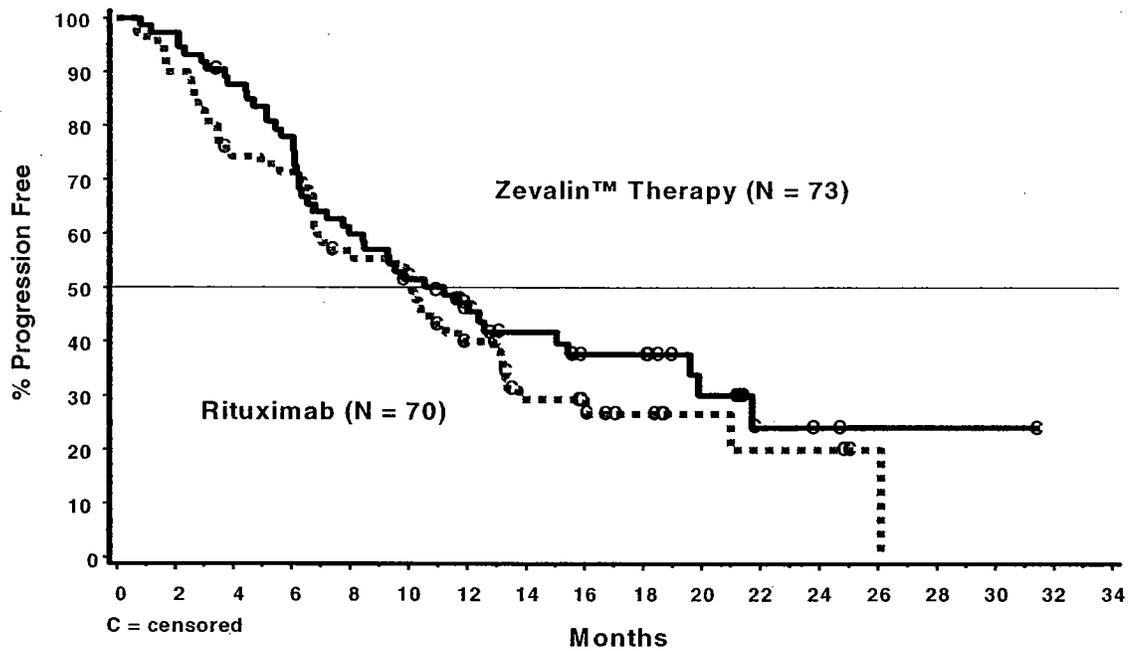
Duration of Response and Time to Progression

Treatment	Variable	IDEC-Y2B8 (n = 73)	Rituximab (n = 70)
Time to Progression (months) All Patients (n=143)	N	73	70
	Median (K-M)	11.2	10.1
	95% CI	(7.8 – 15.4)	(6.8 – 12.9)
	Range	(0.8 – 31.5+)	(0.7 – 26.1)
	Total Censored	27 (37%)	20 (29%)
	Total Failed	46	50
	Total Missing	0	0
Duration of Response (months) (n=86)	N	53	33
	Median (K-M)	14.2	12.1
	95% CI	(9.4, ..)	(8.0, 24.5)
	Range	(0.9 – 28.9+)	(2.1 – 24.5)
	Total Censored	25 (47%)	14 (42%)
	Total Failed	28	19
	Total Missing	20	37

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).

Duration of Response from onset of response to disease progression in months

TTP Kaplan-Meier Analysis



Exploratory Analysis

Duration of Response by Histology

Histology Type		ZEVALIN (N = 53)	Rituximab (N = 33)
A	N Median (mos) Range 95% CI % Censored	6 9.8 (5.0, 20.5) (7.1, 20.5) 17%	3 NA (8.0, 14.5+) (8.0, NA) 67%
Follicular	N Median (mos) Range 95% CI % Censored	42 18.5+ (1.7, 28.9+) (10.0, NA) 52%	27 12.1+ (2.7, 24.5) (7.9, 24.5) 41%
Transformed	N Median(mos) Range 95% CI % Censored	5 6.8 (0.9, 20.3+) (0.9, NA) 40%	3 11.7 (2.1, 17.0+) (2.1, NA) 33%

Overall Response Rates in Subjects with Bulky Disease

Bulky Disease Category	ZEVALIN N/Total (%)	Rituximab N/Total (%)
< 5 cm	31/40 (78)	19/39 (49)
≥ 5 cm	22/33 (67)	14/31 (45)

Quality of Life: FACT-G Analysis

Functional Assessment of Cancer Therapy-General (FACT-G) scores for two separate patient populations (all patients and patients classified as responders) were performed. The paired t-test was performed for within treatment comparisons in each patient population (the total score at baseline and total score at 12-weeks post-treatment). 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 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 were: 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 an increase in QOL.

FACT-G overall score was available at baseline and 12 weeks post-treatment for 45 ZEVALIN therapeutic regimen subjects (62%) and 36 rituximab subjects (51%). The baseline mean overall FACT-G score was 87 in ZEVALIN therapeutic regimen group and 91 in rituximab group. The mean overall FACT-G score at 12 weeks post-treatment was improved: 93.3 in ZEVALIN therapeutic regimen group and 93 in rituximab group. The change in score from baseline to 12 weeks post-treatment was statistically significant in the IDEC-Y2B8 treatment group ($p = 0.001$), but not in the rituximab treatment group ($p = 0.185$).

Below is a summary of the FACT-G scores for paired t-test:

	IDEC Y2B8	RITUXAN
Enrolled	73	70
Completed the FACT-G Survey at Baseline & 12 weeks post-treatment	45 (62%)	36 (51%)
Mean FACT-G Score at the Baseline for completed surveys (n=45, 36)	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)

Quality of Life Conclusions:

This was a tertiary endpoint in the protocol. The protocol stated that QOL would be assessed at baseline, week 4, week 8 and week 12. The week 8 assessment in the RITUXAN arm was missing by design. There was no hypothesis pre-specified in the protocol regarding analyses of QOL. There were significant limitations in interpretation of the QOL data, e.g., modest sample size, lack of pre-specified analytic plan, missing information, informative dropouts, biased baseline values (they were obtained after treatment was administered), no adjustment for endpoint multiplicity adjustments.

Safety—Adverse Events***Non Hematologic Adverse Events*****Safety Evaluation -- Y2B8 DATA**

73 of 73 subjects (100%) experienced a total of 663 non-hematologic AEs for the entire period of follow-up.

**Frequency of Non-Hematologic
AEs by
NCI CTC Grades**

Grade	ZEVALIN N= 663 %	Rituximab N=449 %
1	61	71
2	32	22
3	6	5
4	1	2

Clinically significant AE:

- 1 had allergic Grade 3 reaction (106-04-018-312)
- 6 subjects had AEs associated with a sensation of swelling of the throat and tongue classified as angioedema (3 Grade 1 and 3 Grade 2) (106-04-001-208, 106-04-001-279, 106-04-002-101, 106-04-001-288, 106-04-022-211, 106-04-022-275)
- 4 subjects had respiratory system AEs classified as bronchospasm occurring on a treatment day (1 Grade 1 and 3 Grade 2) (106-04-001-208, 106-04-003-306, 106-04-011-254, 106-04-022-224)
- 1 subject had Grade 2 colitis (106-04-029-244)
- 7 had diarrhea (5 Grade 1 and 1 each for Grade 2 and 3) (106-04-001-116, 106-04-001-252, 106-04-002-267, 106-04-007-295, 106-04-011-287, 106-04-020-289, 106-04-029-244)
- 1 had Grade 2 gastroenteritis (106-04-001-232)
- 3 had GI disease (2 Grade 1 irritable bowel and gastroesophageal reflux, and 1 Grade 2 gastroesophageal reflux) (106-04-011-239, 106-04-014-245, 106-04-020-305)
- 1 had Grade 4 intestinal obstruction (106-04-020-109)

- 1 had Grade 2 herpes zoster (106-04-011-226)
- 2 had myasthenia (1 Grade 1 and 1 Grade 2) (106-04-012-274, 106-04-034-304)
- 3 had Grade 2 urticaria (106-04-001-208, 106-04-001-279, 106-04-003-306)

Safety Evaluation -- RITUXAN™ DATA

68 of 70 subjects (97%) experienced a total of 449 non-hematologic AEs for the entire period of follow-up.

Clinically significant AEs:

- 2 had allergic reaction (1 Grade 1 and 1 Grade 2) (106-04-004-301, 106-04-016-270)
- 11 subjects (8 Grade 1 and 4 Grade 2; one subject had 2 events) had AEs associated with a sensation of swelling of the throat and tongue (classified as angioedema) (106-04-001-113, 106-04-001-242, 106-04-001-247, 106-04-003-102, 106-04-011-280, 106-04-012-253, 106-04-013-221, 106-04-022-408, 106-04-031-283, 106-04-033-241, 106-04-033-273)
- 3 subjects (1 Grade 1 and 2 Grade 2) had respiratory system AEs occurring on a treatment day (classified as bronchospasm) (106-04-002-223, 106-04-011-269, 106-04-012-260)
- 6 had Grade 1 diarrhea (106-04-002-112, 106-04-004-301, 106-04-007-256, 106-04-007-302, 106-04-022-114, 106-04-023-401)
- 1 had Grade 1 gastroenteritis (106-04-013-221)
- 1 had Grade 3 GI disease (106-04-031-231)
- 2 had herpes zoster (1 Grade 1 and 1 Grade 2) (106-04-016-270, 106-04-033-108)
- 1 had Grade 1 myasthenia (106-04-011-269)
- 0 had sepsis
- 3 had urticaria (106-04-001-242, 106-04-001-409, 106-04-013-221)
- 13 had pruritus (11 Grade 1, 3 Grade 2; 1 Grade 3; 2 subjects had 2 events each).
- 1 had a gastrointestinal carcinoma (106-04-031-231)
- 1 had a carcinoma of the skin (106-04-001-213)
- 1 had 2 events associated with edema of the face (1 Grade 1 and 1 Grade 2) (106-04-005-251)

Frequency of Common and Notable Non-Hematologic AEs by Subject

AE (all grades)	Zevlin N=73 subjects %	Rituximab N=70 subjects %
Asthenia	51	44
Nausea	44	21
Chills	26	29
Infection	25	10
Pain	22	17
Abdominal Pain	21	13
Fever	21	19
Vomiting	19	7
Headache	18	24
Irritation Throat	18	16
Increased Cough	16	9
Dizziness	15	7
Dyspnea	15	9
Peripheral edema	15	3
Rash	15	14
Arthralgia	14	7
Anorexia	11	3
Anxiety	11	4
Hypotension	11	10
Myalgia	11	14
Pruritus	11	19
Diarrhea	10	9
Ecchymosis	10	1
Angioedema	8	16
Flushing	8	6
Abdominal Enlargement	5	3
Allergic reaction	1	3

Comparative Analysis of Non-Hematologic AEs:

Gastrointestinal AE

- A two fold increase in adverse events related to the bowel (grades 1-2 nausea, vomiting, and abdominal pain) was noted in the ZEVALIN arm as compared to the control arm (58% versus 34%)

GI toxicity¹

	ZEVALIN AEs = 131 events (73 Subjects) %	RITUXAN AEs = 63 events (70 Subjects) %
Grade 1	63	73
Grade 2	32	19
Grade 3	3	5
Grade 4	2	3

¹ Includes all IDECBODY "DIG" and COSTAR "PAIN ABDO"**Human Anti-Murine Antibody (HAMA) Response:**

2 subjects had a detectable HAMA prior to ZEVALIN therapeutic regimen

- Subject 106-04-001-116 had a HAMA value of 12.6 µg/mL on Study Day -14. This subject was admitted to the hospital on Study Day 9 with a fever of 104°F (Grade 2), nausea (Grade 2), diarrhea (Grade 2), weakness (Grade 2), myalgia (Grade 2), dehydration (Grade 3), hypotension (Grade 2), and tachycardia (Grade 2). Laboratory tests on admission revealed the following: total bilirubin level of 4.9 mg/dL, alkaline phosphatase level of 952 U/mL, and lipase level of 1096 U/mL. All events were related to an obstructed biliary stent. The subject had a Grade 4 cholangitis and Grade 3 sepsis which were reported as a serious adverse events and not related to ZEVALIN therapeutic regimen.
- Subject 106-04-031-272 had a HAMA value of 14.7 µg/mL on Study Day -13 and experienced no Grade 3 or 4 AEs.

1 subject had a detectable HAMA following ZEVALIN therapeutic regimen:

- Subject 106-04-034-304 had a HAMA assay of 13.2 µg/mL on Study Day 39; this patient had no Grade 3 or 4 AEs.

Human Anti-Chimeric Antibody (HACA) Response:

1 subject developed a detectable HACA following rituximab therapy.

- Patient 106-04-003-102 had a HACA assay value of 169 mg/mL on Study Day 102 and did not experience any Grade 3 or 4 AEs.

Hematologic Adverse Events

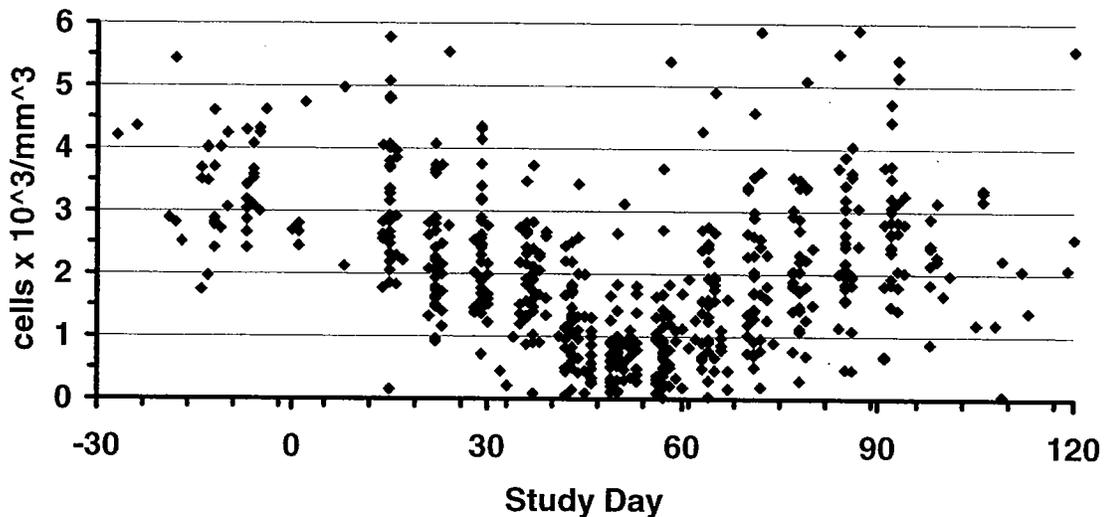
For all hematologic adverse events, duration of Grade ≥ 3 toxicity is defined as end date minus start date, where end date and start date are defined relative to the nadir lab value. A patient's end date is defined as the 1st lab test date after the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit. A patient's start date is defined as the most recent lab test date prior to the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit.

Patients not recovered from Grade ≥ 3 toxicity were censored by one of two rules. If a patient had received next anti-cancer therapy, that patient was censored to the date of the most recent lab test prior to receiving next anti-cancer therapy. If the patient had not received next anti-cancer therapy, that patient was censored to the date of the most recent lab test.

ANC – Y2B8 Group

41 of 73 subjects (56%) in the Y2B8 arm had Grade 3 or 4 ANC within 90 days of initial therapy

106-04 Y2B8 Subjects With Grade 3-4 ANC n = 41/73 (56%)



Median duration of grade 3-4 neutropenia was 27 days (Range 5-65 days)

ANC – Rituximab Group

0 of 70 subjects (0%) randomized to receive RITUXAN™ had Grade 3 or 4 ANC within 90 days of initial therapy

Platelets – Y2B8 Group

44 of 73 subjects (60%) randomized to receive Y2B8 had Grade 3 or 4 thrombocytopenia within 90 days of initial therapy

Median duration of grade 3-thrombocytopenia was 23 days (Range 1-43 days)

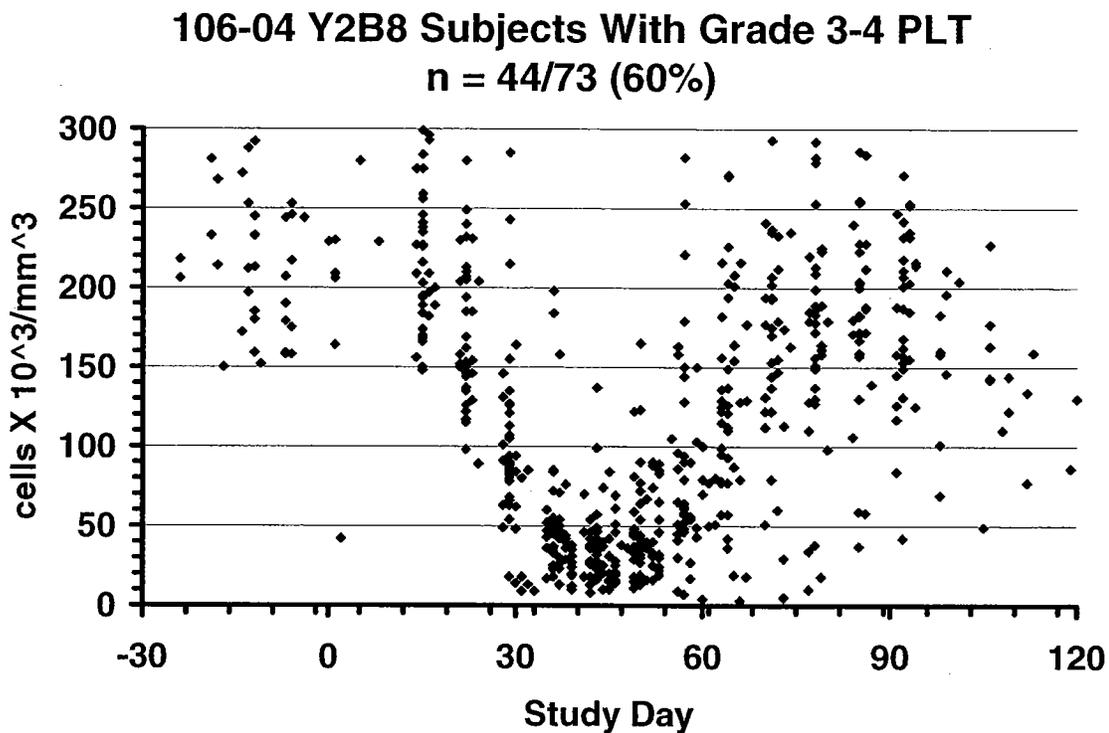
2 subjects failed to have documented platelet recovery:

- 106-04-002-404 never recovered PLT with a 36 day follow-up period. Progressive disease was documented on Study Day 25 and additional therapy instituted on Study 37. The subject expired on Study Day 60.

- -04-001-407 never recovered PLT with a 39 day follow-up period. Progressive disease was documented on Study Day 36 and additional anti-lymphoma therapy initiated on that day. Additional laboratory data was not available. The subject expired on Study Day 94.

Subjects with clinically significant AEs:

- 2 subjects had Grade 1 heme per rectum (106-04-011-115, 020-411)
- 1 subject had Grade 1 retinal hemorrhage (106-04-001-303)
- 3 subjects had epistaxis
- 3 (2 Grade 1 and 1 Grade 2) had petechia (106-04-001-204, 106-04-002-117, 106-04-014-111)



Platelets – Rituximab Group

0 of 70 subjects (0 %) randomized to receive RITUXAN™ had Grade 3 or 4 thrombocytopenia within 90 days of initial therapy

Subjects with clinically significant AEs.

- 1 had Grade 3 GI heme (106-04-023-401)
- 1 had Grade 2 vaginal heme (106-04-022-220)
- 1 had Grade 1 hematuria (106-04-020-412)
- 1 had Grade 1 epistaxis (106-04-011-269)

Immunologic Reconstitution***Quantitative B-cells***

The median absolute B-cell count declined in both treatment groups after treatment onset.

ZEVALIN Therapy group

Baseline data were available for 70 subjects (96%).

- Baseline median cell count was 83.5 cells/ μ L for CD19+. (normal range: 32 - 341 cells/ μ L)
- Four weeks post-therapy the median value decreased to zero and began to recover by post-treatment Month 6 (median count 17.5 cells/ μ L).
- By Study Month 12, the median cell count was 170 cells/ μ L (range 62 to 1273 cells/ μ L).

Rituximab group

Baseline Data were available at for 69 patients (99%).

- Baseline median cell count at was 73.0 cells/ μ L for CD19+.
- Four weeks post-therapy, the median value decreased to zero and began to recover by post-treatment Month 9 (median count 25.0 cells/ μ L).

Quantitative Serum Immunoglobulins

In the ZEVALIN and rituximab treatment groups, median IgG, IgM, and IgA levels remained within normal limits during treatment and follow up.

Within the ZEVALIN treatment group:

- No subjects experienced Grade 3 IgG serum levels
- 8 subjects experienced Grade 3 IgM serum levels
- 2 subjects experienced Grade 3 IgA serum levels

Within the rituximab treatment group:

- 2 subjects experienced Grade 3 IgG serum levels
- 4 subjects experienced Grade 3 IgM serum levels
- 1 subject experienced Grade 3 IgA serum levels

Deaths within Study Day 100

Patient 106-04-002-404 is a 40-year-old male with transformed non-Hodgkins lymphoma, originally diagnosed in _____. The subject was randomized to the ZEVALIN treatment arm and received 31.5 mCi of Y2B8 (0.4 mCi / kg) on 29 _____. Chest and Abominal/Pelvic CT scans done on Study Day 26 _____ revealed progression of disease. On Study Day 37 _____ dexamethasone/methotrexate was started. He died of progressive lymphoma on Study Day 60 (_____) No autopsy was performed.

Patient 106-04-020-412 is a 70-year-old female with transformed non-Hodgkins lymphoma, originally diagnosed in _____. The subject was randomized to the rituximab arm and received 4 weekly rituximab administrations beginning on _____. On Study Day 22 (_____ the day of the fourth rituximab infusion, the subject was admitted with complaints of anorexia, abdominal pain, and increasing bilateral leg edema. She also had elevated liver function tests and jaundice. Chest and Abominal/Pelvic CT scans revealed extensive progression of disease in the chest and abdomen. She was discharged on Study Day 24 _____ with hospice care. She died of progressive lymphoma on Study Day 37 _____. No autopsy was performed.

Patient 106-04-001-407 is a 60-year-old male with transformed NHL. The patient was diagnosed with follicular small-cleaved cell NHL in _____. The histology was diagnosed as transformed in _____. The subject was randomized to the ZEVALIN arm and received 32 mCi IDEC-Y2B8 on _____. CT scans on Study Day 36 _____ showed progression of disease within the abdomen. The patient received no further therapy and died on Study Day 94 _____. No autopsy was performed.

Conclusions

1. The primary objective of superior overall response rate (ORR; complete response [CR] + clinical complete response [CCR] + partial response [PR]) in the intent-to-treat (ITT) population was achieved.
 - ZEVALIN therapeutic regimen was statistically superior to rituximab therapy (ORR = 73% vs. 47%, p-value = 0.002)
2. The Kaplan Meier estimated median duration of response (DR) for ZEVALIN treated subjects is numerically but not statistically longer than that for rituximab subjects
 - In the ITT population, the median DR to ZEVALIN therapeutic regimen was 14.2+ months (range 0.9 to 28.9+ month)
 - In the ITT population, the median DR to Rituximab therapy was 12.1+ months (range 2.1 to 24.5+ months).
3. The Kaplan Meier estimated time to disease progression (TTP) is clinically equivalent between the ZEVALIN and rituximab groups.
 - In the ITT population, the median TTP was 11.2+ months for ZEVALIN therapeutic regimen (range 0.8 to 31.5+ month)
 - In the ITT population, the median TTP was 10.1+ months (range 0.7 to 26.1+ months) for Rituximab therapy.
4. Impact on QOL cannot be assessed.
5. Hematologic toxicity is common with ZEVALIN therapeutic regimen and represents a significant clinical limitation.
 - Median duration of Grade \geq 3 neutropenia within 90 days of ZEVALIN therapeutic regimen was 27 days for 56% of subjects.

- Median duration of Grade ≥ 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen was 23 days for 60% of subjects.

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On Original**

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Study 106-06

PROTOCOL HISTORY

Date	Milestone	Comments
June 11, 1998	Protocol Submitted	
July 7, 1998	Protocol Initiated	
September 21, 1998.	Amendment #1	<ol style="list-style-type: none"> 1. To change from a Phase II study to a single arm Phase III study in a refractory population. 2. To establish a target ORR of 35% in rituximab refractory follicular NHL (N = 50) as clinically significant. 3. To define and expand the subjects included in the study as the following: <ul style="list-style-type: none"> • Subjects with follicular B-cell NHL previously treated with rituximab at 375 mg/m² q wk X 4 in whom the most recent rituximab treatment did not result in an objective response (CR or PR) or who progressed within 6 months of the first rituximab infusion. • Subjects with either small lymphocyte B-cell NHL (IWF A) or transformed B-cell NHL who were treated on the rituximab arm of IDEC Study 106-04 and did not achieve a CR or PR and now have documented disease progression requiring treatment. 4. To utilize a nonrandomized reference group of rituximab non-responders treated with subsequent systemic therapy for comparative analysis of ORR and duration of response (DR). 5. To change the total number of subjects treated with IDEC-Y2B8 to approximately 60 in order to achieve 50 evaluable follicular NHL subjects. 6. To add a minimum requirement of at least one lesion measuring 2.0 cm in a single dimension in the measurable disease section of inclusion criteria. 7. To add <i>bcl-2</i> analysis in peripheral blood and bone marrow by PCR method. 8. To add lymph node biopsy or fine needle aspirate demonstrating histologic confirmation of LG/F NHL within 6 months of the first study treatment. 9. To add a FACT-G questionnaire (quality of life). 10. To add LEXCOR 11. To add the collection of the best response to other anticancer therapy in long-term follow-up survival.
February 26, 1999.	Amendment #2	<p>14 subjects had been enrolled in this study</p> <ol style="list-style-type: none"> 1. Remove the binding assay requirement from ongoing IDEC-Y2B8 clinical trials.

Date	Milestone	Comments
March 16, 1999.	Amendment #3	<p>17 subjects had been enrolled in this study.</p> <ol style="list-style-type: none"> 1. To remove IDEC-In2B8 administration and dosimetry as a study requirement. 2. To modify the statistics section to include a comparison of the ORR and DR for follicular NHL subjects in this trial with the following: <ul style="list-style-type: none"> • ORR and DR from these subjects' most recent rituximab therapy. • ORR and DR from these subjects' last chemotherapy. 3. To remove the requirement for CD20 positive assessment for subjects with follicular NHL. 4. To add a comparison of REAL Classification and International Working Formulations of NHL.

STUDY DESIGN, OBJECTIVES, ELIGIBILITY, AND TREATMENT PLAN

Design

This Phase III open-label, single arm, multi-center study was designed to evaluate ORR and DR in subjects with advanced follicular B-cell non-Hodgkin's lymphoma (NHL), who were refractory to rituximab therapy.

Objectives:

The **primary objectives** of this study were the following:

1. Determine the efficacy of ZEVALIN therapeutic regimen in relapsed or refractory, follicular (IWF B, C, D; also defined as REAL classification Follicular center grade I, II, and III) B-cell NHL patients whose disease was refractory to previous treatment with rituximab.
2. Characterize the safety of ZEVALIN as a therapeutic regimen.

The **secondary objectives** of this study were the following:

1. Determine the duration of response (DR) and time to progression (TTP).
2. Determine complete response (CR), clinical complete response (CCR), and partial response (PR) rates, time to next anticancer treatment, and quality of life.
3. Compare the ORR and DR of follicular NHL patients in this trial with the following:
4. ORR and DR from these patients' most recent rituximab therapy
5. ORR and DR from these patients' last chemotherapy
6. Compare the ORR and DR of follicular NHL patients in this trial with that of a Reference Group.
7. Compare serious adverse events (SAEs) of follicular NHL patients in this trial with those of a Reference Group.

Inclusion Criteria

1. Follicular NHL subjects who were previously treated with rituximab 375 mg/m² times four and
 - Whose most recent treatment did not result in a PR or CR as documented by baseline and post-treatment ct scans and who now have disease progression, or who had progression of disease within 6 months of first rituximab infusion, or
 - Who were enrolled in IDEC study 106-04, randomized to the rituximab arm, did not achieve a PR or CR, and now have documented disease progression requiring treatment.
2. Bidimensionally measurable disease meeting a minimum requirement of at least one lesion measuring 2.0 cm in a single dimension
3. No anticancer therapy for 3 weeks prior to study initiation (6 weeks if patient treated with nitrosourea or Mitomycin C), and fully recovered from all toxicities associated with prior surgery, radiation treatments, chemotherapy, or immunotherapy.
4. 18 years of age or older
5. Expected survival ≥ 3 months
6. WHO performance status of 0, 1, or 2
7. Acceptable hematologic status within 2 weeks prior to initial treatment, including:
 - Absolute neutrophil count ≥ 1,500 cells/mm³
 - Total lymphocyte count < 5,000 cells/mm³ for patients with small lymphocytic lymphoma (IWF A)
 - Platelet count ≥ 150,000 cells/mm³.
8. Less than 25% bone marrow involvement with lymphoma
9. CD20 positive B-cell population in lymph nodes or bone marrow in transformed or IWF A subjects

Exclusion Criteria

1. Treatment with prior myeloablative therapies with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell (PBMC) support
2. Prior radioimmunotherapy, including IDEC-Y2b8
3. Presence of CNS lymphoma
4. Presence of chronic lymphocytic leukemia (CLL)
5. Presence of HIV or AIDS-related lymphoma
6. Presence of small lymphocytic lymphoma (IWF A) with a total lymphocyte count > 5,000 cells/mm³
7. Pleural or peritoneal invasion and/or effusion with positive cytology for lymphoma
8. Abnormal liver function: total bilirubin > 2.0 mg/dl
9. Abnormal renal function: serum creatinine > 2.0 mg/dl
10. Prior external-beam radiation therapy to > 25% of active bone marrow (involved field or regional)
11. Treatment with G-CSF or GM-CSF within 2 weeks of IDEC-Y2B8 treatment
12. Serious nonmalignant disease, active infection.
13. Major surgery, other than diagnostic surgery, within 4 weeks of treatment

14. Another primary malignancy (other than squamous or basal cell carcinoma of the skin or in situ carcinoma of the cervix) for which the patient has not been disease-free for at least 5 years
15. Presence of HAMA/HACA (result required prior to study entry)
16. Concurrent systemic corticosteroid therapy: a single dose ≥ 40 mg of prednisone (or equivalent) or ≤ 40 mg prednisone (or equivalent) for more than six doses

Treatment Plan

Subjects received one infusion of 250 mg/m² rituximab prior to a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of IDEC-In2B8, which was injected as a slow IV push over 10 minutes. Seven days later, a second infusion of 250 mg/m² of rituximab followed by 0.4 mCi/kg (1.6 mg total antibody dose) of IDEC-Y2B8 slow IV push over 10 minutes the following week was administered.

For subjects whose body weight exceeded 80 kg, a maximum dose of 32 mCi of ⁹⁰Y was to be administered.

STUDY RESULTS

Subject Disposition

57 subjects were enrolled in the study

- 57 received two rituximab infusions and the IDEC-Y2B8 dose.
- 28 patients received the injection of IDEC-In2B8. The remaining 29 patients were enrolled after the protocol was amended to remove dosimetry, and thus did not receive the injection of IDEC-In2B8.

13 of 57 subjects (23%) were previously treated in Study 106-04.

Protocol Violations

1. S Subjects 106-06-017-029 and 106-06-039-057 had a TTP longer than 6 months following their last rituximab therapy (8 and 7 months, respectively). These subjects were not included in the ITT efficacy analysis.
2. Subject 106-06-033-037 had a prior rituximab regimen other than 375 mg/m² once weekly times four. The regimen consisted of 375 mg/m² of rituximab once weekly times four and then once monthly times seven.
3. Subject 106-06-005-003 was enrolled with a platelet count of 147,000 cells/mm³ (< 150,000 cells/mm³)
4. Five subjects received an IDEC-Y2B8 dose that exceeded the intended dose of 0.4 mCi/kg or the maximum dose of 32 mCi:
 - Subject 106-06-005-003 received 32.95 mCi.
 - Subject 106-06-012-018 received 0.48 mCi/kg.
 - Subject 106-06-019-040 received 34.4 mCi.
 - Subject 106-06-033-034 received 32.8 mCi.
 - Subject 106-06-040-051 received 35 mCi.

5. Two subjects had a delay between the first treatment day and the second treatment day:
 - Subject 106-06-003-049 had a 10 days interval
 - Subject 106-06-017-048 had 14 days interval
6. Two subjects had a confirmation of response efficacy evaluation less than 28 days from the onset of response:
 - Subject 106-06-002-004 had a confirmation of response evaluation at 26 days.
 - Subject 106-06-041-044 had a confirmation of response evaluation at 27 days
7. Subject 106-06-001-056 received 15 to 20 mg of prednisone during the treatment period for a pre-existing granuloma annulare (prohibited concomitant medication during the treatment period).
8. Infusion data for the first rituximab infusion of Subject 106-06-017-048 was lost at the site. However, the administration of the first rituximab infusion was confirmed by the site.
9. Subject 106-06-002-001 had a platelet count of 119,000 cells/mm³ at study entry, below the required level of $\geq 150,000$ cells/mm³. This patient was treated in the rituximab arm of Study 106-04 and, with FDA permission, was treated in Study 106-06 at a reduced dose (0.3 mCi/kg).
10. Subject 106-06-012-018 was enrolled in the study with IWF A histology type, bulky disease, ascites, and a positive HACA response of 44.70 ng/mL.
11. Subject 106-06-041-046's baseline CT scans were performed 34 days prior to study entry.
12. Subject 106-06-006-014's baseline CT scans were performed 32 days prior to study entry.

Study Population & Disease Characteristics**Demographics and Disease Characteristics (n=57)**

Age (years)	
Mean	54.4
Std	10.4
Median	54.0
Range	34.0 - 73.0
Gender (%)	
Female	51
Male	49
Ethnicity (%)	
Caucasian	95
African-American	2
Other	3
Stratified Histology Type (%)	
A	4
Follicular	95
Transformed	2
Disease Stage at Study Entry (%)	
I/II	7
III/IV	90
Unknown	3
Tumor bulk (%)	
< 5 cm	26
5 - < 7 cm	30
7 - < 10 cm	25
≥ 10 cm	19
Bone Marrow Involvement (%)	
0%	68
0.1 - 5%	5
5 - 20%	21
≥ 20%	5
Splenomegaly (%)	
Yes	12
No	88

Risk Assessment**IPI Risk Group (N=57)**

	%
Low	44
Low/Intermediate	21
Intermediate/High	12
High	7
Unknown	16

Prior Therapy

All subjects (n=57) had a median of 4 prior regimens (range 1-9) prior to receiving ZEVALIN therapeutic regimen. All subjects had prior rituximab therapy.

- **Chemoresistance** was reported as follows
 - 20 subjects (36.4%) were resistant to all chemotherapy,
 - 45 subjects (81.8%) were resistant to at least one chemotherapy regimen,
 - 32 subjects (58.2%) were resistant to their first chemotherapy,
 - 37 subjects (67.3%) were resistant to their last chemotherapy.

**Type of Prior Regimen
(N=57 subjects)**

	%
Rituximab	100
Alkylator +/- Prednisone	32
Purine Analogs	23
Steroids	19
CVP or COP	39
CHOP	56
Other bioimmunotherapy	7
Other Aggressive	65
Prior Radiotherapy	
Yes	30
No	70

Study Results—Primary Efficacy Analysis

The data set for the 1^o efficacy was prospectively defined as the LEXCOR evaluation of ORR (CR + CCR + PR) in follicular subjects only. The 1^o efficacy variable was to be assessed using 95% confidence intervals; and, if the ORR was at least 35%, ZEVALIN therapeutic regimen would be considered clinically effective.

- Of the 57 patients enrolled in the study, 54 were follicular patients.
3 patients with non-follicular histologies were the following:
Subject 106-06-012-018 IWF A
Subject 106-06-003-034 IWF A
Subject 106-06-017-054 IWF G.
- Of the 54 follicular patients enrolled,
2 were excluded from the efficacy analysis because their TTP after rituximab therapy was greater than 6 months, a protocol violation. However, excluding these subjects from the overall primary analysis did not affect the study conclusions. Therefore, all secondary and exploratory analyses presented are for the overall study population.

Overall Response

(CR+CCR+PR) Rate and Complete Response (CR)

	All Follicular Subjects (N=54)		Protocol Eligible Follicular Subjects (N=52)	
	%	95% CI	%	95% CI
ORR				
LEXCOR	59	(45, 82)	58	(43, 71)
Investigator	63	(49, 76)	62	(47, 75)
CR rate				
LEXCOR	4	(1,13)	4	(1,13)
Investigator	19	(9, 31)	17	(8, 30)

Exploratory Analyses of the Primary Endpoint

Agreement Rate Between LEXCOR and Investigators (N=54)

INVESTIGATOR	LEXCOR		
	Overall Response (CR + CCR + PR)		
		Yes	No
	Yes	28	6
	No	4	16
	Concordance Rate		82%
	Complete Response		
	Yes	1	9
	No	1	43
	Concordance Rate		82%

Secondary Analyses

Secondary efficacy variables supporting the primary analysis include time to progression (TTP) duration of response (DR), and comparison of ZEVALIN therapeutic regimen with previous rituximab therapy or previous chemotherapy.

Time to Progression and Duration of Response

	IDEC-Y2B8			
	Estimated Median (K-M)	95% CI	Range	Total Censored
Time to Progression (months)* (N=54)	6.8	(6.1, 9.3)	(1.1, 25.9)	16 (30%)
Duration of Response (months)# (N=32)	7.7	(5.5, 9.1)	(2.3, 24.9+)	10 (31%)

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

#Duration of Response from onset of response to disease progression in months

Duration of Response Relative to Prior NHL Therapy

The overall response rate to ZEVALIN therapeutic regimen was compared to the last prior rituximab therapy and the last prior chemotherapy regimen.

- Median time interval from the start date of last prior therapy (regardless of whether it was rituximab or chemotherapy) to the start date of ZEVALIN treatment: 6.5 months.

Comparison of ZEVALIN Therapy to Previous Rituximab Therapy

- 54 Subjects with follicular NHL received prior rituximab therapy.

**Duration of Response for Subjects with Follicular NHL
As Compared to Prior Rituximab Therapy**

	IDEC-Y2B8 N=32 Responder	Last Rituximab N=17 Responder
Median DR (months) [95% CI]	7.7+ [5.5, 9.1]	4.0 [3.00, 6.00]
Range	2.3+ to 24.9+	1 to 7
Censored (%)	31	0

**Response to ZEVALIN Therapy Compared with
Response to Prior Rituximab Therapy**

		ZEVALIN Therapy		
		Responder	Non-responder	Total
Prior RITUXAN™ Therapy	Responder	13	4	17
	Non-responder	19	18	37
	Total	32	22	

Duration of response for ZEVALIN therapeutic regimen was compared to the prior rituximab therapy using subjects as their own control. In this analysis, the length of the duration of response was categorized as longer for ZEVALIN, equivalent, or longer for RITUXAN. If the duration of response for ZEVALIN therapeutic regimen was longer than DR to RITUXAN by more than 1 month, then the ZEVALIN therapeutic regimen was considered beneficial (i.e., in favor of ZEVALIN). If this difference was ≤ 1 month, then the responses were called equivalent. If the duration of response to prior RITUXAN was longer than DR to ZEVALIN therapeutic regimen by more than 1 months then ZEVALIN therapeutic regimen was considered not beneficial to patients (i.e., in favor of rituximab).

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

ZEVALIN Therapy Compared To Prior Rituximab Therapy

Response Duration	# Subjects	%
Favor ZEVALIN	29	54
Equivalent	20	37
Favor RITUXAN	5	9
p-value using sign-rank test in favor of ZEVALIN		

Among the 32 subjects who achieved an objective response to ZEVALIN, 29 had a response that was longer in duration than their response to prior rituximab. The proportion of subjects with a longer duration of response to ZEVALIN was statistically significant (sign-rank test).

Comparison of ZEVALIN Therapy to Previous Chemotherapy

- 52 of 54 subjects with follicular NHL received prior chemotherapy.
- 1 of 52 subjects had missing data pertaining to duration of response to the prior chemotherapy. Hence for this analysis, the total population included 51 subjects.
- Median time interval from the start date of last prior chemotherapy to the start date of ZEVALIN treatment was 16 months.

**Duration of Response for Subjects with Follicular NHL
As Compared to Prior Chemotherapy Regimen
(n=51 Subjects)**

	IDEC-Y2B8 N=32 Responder	Last Chemotherapy N=34 Responder
Median DR (months) [95% CI]	7.7+ [5.5, 9.1]	6.5 [4.0, 10.0]
Range	2.3+ to 24.9+	1 to 175
Censored (%)	31	0

**Response to ZEVALIN Therapy Compared with
Response to Prior Chemotherapy
(n=51 Subjects)**

		ZEVALIN Therapy		
		Responder	Non-responder	Total
Prior Chemotherapy	Responder	22	12	34
	Non-responder	8	9	17
	Total	30	21	

Duration of response for ZEVALIN therapeutic regimen was compared to the DR of prior chemotherapy using subjects as their own control. In this analysis, the length of the duration of response was categorized as longer for ZEVALIN, equivalent, or longer for chemotherapy. If the duration of response for ZEVALIN therapeutic regimen was longer than DR to chemotherapy by more than 1 month, then the ZEVALIN therapeutic regimen was considered beneficial (i.e., in favor of ZEVALIN). If this difference was ≤ 1 month, then the responses were called equivalent. If the duration of response to prior chemotherapy was longer than DR to ZEVALIN therapeutic regimen by more than 1 months then ZEVALIN therapeutic regimen was considered not beneficial to patients (i.e., in favor of previous chemotherapy).

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

ZEVALIN therapeutic regimen compared to last prior Chemotherapy
N=51

Response	Frequency	%
Favor ZEVALIN	16	31
Equivalent	15	30
Favor Chemo	20	39

Among the 32 subjects who achieved an objective response to ZEVALIN, 16 had a response that was longer in duration than their response to prior chemotherapy. The proportion of subjects with a longer duration of response to ZEVALIN was not statistically significant (sign-rank test).

Safety -- Adverse Events

Non Hematologic Adverse Events

56 of 57 subjects (98%) experienced a total of 447 non-hematologic AEs for the entire period of follow-up. Sixty three percent were Grade 1, 30% Grade 2, 4% Grade 3, and 2% Grade 4 by the NCI CTC grade criteria.

Clinically Significant AEs:

- 1 subject had Grade 1 gastritis (106-06-017-022)
- 2 subject had Grade 1 GI disturbance (106-06-003-049, 106-06-014-033)
- 1 subject had Grade 2 herpes simplex (106-06-018-036)
- 1 subject had Grade 4 pneumonia (106-06-001-031)
- 1 subject had Grade 4 sepsis (106-06-001-031)
- 1 subject had Grade 1 edema of the face (106-06-003-038)
- 1 subject had an AML (106-06-018-036)

This subject was diagnosed with acute myelogenous leukemia on Study Day 244, follicular small-cleaved cell NHL diagnosed in 1995. He was treated previously with multiple chemotherapeutic agents, followed by rituximab. By Week 9 of

ZEVALIN therapeutic regimen, his WBC dropped to 3600 cells/mm³, and fell further to 1300 cells/mm³ by Month 6. A bone marrow aspirate and biopsy was performed on Study Day 191, which showed a hypocellular marrow with markedly decreased megakaryocytes and a decreased myeloid to erythroid ratio. Myelopoiesis was morphologically unremarkable; however, and the peripheral blood smear did not show malignant immature forms. The patient's WBC continued to fall and was 900 cells/mm³ by Study Day 233. Peripheral blood revealed leukopenia with circulating blasts. Another bone marrow aspirate and biopsy showed that the marrow was hypoplastic, with myeloid maturation arrest and an increased number of blasts. A diagnosis of myelodysplasia with excess blasts was made. Flow cytometry confirmed the presence of increased myeloid blasts consistent with acute myelogenous leukemia (AML) of the M1 subtype, according to the FAB classification. A repeat bone marrow on Study Day 280 revealed 33% blasts, consistent with AML of the M0 subtype. Peripheral blood counts on Study Day 280 revealed a WBC of 2000 cells/mm³, with 6% neutrophils, 1% bands, 22% lymphocytes, and 70% blasts. The investigator and the sponsor concur that the AML was related to the heavy exposure to prior alkylator therapy, as evidenced by the hypoplastic marrow prior to study entry and the occasional presence of blasts in the peripheral blood 28 days following therapy with ZEVALIN therapeutic regimen.

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**Frequency of Common and Notable
Non-Hematologic AEs by Subject (N=57 Subjects)**

AE (all grades)	%
Asthenia	77
Nausea	40
Chills	28
Fever	26
Abdominal Pain	21
Diarrhea	19
Headache	19
Dyspnea	18
Increased Cough	18
Irritation Throat	18
Pain	16
Anorexia	14
Vomiting	14
Ecchymosis	12
Infection	12
Myalgia	11
Arthralgia	9
Dizziness	9
Pruritus	9
Peripheral edema	7
Abdominal Enlargement	5
Hypotension	5
Rash	5
Flushing	4
Allergic reaction	2
Angioedema	2
Anxiety	2

Human Anti-Chimeric Antibody (HACA) Response:

No subject developed HACA during the study.

2/57 subject (3.5%) had a detectable HACA prior to treatment.

- Subject 106-06-003-028 had a HACA level of 30.6 ng/mL on Study Day -29 that was not detectable on Study Day -13. Following ZEVALIN therapeutic regimen a PR was achieved. The subject did not experience any Grade 3 or 4 AEs, or any SAEs.
- Subject 106-06-012-018 had a HACA level of 44.7 ng/mL on Study Day -4, 159,500 ng/mL on Study Day 37, and 41,800 ng/mL on Study Day 78. Best response was SD. The subject did not experience any Grade 3 or 4 AEs, or any SAEs

Human Anti-Murine Antibody Response

1/57 (2%) subject developed a HAMA response during the study.

- Subject 106-06-001-032, who previously received rituximab on IDEC Study 106-04, had a HAMA level of 29 µg/mL on Study Day 42 and 24.7 µg/mL on Study Day 101. This patient achieved a CR, and did not experience any study-related AEs.

Hematologic Adverse Events

For all hematologic adverse events, duration of Grade ≥ 3 toxicity is defined as end date minus start date, where end date and start date are defined relative to the nadir lab value. A patient's end date is defined as the 1st lab test date after the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit. A patient's start date is defined as the most recent lab test date prior to the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit.

Patients not recovered from Grade ≥ 3 toxicity were censored by one of two rules. If a patient had received next anti-cancer therapy, that patient was censored to the date of the most recent lab test prior to receiving next anti-cancer therapy. If the patient had not received next anti-cancer therapy, that patient was censored to the date of the most recent lab test.

ANC

39 of 57 subjects (68%) treated with Y2B8 had Grade 3 or 4 ANC within 90 days of initial therapy

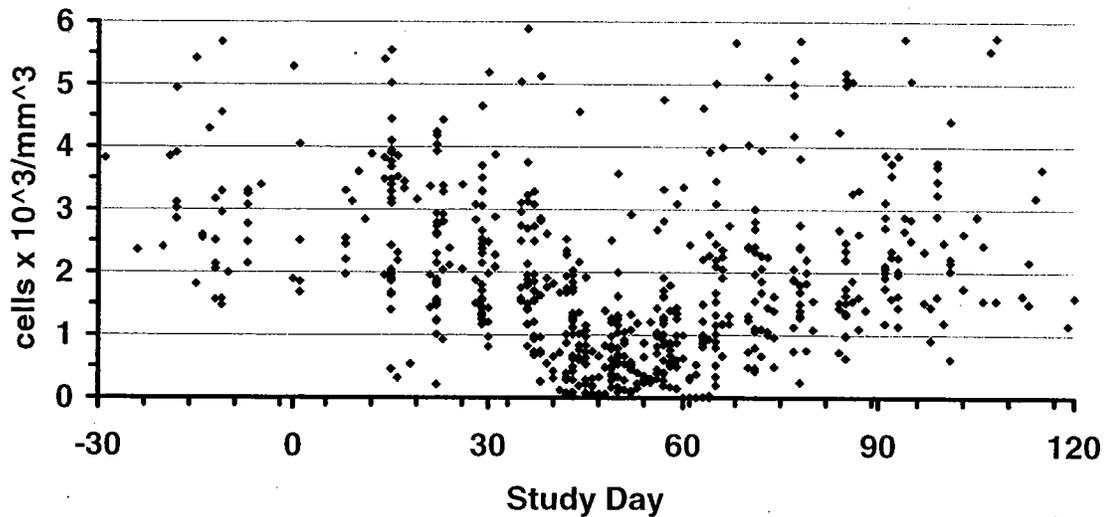
1 Subject failed to have documented ANC recovery.

- 106-06-017-054 never recovered ANC with a 54-day follow-up period. The subject experienced progressive lymphoma on Study Day 36 and went on to hospice care. He died of lymphoma on Study Day 64. Additional laboratory data through Study Day 54 were collected.

Median duration of grade 3-4 neutropenia was 22 days (Range 8-64 days)

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106-06 Subjects With Grade 3-4 ANC
n = 39/57 (68%)



Platelets

43 of 57 subjects (75%) treated with Y2B8 had Grade 3 or 4 thrombocytopenia within 90 days of initial therapy

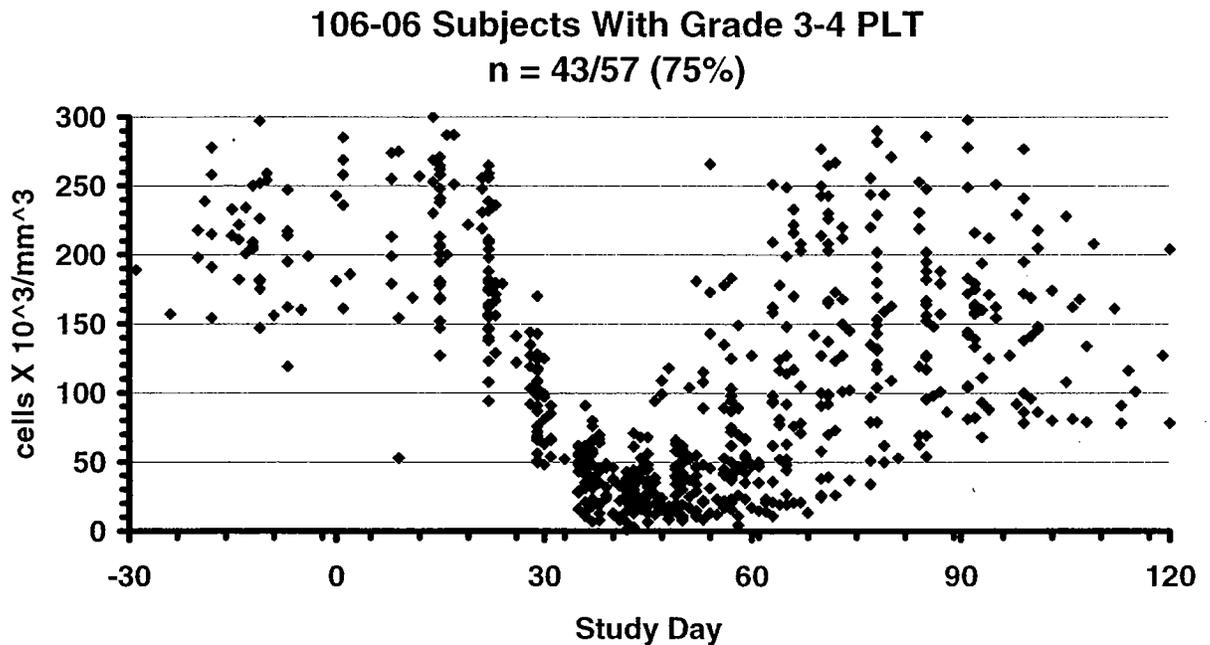
2 subjects failed to have documented platelet recovery.

- 106-06-017-021 never recovered PLT with a 37-day follow-up period. The subject experienced progressive lymphoma on Study Day 35 and received cyclophosphamide/doxorubicin/vincristine/dexamethasone/ etoposide chemotherapy beginning Study Day 37. Weekly laboratory data through Study Day 35 were included in the original submission.
- 106-06-017-054 never recovered PLT with a 54-day follow-up period. The subject experienced progressive lymphoma on Study Day 36 and went on to hospice care. He died of lymphoma on Study Day 64. Additional laboratory data through Study Day 54 were collected.

Subjects with clinically significant AEs.

- 2 subjects had Grade 1 bleeding gums (106-06-012-018, 106-06-017-022)
- 2 had rectal bleeding (1 Grade 1 and 1 Grade 2) (106-06-002-007, 106-06-017-029)
- 2 had vaginal bleeding (1 Grade 1 and 1 Grade 3) (106-06-001-031, 106-06-014-033)
- 1 had subdural hematoma (106-06-001-031)
- 4 had petichae (2 Grade 1 and 2 Grade 2) (106-06-003-013, 106-06-014-019, 106-06-033-025, 106-06-040-051)

Median duration of grade 3-4 thrombocytopenia was 24 days (Range 7-53 days)



Immunologic Reconstitution

Quantitative B-cells

The median absolute B-cell count declined after treatment onset. Recovery started by 6 months post-treatment, and median counts returned to the normal range by 9 months post-treatment.

Quantitative Serum Immunoglobulins

51 subjects had values tested at baseline

Mean IgG, IgM, and IgA levels remained within the normal range throughout the treatment period and follow up.

- 2 subjects had a Grade 3 nadir (< 275 mg/dL) in serum IgG level.
- 3 subjects had a Grade 3 nadir (< 22.5 mg/dL) in serum IgM level.
- 3 subjects had a Grade 3 nadir (< 30 mg/dL) in serum IgA level.

Deaths within Study Day 100

Subject 106-06-017-054 is a 71-year-old male with large-cell NHL, diagnosed in

The subject received ZEVALIN therapeutic regimen on CT scans obtained on Study Day 36 showed disease progression within the abdomen. A follow up CT scans done on Study Day 54 demonstrated worsening disease. On Study Day 62, the subject had an ANC of 1000 cells/mm³, a Hct of 28%, and a platelet count of 32,000/mm³, which was up from a nadir of 16,000/mm³. The subject received hospice care and died on Study Day 64. No autopsy was performed.

Subject 106-06-001-031 was a 69-year-old female with follicular NHL diagnosed in previously treated with total body irradiation, CVP, etoposide/doxorubicin/prednisone, chlorambucil, and rituximab. She also had a history of deep vein thrombosis (DVT). The subject was taking intermittent ibuprofen and warfarin (2.5 mg alternating with 5 mg) because of a history of DVT. She received ZEVALIN therapeutic regimen on _____. On Study Day 49 _____, the subject fell at home and struck her head, resulting in a headache (Grade 3). Two days later on Study Day 51 _____ she was hospitalized with confusion and was found to have ecchymosis (Grade 3) and subdural hematomas. Platelet count was 25,000 cells/mm³ and hemoglobin level was 7.5 g/dL. She received platelet, RBC, and cryoprecipitate transfusions. While hospitalized, she developed bilateral pulmonary infiltrates, pneumonia (Grade 4), and adult respiratory distress syndrome (Grade 4) requiring intubation. She also experienced bowel obstruction (Grade 3), uterine bleeding (Grade 3), kidney failure (Grade 4), and liver failure (Grade 4). She developed signs of worsening sepsis (Grade 4) with high fevers (Grade 3), tachycardia (Grade 2), hypotension (Grade 3), and progressive skin mottling in her extremities. The subject subsequently developed encephalopathy (Grade 3) complicated by seizure activity (Grade 3). She died on Study Day 70 _____. The event of thrombocytopenia was considered probably related to the study drug by the principle investigator and sponsor. An autopsy was not performed.

Conclusions

1. The primary ORR objective for ZEVALIN therapeutic regimen was achieved.
 - The prospectively defined targeted ORR was 35% in subjects with follicular histology who were refractory to RITUXAN.
 - ZEVALIN therapeutic regimen induced responses (ORR: 59%) in relapsed or refractory, follicular (IWF B, C, D; also defined as REAL classification Follicular center grade I, II, and III) B-cell NHL subjects whose disease was refractory (TTP < 6 months) to previous treatment with rituximab.
2. ZEVALIN therapeutic regimen resulted with a longer DR to that achieved with prior RITUXAN (7.7 vs. 4.0 months).
3. Median duration of Grade \geq 3 neutropenia within 90 days of ZEVALIN therapeutic regimen was 22 days for 68% of subjects.
4. Median duration of Grade \geq 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen was 24 days for 75% of subjects

BIODISTRIBUTION AND RADIATION DOSIMETRY

INTRODUCTION

Prior to the administration of Y-90-2B8 therapy, the clinical sites performed a biodistribution imaging study for each subject. The biodistribution study, performed with In-111-2B8, resulted in whole body images at five time points. Based on the biodistribution study, the clinical sites determined the normal organ dosimetry for the subject. To allow the therapeutic administration, the normal organ dosimetry findings were required to be consistent with the eligibility criteria (maximum allowable absorbed radiation dose to organs: 2,000 cGy for normal organs and 300 cGy for red marrow).

To provide a standardized methodology for the normal organ dosimetry and tumor dosimetry, the Mayo Clinic and the Oak Ridge Associated Universities (ORAU) accomplished a central analysis of the normal organ dosimetry from the controlled trials (106-03, 106-04, 106-05, and 106-06). The centralized analyses of the normal organ dosimetry results for 179 patients, as well as the tumor dosimetry for 57 selected tumor sites, were submitted to the BLA.

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

- A review of the imaging findings from the biodistribution imaging studies with In-111-2B8
- Analyzed and recalculated the submitted normal organ dosimetry for Y-90-2B8
- Analyzed and recalculated the submitted normal organ dosimetry for In-111-2B8
- Analyzed and recalculated the submitted tumor dosimetry

At Risk - Worst Case Assessments

In support of the biodistribution and dosimetry review, the following three "worst case" analyses have been performed:

ASSESSMENT OF ADJACENT STRUCTURES AT RISK.

The path-length of Yttrium-90 is 5 mm and the energy is 2.3 MeV. Normal structures adjacent to tumor sites will have absorbed radiation from the tumor sites. The dosimetry evaluations of selected tumor sites have demonstrated one tumor site with an estimated radiation absorbed dose of 24,254 cGy. Six radiation absorbed dose estimates have been analyzed for the presence of such a tumor site in various anatomical locations.

ALTERATION IN BIODISTRIBUTION OF THE RADIOLABELED ANTIBODY.

The presence of an immune response, e.g., HAMA, HACA, may alter the biodistribution of a radiolabeled antibody. A large colloid model has been utilized to estimate the normal organ dosimetry of Y-90-2B8 with an altered biodistribution.

OBSTRUCTED ROUTE OF RENAL/URINARY TRACT CLEARANCE PATHWAY.

The stated route of clearance for Y-90-2B8 is renal/urinary tract. Based on renal obstruction, the normal organ dosimetry has been estimated.

DESIGN OF THE BIODISTRIBUTION IMAGING AND ORGAN DOSIMETRY

The therapy radioisotope, Yttrium-90, is essentially a pure beta emitter. Yttrium-90 is not an imaging agent for biodistribution imaging, normal organ dosimetry and tumor dosimetry quantification. Indium-111 is the surrogate diagnostic radiolabel for Y-90 and it is assumed that the biodistribution of the therapeutic Y-90-2B8, and the diagnostic In-111-2B8 are essentially identical.

Whole Body Biodistribution Imaging

On day 0, subjects received 250 mg/m² rituximab immediately followed by 5 mCi ¹¹¹In-2B8 for biodistribution imaging and dosimetry evaluation.

The nuclear medicine camera acquired whole body images with a medium energy collimator with photopeak settings at 172 and 247 keV and a 15% window.

Serial anterior and posterior whole body images were collected at each of five imaging time points in a 256 by 1024 matrix.

Time Points Evaluated

The whole body biodistribution imaging time points were scheduled as the follows:

1. 0.5 hours
2. 4 hours
3. 24 hours
4. 72 hours
5. 144 hours

Subject Population

IDEC has submitted normal organ dosimetry findings for 179 patients to the BLA. The submitted subjects are from four clinical trials.

TABLE: NORMAL ORGAN DOSIMETRY – SUBJECT POPULATION

Clinical Trial	Subjects Enrolled	Subjects Submitted for Dosimetry Evaluation
106-03	58	50
106-04	73	72
106-05	30	30
106-06	57	27

Electronic Submission

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

BIODISTRIBUTION IMAGING FINDINGS

Biodistribution Imaging – Normal Organs

In the biodistribution imaging, the normal organs are visualized by having uptake of In-111-2B8 in the organ greater than the adjacent whole body background activity.

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

LIVER AND SPLEEN

The imaging of the liver and spleen demonstrate an intense and uniform uptake pattern seen commonly with diagnostic ¹¹¹In-radiolabeled antibodies. Excellent anatomical details are seen for both organs.

BONE MARROW

The bone marrow compartment is well seen in the expected distribution of the red marrow in adults. In many patients there appears to be active uptake of the In-111-2B8 in the expected regions of the yellow marrow in adults. In multiple patients, the bone marrow imaging demonstrated patchy areas of increased localization, suggesting possible imaging of NHL bone marrow involvement.

TESTES

Imaging of the testes is remarkable for the intensity and the uniformity of the radiotracer localization (equivalent to the spleen). No asymmetry of the testes or focal localization to suggest imaging of occult, focal NHL was identified. Correlation with the pre-clinical human tissue binding studies notes no known normal tissues in the testes targeted by the 2B8 antibody. No follow up laboratory evaluation of testicular function has been performed in the controlled trials.

KIDNEY, URINARY BLADDER

The kidneys and urinary bladder are well defined by In-111-2B8. The urinary bladder is variable in its configuration and partially filled with radiotracer, compatible with the urinary tract function as the clearance pathway of the radiolabel. In occasional subjects, elevation of the central region of the urinary bladder is seen, compatible with prostatic enlargement.

BOWEL

IDEC established an independent panel of Nuclear Medicine physicians to assess the 179 biodistribution imaging studies for the presence of bowel imaging. The independent panel found 174 of 179 biodistribution imaging studies to be adequate for assessment of bowel imaging. The independent panel described bowel imaging in 32% (55/174) of the biodistribution imaging studies.

LARGE BOWEL

Variable regions of the large bowel demonstrate well-defined localization of In-111-2B8 in subjects. The localization of In-111-2B8 in the large bowel is commonly seen by 72 hours, and once seen, appears unchanging in its anatomical distribution through the last imaging time point. In many patients, the localization of the radiotracer defines both walls of the large bowel. This imaging of both walls of the large bowel suggests prominent localization in the bowel wall as compared to presence of the radiolabel in the bowel lumen. The imaging of the large bowel is compatible with In-111-2B8 targeting normal sites of lymphoid aggregates in the bowel wall as well as sites of NHL. In addition, the imaging of the large bowel may represent the presence of an occult second clearance pathway in the bowel.

SMALL BOWEL

Variable regions of the small bowel appear to be imaged in patients. The small bowel is less well defined by In-111-2B8 imaging as compared to the imaging of the large bowel. The imaging of the small bowel is commonly seen by 72 hours and once seen, appears unchanging through the last imaging time point.

HEART, LARGE VASCULAR STRUCTURES

The cardiac chambers and major vascular structures demonstrate well-defined localization in the initial imaging with the expected loss of imaging by the 48 to 72 hours imaging. This imaging pattern is compatible with the infusion of In-111-2B8, and the expected clearance of the radiolabeled antibody from the vascular space.

LUNG FIELDS

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

Biodistribution Imaging – Tumor Sites

Many imaged tumor sites are seen and have well-defined localization of In-111-2B8. Many tumor sites are of greater imaging intensity in the localization of In-111-2B8 as compared to the normal organs.

Biodistribution Review Comments

In-111-2B8 whole body biodistribution imaging provides diagnostic quality whole body images at the five time points. Excellent definition of the liver, spleen, testes, bone marrow, kidneys, urinary bladder, large bowel, heart and major vascular structures has been demonstrated in the submitted whole body images from the controlled clinical trials.

The biodistribution imaging with In-111-2B8 provides supportive information for the safe administration of Y-90-2B8 as follows:

The biodistribution images confirm the presence of the expected pattern of In-111-2B8 in the normal organs. An alteration in the biodistribution in normal organs suggests the presence of one or more of the following conditions:

- Immune response, e.g., HAMA, HACA.
- Organ dysfunction, e.g., urinary tract obstruction.
- Improper preparation of the In-111-2B8 imaging agent.
- Presence of occult NHL.

The biodistribution images establish the “normal structures at risk” due to the radiation absorbed dose exposures from adjacent tumor sites.

In addition, the performance of the biodistribution imaging allows the following:

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

NORMAL ORGAN DOSIMETRY

In the multiple controlled clinical trials supporting the BLA, IDEC has utilized In-111-2B8 for biodistribution imaging, which is the basis for the determination of the normal organ dosimetry for Y-90-2B8.

In-111-2B8 biodistribution whole body imaging at five time points was completed for the controlled clinical trials (106-03, 106-04, 106-05, and 106-06). From these whole body biodistribution images, the residence times in the normal organs for the radiolabeled antibody, $^{111}\text{In}/^{90}\text{Y}$ -2B8, was determined by assigning regions of interest for each visualized organ. Based on the residence times, the normal organ dosimetry was estimated by the MIRDOSE software.

Organs To Be Evaluated By Time Activity Curves

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

Subject Population and Regions of Interest

For 15 patients randomly selected from the 179 patients submitted with normal organ dosimetry, IDEC has evaluated the following listed organs/tissues and total body activity:

1. Total Body
2. Blood
3. Heart
4. Lung
5. Liver
6. Small Intestine
7. Large Intestine
8. Spleen
9. Testes
10. Kidneys

11. Sacrum (Bone Marrow)

Route of Excretion

IDEC assumed the only excretion route is through the urinary tract. Therefore, IDEC has elected to estimate urinary excretion as equal to 100% of administered activity minus the whole body retained radioactivity as determined by the whole body biodistribution imaging. No assessment for gastrointestinal clearance was performed.

CBER Review Comment:

CBER's review of the whole body biodistribution images demonstrates localization of the radiotracer in both the small and large bowel in patients. The biodistribution findings over multiple time points suggests fixed localization to the bowel wall rather than a changing pattern of activity to suggest clearance passage in the lumen.

The pre-clinical human tissue binding studies establish that $^{111}\text{In}/^{90}\text{Y}$ -2B8 will localize in lymphoid aggregates in the bowel wall as well as non-Hodgkin's lymphoma (NHL). Therefore, the source of this activity in the bowel may be attributable to localization of In-111-2B8 in NHL and/or lymphoid aggregates in the bowel wall.

However, IDEC has not provided evaluations of stool collections to establish the presence or absence of bowel clearance. Therefore, the possible contribution of activity in the bowel lumen from a second route of clearance in the bowel has not been ruled out. Thus, IDEC's dosimetry study results are indeterminate to document all possible routes of clearance.

If determined to be clinically significant, IDEC should perform future dosimetry study evaluations for fecal clearance of the radiolabel to determine if a second route of clearance is present.

Image Quantification

Image quantification determines the time activity curves for In-111-2B8 in the various organs/tissues for the dosimetry determination. This section provides the following:

A review of the image quantification methods utilized by IDEC.

CBER performed comparison studies for three patients based on IDEC's quantification methods.

IDEC METHODOLOGY FOR IMAGE QUANTIFICATION

- On day 0, subjects received 250 mg/m² rituximab immediately followed by 5 mCi ¹¹¹In-2B8 for biodistribution and dosimetry evaluation.
- Serial anterior and posterior whole body images were collected at each of 5 imaging time points in a 256 by 1024 matrix. Images were acquired using a medium energy collimator with the nuclear medicine camera photopeak settings of 172 and 247 keV with a 15% window.
- Based on the whole body images, regions of interest (ROIs) were selected and drawn around specified organs/tissues, e.g., whole body, lungs, liver, spleen, kidneys, sacrum, upper large intestine (ULI), lower large intestine (LLI), small intestine (SI), heart, and testes.
- Activity in each organ/tissue selected by a region of interest at each time point (activity is expressed as percent of [administered] injected activity) was determined by the following:

Taking the geometric mean of the anterior and posterior counts in each organ ROI and dividing by the geometric mean of the whole body counts ROI.

The use of the geometric mean is intended to account for attenuation by body structures of the radioactive emissions. To improve the precision of this process, consistent camera settings were assured through the use of a known activity standard with the imaging.

As an example of the use of the geometric mean, the percent of the injected activity in liver at some time point x is found as follows:

Posterior counts in liver ROI at time x = 9,000
 Anterior counts in liver ROI at time x = 10,000
 Geometric mean of anterior and posterior liver ROI counts at time x. = 9487

Where Geometric Mean (GM) of A and B is:

$$GM = (A \cdot B)^{\frac{1}{2}}$$

Posterior whole body ROI counts at first image time = 1,000,000
 Anterior whole body ROI counts at first image time = 1,100,000
 Geometric mean of anterior and posterior whole body ROI counts at first image time. = 1,048,808
 Percent Injected activity in liver at time x = 9487 / 1,048,808 = 0.009 or 0.9%

This example assumes the whole body scan times were identical.

The baseline CT scan was used to determine patient-specific spleen and liver mass corrected doses for the central dosimetry evaluations.

The initial estimates of radiation absorbed dose were made at the clinical sites, prior to the administration of Y-90-2B8. Subsequently, the Mayo Clinic and the Radiation Internal Dose Information Center, Oak Ridge Institute of Science and Education (ORISE) performed centralized dosimetric analyses of all patients.

CBER Review Comment:

This methodology is assumed to yield reasonable results for most organs. However, for regions such as lungs, which have a higher transmission factor than soft tissue, the IDEC methodology is considered to likely overestimate the activity. Thus the IDEC dosimetry estimates for lungs are likely overestimates. For regions involving thick bone components, such as sacrum (bone marrow), the IDEC methodology would likely result in an underestimate of activity. For testes, with reduced overlying tissue as compared to the adjacent abdominal region, the methodology may result in an overestimation of the absorbed radiation dose.

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CBER EVALUATION OF IMAGE QUANTIFICATION

In the image quantification evaluation, CBER emulated IDEC's regions of interest for the organs and utilized the same methodology for image quantification as that used by IDEC.

Planar image data from two patients (106-04-003-215 and 106-04-007-250) were selected. CBER drew regions of interest around the liver, spleen, kidneys, and lungs, which demonstrated visible uptake of In-111-2B8 as compared to the whole body background activity.

Patient 106-04-003-215

**TABLE: PERCENT-INJECTED DOSE RESULTS COMPARISON
IDEC results/CBER results**

Organ		Time Points (hours)				
		0.5	4	24	72	142
RATIO IDEC CBER	Whole Body	97.1/100	94.2/98.5	74.6/78.6	43.2/44.9	16.1/17.1
	Liver	11.6/9	11.6/9.6	9.5/6.5	5.7/4.4	2.3/1.8
	Spleen	3.0/2.4	3.1/1.9	2.5/1.3	1.5/0.8	0.6/0.4
	Kidneys	0.3/1.8	0.3/1.2	0.3/1.0	0.1/0.4	0.1/0.2
	Lungs	5.5/3.5	5.3/3.9	3.9/1.9	1.9/1.1	0.7/0.6

Percent-injected dose results comparison

**TABLE: % RATIO OF IDEC RESULTS TO CBER RESULTS
(IDEC value/CBER value)**

Organ		Time Points (hours)				
		0.5	4	24	72	142
RATIO IDEC CBER	Whole Body	0.97	0.96	0.95	0.96	0.95
	Liver	1.30	1.21	1.46	1.31	1.28
	Spleen	1.24	1.61	1.94	1.75	1.44
	Kidneys	0.14	0.25	0.33	0.19	0.30
	Lungs	1.60	1.36	1.99	1.72	1.15

Patient 106-04-007-250**TABLE: PERCENT-INJECTED DOSE RESULTS COMPARISON
IDEC results/CBER results**

Organ		Time Points (hours)				
		0.5	4	24	72	142
RATIO	Whole Body	99/100	93/97	76/75	42/44	20/21
	Liver	15.6/14.4	14.8/13.4	13.7/11.4	9.1/7.9	4.3/3.7
IDEC / CBER	Kidneys	1.3/1.9	1.1/1.9	1.1/2.3	0.6/0.9	0.3/0.5
	Lungs	6.3/5.6	6.3/4.8	4.7/3.9	2.2/1.5	1.1/0.5

Percent-Injected Dose Results Comparison**TABLE: % RATIO OF IDEC RESULTS TO CBER RESULTS
(IDEC value/CBER value)**

Organ		Time Points (hours)				
		0.5	4	24	72	142
RATIO	Whole Body	0.99	0.96	1.01	0.95	0.95
	Liver	1.08	1.10	1.20	1.15	1.16
IDEC / CBER	Kidneys	0.68	0.58	0.48	0.67	0.60
	Lungs	1.13	1.31	1.21	1.47	2.20

IDEC submitted image quantification results for testes, small intestine, upper large intestine, lower large intestine, sacrum (bone marrow), and heart contents. In this evaluation, CBER emulated IDEC's regions of interest for these organs and utilized the same methodology for image quantification as that used by IDEC.

CBER's analysis of IDEC's methodology for image quantification notes IDEC had not utilized background subtraction. IDEC's approach, as compared to the use of background subtraction, will produce a significant difference with reported higher estimated percent injected doses to these organs. For comparison purposes, CBER has calculated the percent injected doses in the organs/tissues without background subtraction.

Patient 106-04-001-116**TABLE: PERCENT INJECTED DOSE (WITHOUT BACKGROUND SUBTRACTION APPLIED)
IDEC results/CBER results.**

Organs	Time Points (hours)					
	0.45	4.07	19.2	66.7	163.7	
RATIO IDEC / CBER	Heart	8.6/8.3	7.4/7.3	6.2/6.6	3.7/4.9	2.6/3.2
	Small Intestine (SI)	2.3/3.7	2.1/3.3	2.1/3.4	1.8/2.7	1.4/2.6
	Upper Large Intestine (ULI)	2.7/3.1	2.5/2.7	2.7/2.6	2.3/2.1	1.7/1.7
	Lower Large Intestine (LLI)	2.6/1.5	2.3/1.4	2.3/1.3	1.9/1.0	1.4/0.9
	Testes	1.8/1.2	1.5/0.8	1.1/0.7	0.7/0.3	0.5/0.3
	Sacral Marrow	0.8/0.7	0.7/0.7	0.6/0.8	0.3/0.6	0.1/0.5

TABLE: % RATIO OF PERCENT INJECTED DOSE (WITHOUT BACKGROUND SUBTRACTION APPLIED)**Ratio of IDEC results to Reviewer results (IDEC value/Reviewer value)**

Organs	Time (hours)					
	0.45	4.07	19.2	66.7	163.7	
RATIO IDEC / CBER	Heart Contents	1.0	1.0	0.9	0.8	0.8
	SI	0.6	0.6	0.6	0.7	0.5
	ULI	0.9	0.9	1.0	1.1	1.0
	LLI	1.7	1.7	1.8	1.8	1.6
	Testes	1.5	1.9	1.6	2.3	1.7
	Sacral Marrow	1.1	1.0	0.7	0.5	0.2

CBER Review Comment

Based on the results of two patients (106-04-003-215 and 106-04-007-250) the results of IDEC and CBER for whole body, liver, spleen, lungs, and kidney are very similar and considered within expected limitations of the assessment methodology.

For the 3rd patient (106-04-001-116), heart contents, SI, ULI, LLI, sacral marrow, and testes results were compared. CBER performed the evaluation without background subtraction and with IDEC's ROIs. CBER's results were similar to IDEC's results.

KINETIC MODELING

This section describes the methods IDEC has utilized to determine the organ/tissue residence times for the radiolabeled antibody from the time activity source data obtained from the following:

- 1) Whole body imaging
- 2) Excreta sampling
- 3) Blood sampling

Mathematical Models Used By IDEC To Estimate Organ Residence Times

ORGAN RESIDENCE TIMES

All quantified organs/tissues (whole body, blood, liver, spleen, lung, kidneys) were determined by curve fitting the collected data with sums of exponentials and integrating the resulting functions.

URINE RESIDENCE TIMES

Urine residence times were found using the parameters of the whole body fits to determine the biological half-life (lives) of excretion. A 4.8 hours voiding bladder model was then applied to the integration process.

CBER Review Comment

If significant activity was removed from the body via the gastrointestinal tract, the bladder wall absorbed doses determined by IDEC are likely overestimates.)

RED MARROW RESIDENCE TIMES

Red marrow residence times were determined using sacral marrow regions of interest. The blood data and the methodology described by Squoros [J Nucl Med 1993;34:689-694] has also been submitted to the BLA, but set aside in the final review of the normal organ dosimetry. The Squoros model involves curve fitting the blood data using sums of exponentials and assumes that bone marrow activity is proportional to blood activity.

CBER Review Comment

The Squoros methodology is appropriate for the estimation of bone marrow radiation exposure only when the administered radiolabeled agent has no specific localization in the bone marrow space and/or its elements. The radiolabeled anti-CD20 antibody ($^{111}\text{In}/^{90}\text{Y}$ -2B8) targets both benign lymphoid tissues and NHL. The evaluated BLA subject population has normal lymphoid tissues and tumor, NHL, present in the bone marrow. Indeed, the inclusion criteria allowed patients with up to 25% bone marrow replacement by NHL, which is targeted by the radiolabeled antibody, $^{111}\text{In}/^{90}\text{Y}$ -2B8. Therefore, the Squoros methodology is an inappropriate bone marrow dosimetry model for $^{111}\text{In}/^{90}\text{Y}$ -2B8 in subjects with NHL.

REMAINDER OF BODY RESIDENCE TIMES

Remainder of body residence times was determined by subtracting the organ residence times from the whole body residence times. After the last time point imaged, the time-activity curve was assumed to continue to follow the mathematical fit that was determined using the data collected. (sums of exponentials).

CONSERVATION OF ACTIVITY

To insure the model accounts for 100% of the injected activity at all times (that is, it conserves activity), the dosimetry model uses whole body imaging with the determination of remainder of body residence times by subtracting organ residence times from whole body residence times.

DOSIMETRY METHODS

Dosimetry Methods: Dosimetry estimates were based on the following:

- ❖ Residence times as described in the Kinetic Modeling section
- ❖ MIRDOSE 3.1 software
- ❖ S-values Source: MIRDOSE 3.1 software

DOSIMETRY RESULTS

This section displays and compares IDEC's and CBER's results of the MIRDOSE software estimation of the radiation absorbed doses using the residence times described in the Kinetic Modeling section. The results obtained by CBER in this section are based on

the time-activity data submitted to the BLA by IDEC. The differences are compatible with the smaller sample (6 patients) used by CBER for the comparison.

Y-90-2B8 Dosimetry

TABLE: Y-90-2B8 NORMAL ORGANS ABSORBED RADIATION DOSES IN cGy/mCi

Organs/Tissues	Source of Data for Dosimetry	IDEC cGy/mCi	Range	CBER cGy/mCi	Range	IDEC/ CBER
Adrenals	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Brain	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Breasts	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Gallbladder Wall	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Lower Large Intestine (LLI) Wall	Organ ROI	11.5	(6.8-18.3)	11.5	(8.0-14.6)	1.00
Small Intestine (SI)	Organ ROI	4.3	(2.4-6.3)	4.1	(2.4-5.0)	1.05
Stomach	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Upper Large Intestine (ULI) Wall	Organ ROI	7.0	(3.7-12.1)	6.6	(3.8-9.0)	1.06
Heart Wall	Organ ROI	9.6	(5.5-11.9)	8.9	(5.6-11.0)	1.08
Kidneys	Organ ROI	0.4	(0.0-0.8)	0.2	(0.0-0.8)	1.84
Liver	Organ ROI	20.0	(8.4-29.9)	17.1	(10.9-27.5)	1.17
Lungs	Organ ROI	7.1	(4.3-12.4)	6.2	(4.5-8.0)	1.13
Muscle	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Ovaries	Whole Body ROI	1.4	(1.3-1.7)	1.1	(0.7-1.3)	1.29
Pancreas	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Red Marrow	Sacrum ROI	4.7	(2.6-6.8)	2.8	(2.2-3.3)	1.69
Bone Surfaces	Sacrum ROI	3.3	(1.8-4.3)	2.2	(1.8-2.4)	1.50
Skin	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Spleen	Organ ROI	35.0	(6.7-53.2)	42.2	(24.4-74.0)	0.83
Testes	Organ ROI	33.1	(19.9-42.3)	29.7	(1.2-37.7)	1.11
Thymus	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Thyroid	Whole Body ROI	1.0	(0.1-1.7)	1.1	(0.7-1.3)	0.93
Urinary Bladder Wall	Whole Body ROI	3.9	(2.6-7.8)	3.2	(2.8-3.5)	1.21
Uterus	Whole Body ROI	1.4	(1.3-1.7)	1.1	(0.7-1.3)	1.29
Total Body	Whole Body ROI	1.9	(0.7-2.6)	1.9	(1.8-2.0)	1.04

* All excretion assumed to be urinary. Whole body fits were used to determined excretion parameters.

In-111-2B8 Dosimetry

Dosimetry for In-111 was determined by CBER for 6 patients and compared to the results reported by IDEC. CBER's results were based on the kinetic data as provided by IDEC. The absorbed doses found by CBER were similar to those found by IDEC.

TABLE: IN-111-2B8 NORMAL ORGANS RADIATION ABSORBED DOSES IN cGy/mCi

Organs/Tissues	Source of Data for Dosimetry	IDEC cGy/mCi	Range	CBER cGy/mCi	Range	IDEC/ CBER
Adrenals	Whole Body ROI	0.8	(0.4-1.0)	0.7	(0.7-0.9)	1.06
Brain	Whole Body ROI	0.2	(0.0-0.3)	0.2	(0.2-0.3)	0.97
Breasts	Whole Body ROI	0.3	(0.1-0.4)	0.3	(0.3-0.3)	1.02
Gallbladder Wall	Whole Body ROI	1.1	(0.5-1.4)	1.0	(0.8-1.3)	1.07
LLI Wall	Organ ROI	1.1	(0.7-1.8)	1.1	(0.8-1.3)	1.03
Small Intestine	Organ ROI	0.8	(0.4-1.1)	0.7	(0.6-0.8)	1.05
Stomach	Whole Body ROI	0.6	(0.3-0.8)	0.6	(0.5-0.7)	0.99
ULI Wall	Organ ROI	1.0	(0.7-1.6)	1.0	(0.8-1.2)	1.07
Heart Wall	Organ ROI	1.4	(0.9-1.7)	1.3	(0.9-1.5)	1.09
Kidneys	Organ ROI	0.6	(0.3-0.7)	0.6	(0.5-0.6)	1.05
Liver	Organ ROI	2.7	(1.2-4.0)	2.4	(1.6-3.7)	1.14
Lungs	Organ ROI	0.9	(0.5-1.4)	0.8	(0.8-0.9)	1.12
Muscle	Whole Body ROI	0.4	(0.1-0.5)	0.4	(0.3-0.4)	1.00
Ovaries	Whole Body ROI	0.7	(0.6-0.8)	0.6	(0.4-0.6)	1.35
Pancreas	Whole Body ROI	0.9	(0.5-1.1)	0.9	(0.7-1.0)	1.00
Red Marrow	Sacrum ROI	0.6	(0.4-0.8)	0.5	(0.5-0.5)	1.29
Bone Surfaces	Sacrum ROI	0.7	(0.3-0.9)	0.6	(0.5-0.6)	1.13
Skin	Whole Body ROI	0.2	(0.1-0.3)	0.2	(0.2-0.2)	0.97
Spleen	Organ ROI	3.2	(0.8-4.6)	3.8	(2.4-6.5)	0.84
Testes	Organ ROI	2.3	(1.4-3.0)	2.0	(0.3-2.6)	1.18
Thymus	Whole Body ROI	0.5	(0.3-0.6)	0.5	(0.4-0.5)	1.02
Thyroid	Whole Body ROI	0.3	(0.0-0.4)	0.3	(0.2-0.3)	0.92
Urine Bladder Wall	Whole Body ROI	0.6	(0.5-0.8)	0.6	(0.5-0.6)	1.09
Uterus	Whole Body ROI	0.6	(0.5-0.7)	0.5	(0.4-0.5)	1.28
Total Body	Whole Body ROI	0.5	(0.2-0.6)	0.4	(0.4-0.5)	1.03

Selected Tumor Dosimetry

The following tables (data reported in two consecutive tables due to size/space limitation) display the tumor radiation absorbed doses as determined by IDEC. The tumor dosimetry is listed in order of highest absorbed dose to lowest absorbed dose for tumors. Following these tables is a log-log scatter plot of absorbed dose vs. mass.

TABLE: TUMOR DOSIMETRY TABLE WITH TUMOR MASS AND LOCATION

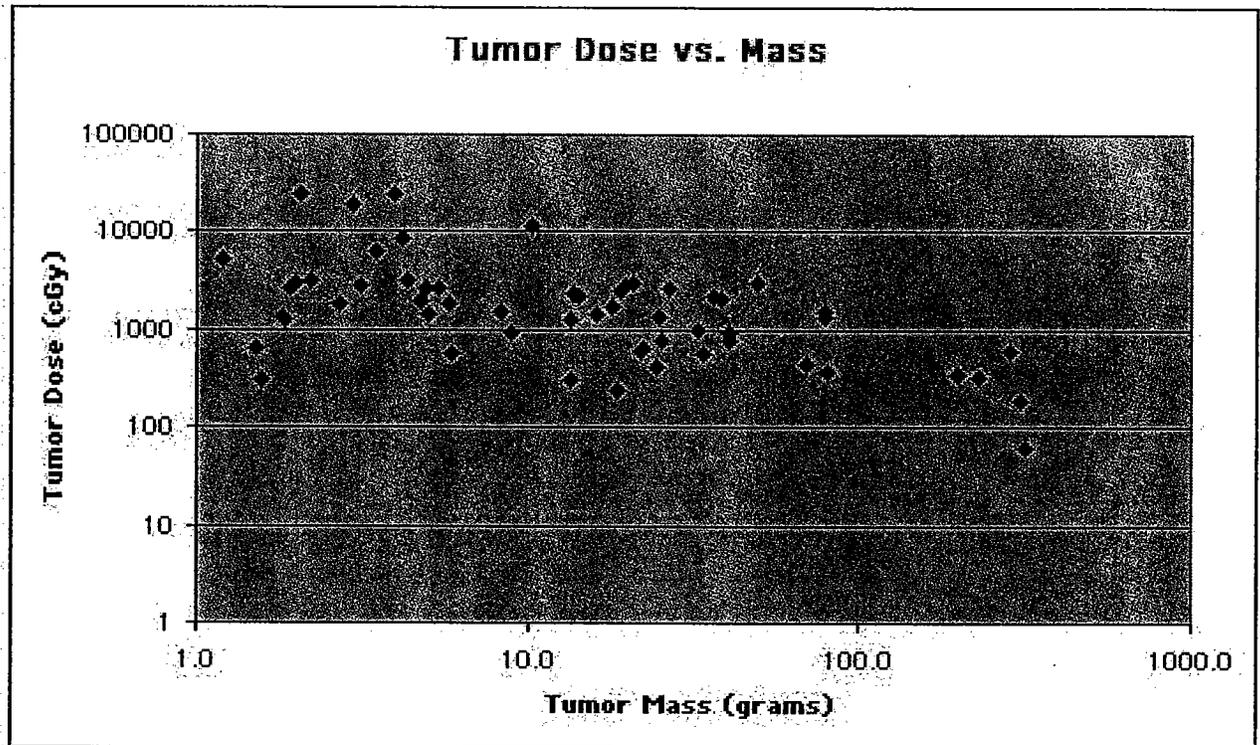
	Patient Number	Tumor Location	Tumor Mass (grams)	Tumor Dose (cGy)
1	10604020411	R. Lung	4.0	24274
2	10604001252	Neck	2.1	23766
3	10604001293	Abdomen	2.9	19200
4	10604001204	Abdomen	10.2	11814
5	10604001303	Neck	4.2	8696
6	10603002305	L. Lumbar Spine	3.5	6363
7	10603008302	Neck	1.2	5073
8	10604001106	Abdomen	4.3	3231
9	10604002246	L. Neck	2.2	3136
10	10604001279	Abdomen	20.9	2996
11	10603009335	L. Neck	2.0	2993
12	10604001300	Abdomen	49.1	2940
13	10604014111	R. Inguinal	3.1	2893
14	10603007212	L. Neck	19.6	2755
15	10604001208	L. Chest	5.4	2688
15	10604001208	Abdomen	26.8	2624
17	10604007250	R. Axilla	1.9	2615
18	10604023277	L. Submandibular	4.9	2608
19	10603002333	L. Groin	18.9	2462
20	10604001279	Upper Chest	13.6	2352
21	10603002333	R. Groin	14.1	2240
22	10603002210	R. Lumbar Spine	36.2	2179
23	10603002210	L. Lumbar Spine	38.2	2121
24	10603009335	R. Neck	4.7	1989
25	10604002101	L. Sub Axilla	5.7	1879
26	10604002101	L. Internal Axilla	2.7	1879
27	10604011239	L. Supraclavicular	17.8	1736
28	10604001291	Abdomen	78.4	1528
29	10604001210	Abdomen	8.3	1484
30	10604001259	Pelvis	16.1	1468
31	10603002205	R. Neck	5.0	1434
32	10604003205	Chest	24.8	1338
33	10603007212	L. Thoracic Spine	79.2	1331
34	10604001105	L. Neck	1.8	1309
35	10604011268	L. Inguinal	1.8	1280
36	10603002333	R. Neck	13.4	1253
37	10604001279	L. Inguinal	32.8	980
38	10603009335	R. Pelvis	40.7	955
39	10604001202	R. Chest	8.9	947

TABLE: TUMOR DOSIMETRY TABLE WITH TUMOR MASS AND LOCATION (CONTINUED)

	Patient Number	Tumor Location	Tumor Mass(grams)	Tumor Dose(cGy)
40	10604001232	Pelvis	25.1	790
41	10603009335	L. Pelvis	40.7	761
42	10604001202	L. Chest	22.1	646
43	10604001105	R. Neck	1.5	638
44	10603002307	Pelvis	284.9	608
45	10603002206	Abdomen	21.8	586
46	10603002333	L. Neck	5.9	578
47	10603002333	Upper Abdomen	33.5	575
48	10604031217	Mesenteric	69.6	448
49	10604001303	Abdomen	24.3	416
50	10604001232	R. Chest	80.8	379
51	10604001300	Pelvis	198.7	357
52	10604001230	Pelvis	227.6	336
53	10604002267	L. Parotid	1.6	306
54	10604029222	R. Axilla	13.4	306
55	10604001202	L. Pelvis	18.7	237
56	10604001407	Abdomen	302.5	192
57	10604001116	Abdomen	317.0	61

Tumor radiation absorbed dose estimates by both IDEC and CBER were obtained using absorbed fractions that were based on the average beta energy emission of Y-90, and the assumption that the tumors could be modeled as spheres for radiation transport purposes.

GRAPH: SCATTER PLOT OF TUMOR ABSORBED DOSE VS. MASS



CBER Review Comment

Review of IDEC's reported tumor dosimetry evaluations notes the tumor mass appears inversely related to the absorbed radiation dose. This trend suggests the possibility of a decreasing estimated radiation exposure to the tumor site as the tumor mass increases in size. However, the evaluated tumor sites are a minority of the imaged tumor sites and may not be representative of the total population of the tumor sites. Furthermore, these tumors were selected in a non-random, uncontrolled manner without a prospectively designed protocol. Therefore, future studies should be considered to evaluate the possible relationships between tumor mass, estimated tumor radiation absorbed dose, and the confirmed response by the tumor site.

CBER'S EVALUATION OF DOSIMETRY FOR 15 SELECTED TUMORS.

CBER has performed a re-evaluation of the absorbed radiation dose estimates for 15 tumors. CBER's dosimetry data are based on the kinetic data, and the tumor mass data provided by IDEC.

	Patient ID	Tumor Location	Tumor Mass grams	IDEC Dose $\mu\text{Gy/mCi}$	CBER Dose $\mu\text{Gy/mCi}$	CBER/IDEC
1	106-04-001-252	Neck	2.1	749	1150	1.54
2	106-04-020-411	R. Lung	4	778	815	1.05
3	106-04-001-279	Abdomen	20.9	107	158	1.48
4	106-04-001-106	Abdomen	4.3	136	142	1.05
5	106-04-011-239	L. Supraclavicular	17.8	80	81	1.01
6	106-04-001-303	Abdomen	24.3	14	63	4.5
7	106-04-001-259	Pelvis	16.1	54	63	1.16
8	106-04-003-205	Chest	24.8	60	53	0.88
9	106-04-001-291	Abdomen	78.4	48	50	1.04
10	106-04-001-202	L. Chest	22.1	30	30	0.99
11	106-04-029-222	R. Axilla	13.4	17	16	0.96
12	106-04-031-217	Mesenteric	69.6	14	15	1.06
13	106-04-001-230	Pelvis	227.6	12	13	1.05
14	106-04-001-300	Pelvis	198.7	13	13	1.03
15	106-04-001-407	Abdomen	302.5	6	6	1.07

CBER Review Comment

For 9 of the 15 tumors, CBER found results within 10% of the results obtained by IDEC, and for 12 of the 15, within 20% of the result found by IDEC. In summary, CBER's results are compatible with IDEC's results.

Tumor radiation absorbed dose estimates by both IDEC and CBER were obtained using absorbed fractions that were based on the average beta energy emission of Y-90, and the assumption that the tumors could be modeled as spheres for radiation

transport purposes. Both of these assumptions are considered conservative, and the assumptions are expected to result in an overestimate of the actual radiation absorbed dose to the tumors.

Absorbed Radiation Dose Depth Profiles For Surrounding Tissues From Theoretical Tumor Models

Given the radiation absorbed doses reported by IDEC in several tumors, and the relatively long path length (5 mm) of the Y-90 beta emission, there exists the possibility of significant absorbed radiation doses to tissues immediately adjacent to the tumor sites.

This section describes the use of several geometric models and radiation transport simulations to estimate radiation absorbed dose to structures adjacent to theoretical tumors.

Three models were constructed, with two tumor sizes each, to investigate various situations including tumor around the pulmonary artery, tumor around a small cylinder such as a nerve, and tumor impinging on the pericardium or bowel wall. These models are discussed in the following text.

Depth absorbed dose profiles for all models were calculated for Y-90. This calculation was performed by determining absorbed fractions using Monte Carlo simulation of the radiation transport models. For each simulation between 100 thousand and 20 million particle histories were run. Full beta spectrums were generated for the simulations. Photon emission simulations were run but contributed far less than 1% of the absorbed dose in all cases. For the electron simulations, sufficient numbers of histories were run such that the relative errors were less than 10%. The MCNP (Monte Carlo N-Particle Transport Code System) relative error criteria for generally reliable results is 10% or less.

Tumor Adjacent to Pericardium or Bowel Wall

This simulation was designed to model a hemispherical tumor located on the bowel wall, on the surface of the pericardium, or any other soft tissue structure. The tumor was modeled as a hemispherical source, and the radiation absorbed dose was determined as a function of distance away from the planar surface of the hemispherical tumor. The target tissue of interest was subdivided using cutting planes such that a depth-absorbed dose profile could be obtained. The first table lists the depth absorbed dose in terms of percent of "tumor" absorbed dose into the tissue of interest for a 5 gram hemispherical tumor model. The second table lists the depth absorbed dose profile into the tissue of interest for the 20 grams hemispherical tumor model.

TABLE: 5G HEMISPHERICAL TUMOR DEPTH ABSORBED DOSE PROFILE FOR TISSUE

Depth (mm)	Percent of Source Absorbed Dose
Source ("tumor")	100.0%
0.25	51.4%
0.75	36.5%
1.25	26.4%
1.75	18.7%
2.5	11.6%
3.5	5.9%
5.0	1.7%

TABLE: 20G HEMISPHERICAL TUMOR DEPTH ABSORBED DOSE PROFILE FOR TISSUE

Depth (mm)	Percent of Source Absorbed Dose
Source ("tumor")	100.0%
0.25	47.1%
0.75	32.9%
1.5	20.1%
2.5	10.3%
3.5	4.9%
5.0	1.6%

Tumor Surrounding Small Cylindrical Structure (nerve or artery)

This simulation was designed to model a tumor wrapped around a small cylindrical structure. In this model the small cylinder had a radius of 2 mm, which would represent a small artery or nerve. Tumors were modeled as spherical sources. The cylindrical target shell was subdivided into many thin shells such that a depth-absorbed dose could be obtained. The model was configured so that the tumors completely encased the small cylindrical target. Two sizes of tumors were modeled, 5 grams and 20 grams. The first table lists the depth absorbed dose profile in terms of percent of the absorbed dose in the tumor as a function of depth into the cylinder for the 5 grams model. The second table lists the depth absorbed dose profile for the cylinder using a 20 grams tumor model.

TABLE: ENCIRCLING 5G TUMOR DEPTH ABSORBED DOSE PROFILE FOR SMALL CYLINDRICAL TARGET

Depth (mm)	Percent Source Absorbed Dose
Source ("tumor")	100.0%
0.05	85.3%
0.15	76.6%
0.25	76.5%
0.35	75.2%
0.45	74.2%
0.55	69.8%
0.65	64.6%
0.75	58.8%
0.85	60.0%
0.95	56.8%
1.05	51.0%
1.15	58.0%
1.25	56.8%
1.35	55.1%

TABLE: ENCIRCLING 20G TUMOR DEPTH ABSORBED DOSE PROFILE FOR SMALL CYLINDRICAL TARGET

Depth (mm)	Percent Source Absorbed Dose
Source ("tumor")	100.0%
0.05	74.8%
0.15	68.2%
0.25	66.5%
0.35	60.1%
0.45	57.7%
0.55	56.9%
0.65	58.8%
0.75	57.0%
0.85	54.7%
0.95	54.0%
1.05	52.9%
1.15	54.7%
1.25	60.5%
1.35	55.6%

Tumor Adjacent to Pulmonary Artery

This simulation was designed to model a tumor that was wrapped around the pulmonary artery. The model consisted of a spherical source (representing tumor) with a cylinder running through the center to represent the pulmonary artery. This cylinder was further sub-divided into many cylindrical target shells such that the radiation absorbed dose could be determined as a function of depth. The pulmonary artery wall was modeled using the dimensions specified in ICRP 23. The model was configured such that the tumors completely surrounded the artery. Two sizes of tumors were modeled, 10 grams and 20 grams. The first table lists the depth absorbed dose profile for the 10 gram tumor model in terms of percent of the absorbed dose in the tumor as a function of depth into

the artery wall. The second table lists the depth absorbed dose profile for the artery wall using a 20 gram tumor model.

TABLE: 10G TUMOR DEPTH ABSORBED DOSE PROFILE FOR THE PULMONARY ARTERY WALL

Depth (mm)	Percent of Source Absorbed Dose
Source ("tumor")	100.0%
0.05	74.4%
0.2	64.8%
0.45	54.2%
0.75	45.1%
1.1	36.6%

TABLE: 20G TUMOR DEPTH ABSORBED DOSE PROFILE FOR THE PULMONARY ARTERY WALL

Depth (mm)	Percent of Source Absorbed Dose
Source ("tumor")	100.0%
0.05	66.4%
0.2	57.8%
0.45	48.6%
0.75	39.9%
1.1	32.2%

CBER Review Comment

The theoretical models demonstrate the potential for a significant absorbed radiation dose to the surface of a normal structure from an adjacent tumor site.

Radiation Absorbed Doses to Adjacent Structures from a Reported Tumor

IDEC reported a radiation absorbed dose of 24,274 cGy for a tumor site in patient number 106-04-020-411. Given this reported radiation absorbed dose for a tumor site, the relatively long path length (5 mm) of the Y-90 beta emission, and the presented theoretical models, there exists the possibility of significant radiation absorbed doses to tissues immediately adjacent to such a reported tumor.

Assuming an equivalent tumor site radiation absorbed dose (24,274 cGy), the radiation absorbed dose as a function of depth was determined for the six "worst case" scenarios. These results are displayed in the following six tables.

TABLE: ESTIMATED ABSORBED DOSE TO PULMONARY ARTERY FROM AN ADJACENT 10G TUMOR

Depth (mm) Into Pulmonary Artery Wall	Absorbed Dose (cGy)
Source ("tumor")	24,274
0.05	18,057
0.2	15,738
0.45	13,154
0.75	10,957
1.1	8,883

TABLE: ESTIMATED ABSORBED DOSE TO PULMONARY ARTERY FROM AN ADJACENT 20G TUMOR

Depth (mm) Into Pulmonary Artery Wall	Absorbed Dose (cGy)
Source ("tumor")	24,274
0.05	16,128
0.2	14,039
0.45	11,795
0.75	9,680
1.1	7,818

TABLE: ESTIMATED ABSORBED DOSE TO TISSUE FROM AN ADJACENT HEMISPHERICAL 5G TUMOR

Depth (mm) into Adjacent Tissue	Absorbed Dose (cGy)
Source ("tumor")	24,274
0.25	12,477
0.75	8,865
1.25	6,422
1.75	4,549
2.5	2,811
3.5	1,440
5.0	426

TABLE: ESTIMATED ABSORBED DOSE TO TISSUE FROM AN ADJACENT HEMISPHERICAL 20G TUMOR

Depth (mm) into Adjacent Tissue	Absorbed Dose (cGy)
Source ("tumor")	24,274
0.25	11,438
0.75	7,988
1.5	4,886
2.5	2,513
3.5	1,200
5.0	383
7.0	45

TABLE: ESTIMATED ABSORBED DOSE TO SMALL CYLINDER FROM AN ENCIRCLING 5G TUMOR

Depth (mm) into Small Cylinder Source ("tumor")	Absorbed Dose (cGy)
	24,274
0.05	20,706
0.15	18,594
0.25	18,570
0.35	18,254
0.45	18,011
0.55	16,943
0.65	15,681
0.75	14,273
0.85	14,564
0.95	13,788
1.05	12,380
1.15	14,079
1.25	13,788
1.35	13,375

TABLE: ESTIMATED ABSORBED DOSE TO SMALL CYLINDER FROM AN ENCIRCLING 20G TUMOR

Depth (mm) into Small Cylinder Source ("tumor")	Absorbed Dose (cGy)
	24,274
0.05	18,157
0.15	16,555
0.25	16,142
0.35	14,589
0.45	14,006
0.55	13,812
0.65	14,273
0.75	13,836
0.85	13,278
0.95	13,108
1.05	12,841
1.15	13,278
1.25	14,686
1.35	13,496

CBER Review Comment

Based on the reported estimated absorbed radiation dose in a tumor site (24,274 cGy) and the presented theoretical models, there is a potential risk of significant absorbed radiation in a normal structure from an adjacent tumor site.

Dosimetry Assuming Altered Biodistribution (Model = Large Colloid Type)

Dosimetry estimates for Y-90 were determined using a colloid type distribution, based on the model described in ICRP-53 [ICRP 1988]. The model assumes "large" colloids (100-1000 nm diameter), with distributions of 70% in liver, and 10% each in spleen, red marrow, and remaining tissue. It was further assumed that removal of activity was by physical decay only.

TABLE: COLLOID DISTRIBUTION OF Y-90-2B8 FOR THE MAXIMUM ALLOWABLE 32 MCI DOSE

	Normal Organ Dosimetry	Normal Organ Dosimetry	Altered Biodistribution Dosimetry	Normal Organ Dosimetry IDEC	Normal Organ Dosimetry CBER	Altered Biodistribution Dosimetry
	IDEC (cGy/mCi)	CBER (cGy/mCi)	Colloid Distribution (cGy/mCi)	(cGy/32 mCi)	(cGy/32 mCi)	Colloid Distribution (cGy/32 mCi)
Adrenals	1.0	1.1	0.3	33	35	9.6
Brain	1.0	1.1	0.3	33	35	9.6
Breasts	1.0	1.1	0.3	33	35	9.6
Gallbladder Wall	1.0	1.1	0.3	33	35	9.6
LLI Wall	11.5	11.5	0.3	367	367	9.6
Small Intestine	4.3	4.1	0.3	138	131	9.6
Stomach	1.0	1.1	0.3	33	35	9.6
ULI Wall	7.0	6.6	0.3	224	211	9.6
Heart Wall	9.6	8.9	0.3	309	286	9.6
Kidneys	0.4	0.2	0.3	12	6	9.6
Liver	20.0	17.1	67	639	546	2144
Lungs	7.1	6.2	0.3	226	200	9.6
Muscle	1.0	1.1	0.3	33	35	9.6
Ovaries	1.4	1.1	0.3	45	35	9.6
Pancreas	1.0	1.1	0.3	33	35	9.6
Red Marrow	4.7	2.8	7.4	152	89	236.8
Bone Surfaces†	3.3	2.2	4.8	105	70	153.6
Skin	1.0	1.1	0.3	33	35	9.6
Spleen	35.0	42.2	101	1120	1350	3232
Testes	33.1	29.7	0.3	1060	952	9.6
Thymus	1.0	1.1	0.3	33	35	9.6
Thyroid	1.0	1.1	0.3	33	35	9.6
Urine Bladder Wall	3.1	3.2	0.3	99	102	9.6
Uterus	1.5	1.1	0.3	48	35	9.6

† Absorbed dose due to activity assumed to be in red marrow as described above.

CBER Review Comment

The altered biodistribution scenario, as represented by the large colloid model, estimated the radiation absorbed doses to the spleen at 3,232 cGy and to the liver at

2,144 cGy. These values exceed the controlled trials prospectively designed maximum absorbed radiation organ exposure of 2,000 cGy. The safety and efficacy of Y-90-2B8 has not been studied in presence of normal organ radiation absorbed doses at these levels.

Dosimetry for Renal Obstruction

The stated clearance pathway for Y-90-2B8 is renal/urinary tract. Based on the kinetic data collected, 7.3% of Y-90-2B8 will clear through unobstructed kidneys following the administration of the maximum allowable dose (32 mCi) of Y-90-2B8. For the “worst case” evaluation of renal obstruction, this 7.3% will be transferred into the kidneys with a 46 hour biological half-time. For renal obstruction, once the activity is in the kidneys, the activity is assumed to be retained with an indefinite biological half-life. This will result in an absorbed dose to kidneys of approximately 21 cGy/mCi, and with an administered activity of 32 mCi, a total absorbed dose of 840 cGy.

EXTERNAL BEAM RADIATION THERAPY - RADIATION TOLERANCE DOSES*

CBER Review Comment

The following data are not considered to be directly applicable to absorbed radiation doses from unsealed radiation therapy, e.g., radiolabeled monoclonal antibody therapy. This information is provided for background reference only.

The following table lists the radiation absorbed doses from external radiation therapy required to produce the listed effects in the listed organs. The primary source of these data is from external beam radiation therapy applications.

TD 5/5 is the absorbed dose level required to produce the described injury within 5 years in 5% of those so exposed. TD 50/5 is the absorbed dose level required to produce the described injury within 5 years in 50% of those so exposed. The %-irradiated column describes the amount of the organ that was exposed to the radiation.

TABLE: EXTERNAL BEAM RADIATION THERAPY - RADIATION TOLERANCE DOSES*

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

*Sources:

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

OVERALL SUMMARY

OVERALL SUMMARY

GENERAL

ZEVALIN Therapy Clinical Studies

Data Set	IDEC Studies	N
Overall-Efficacy Analysis Relapsed or refractory, low grade or follicular B-cell NHL	Study 106-04 IDEC-Y2B8 Subjects (N = 73) Rituximab Subjects (N = 70)	143
Overall-Efficacy Analysis Relapsed or refractory, follicular B-cell NHL, refractory to rituximab therapy	Study 106-06 ^{&} (N = 54)	54
Overall Safety Analysis	Integrated data from Studies 106-03 [#] , 106-04*, 106-05, 106-06 [§] , and data from 138 subjects in Study 106-98 [@]	348
Overall Non-Hematologic Adverse Event Analysis	Integrated data from Studies 106-03 [#] , 106-04*, 106-05, 106-06 [§] , and data from 148 subjects in Study 106-98 [@]	358
Overall Hematologic Adverse Event Analysis	Integrated data from Studies 106-03 [#] , 106-04*, 106-05, 106-06 [§] , and data from 182 subjects in Study 106-98	392
Safety Comparison of Treatment with IDEC-Y2B8 alone versus IDEC-Y2B8 with prior IDEC-In2B8	IDEC-In2B8/IDEC-Y2B8 Subjects from Studies 106- 03, 106-04*, 106-05, and 106-06 (N = 182) IDEC-Y2B8 Only Subjects from Studies 106-06 and 106-98 (N = 167)	348

[&] Includes 54 of 57 subjects with follicular histology as was prospectively defined for inclusion in the overall efficacy analysis. The remaining 3 subjects had tumor histology other than follicle center cell.

[#] Includes 50 of 51 ITT subjects treated with ZEVALIN therapeutic regimen. 1 subject was enrolled but did not receive ZEVALIN therapeutic regimen.

^{*} Includes the 73 ITT subjects who were randomized to the ZEVALIN treatment group.

[§] Includes all 57 ITT subjects.

[@] Includes 148 subjects for whom adverse event data was provided in the June 2001 updated safety dataset. However, 10 subjects who were included in the dataset had not yet completed 13 weeks of clinical follow-up and information pertaining to these 10 subjects may be incomplete. FDA included these subjects in the overall non-hematologic adverse event analysis (the sponsor omitted these subjects from their analysis), but only considered the 138 subjects who had completed 13 weeks of clinical follow-up for the overall safety analysis (same as the sponsor).

SUMMARY OF EFFICACY DATA

Primary Efficacy Endpoints

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.

FDA has confirmed the primary efficacy evaluation of higher overall response rate in the ZEVALIN therapeutic regimen arm as compared to the rituximab arm in Study 106-04 and agrees with the sponsor's analysis. ZEVALIN therapeutic regimen is effective and produced an ORR of 73% with a median of 14.2 months duration of response in subjects with relapsed or refractory, low grade or follicular B-cell NHL. In comparison, rituximab yielded a 47% ORR with a median duration of response of 12.1 months. The increased overall response rate (ZEVALIN therapeutic regimen activity) was observed for subjects with IWF A and follicular histology but not for subjects with transformed histology (5 of 9 ZEVALIN responder vs. 3 of 4 RITUXAN™ responder).

We have confirmed the primary efficacy evaluation of overall response rate and duration of response rate in ZEVALIN therapeutic regimen treated subjects with advanced, relapsed or refractory, follicular B-cell NHL who were refractory to rituximab therapy. ZEVALIN therapeutic regimen yielded a 59% ORR with a median duration of response of 7.7 months.

Insufficient data was provided to assess overall response rates and duration of response for subjects with transformed low grade NHL.

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SUMMARY OF SAFETY DATA

Non Hematologic Adverse Events

- The analyses of non-hematologic adverse events are based on results in 358 subjects from 5 clinical trials.
- Other clinical safety summary analyses exclude 10 subjects enrolled in the 106-98 for whom some adverse events were reported but have not completed 13 weeks of clinical follow-up.

ZEVALIN Therapy Dose Level	N=358	Trials
0.4 mCi/kg	296	106-03 (N = 30), 106-04 (N = 73), 106-06 (N = 57), and 106-98 (N = 136)*
0.3 mCi/kg	58	106-03 (N = 16), 106-05 (N = 30), and 106-98 (N = 12)*
0.2 mCi/kg	4	106-03, N= 4

* Includes 10 subjects who have not yet completed 13 weeks of clinical follow-up

NON-HEMATOLOGIC AES BY NCI CTC GRADE

A total of 2414 non-hematologic adverse events have been reported to date. Sixty-two percent were Grade 1, 29% Grade 2, 7% Grade 3, and 2 % Grade 4 by NCI CTC Grade Criteria.

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INCIDENCE OF NON-CYTOPENIC AES**Per Patient Incidence of Common and Notable
Non-Hematologic AEs (N=358 Subjects)**

AE (COSTART)	all grades (%)	Grade 3-4 (%)
Asthenia	52	3
Nausea	37	<1
Chills	28	<1
Fever	26	3
Infection	19	<1
Abdominal Pain	18	3
Dyspnea	16	2
Headache	16	<1
Increased Cough	15	0
Pain	15	<1
Vomiting	14	0
Dizziness	12	<1
Irritation Throat	11	0
Peripheral edema	11	<1
Pruritus	11	<1
Anorexia	10	0
Diarrhea	10	<1
Rash	10	<1
Arthralgia	9	<1
Ecchymosis	8	<1
Myalgia	7	<1
Flushing	6	0
Hypotension	6	1
Abdominal Enlargement	5	0
Angioedema	5	<1
Anxiety	4	<1
Allergic reaction	2	<1

NCI CTC GRADE 3 AND 4 ADVERSE EVENTS EXCLUDING CYTOPENIA

The following table lists all non-hematologic, Grade ≥ 3 adverse events. More than one event may have occurred in a single individual and a single event may have been coded using multiple COSTART terms (e.g., Liver Failure and SGOT increase).

Number of Grade ≥ 3 AE Reports by Event Term (Alphabetical listing)

COSTART Term	Grade 3	Grade 4	Total #
Abdominal Pain	11	0	11
Acute Myelogenous Leukemia	0	3	3
Alkaline Phosphatase Increase	2	0	2
Allergic Reaction	3	1	4
Angioedema	1	0	1
Anxiety	2	0	2
Apnea	0	3	3

COSTART Term	Grade 3	Grade 4	Total #
Arrhythmia	2	0	2
Arthralgia	1	1	2
Arthritis	1	0	1
Ascites	1	1	2
Asthenia	8	1	9
Atrial Fibrillation	1	0	1
Bilirubinemia	2	0	2
Cachexia	1	0	1
Cellulitis	1	0	1
Chills	1	0	1
Cholangitis	0	1	1
Cholecystitis	1	0	1
Colitis	1	0	1
Constipation	2	0	2
Convulsion	3	0	3
Coronary Artery Disease	1	0	1
Deep Thrombophlebitis	2	0	2
Dehydration	4	0	4
Depression	2	0	2
Diarrhea	2	0	2
Diplopia	1	0	1
Dizziness	1	0	1
Dyspnea	5	2	7
Easy Bruisability	1	0	1
Ecchymosis	1	0	1
Edema Lung	1	0	1
Encephalopathy	1	0	1
Febrile Neutropenia	7	2	9
Fever	2	1	3
GI Heme	4	0	4
Headache	2	0	2
Heart Fail Right	1	0	1
Hematemesis	1	0	1
Hepatitis	1	0	1
Hypercalcemia	1	1	2
Hyperglycemia	5	0	5
Hyperuricemia	0	1	1
Hyperventilation	1	0	1
Hypoproteinemia	1	0	1
Hypotension	2	1	3
Hypoxia	3	0	3
Infection	1	0	1
Infection Bacterial	0	1	1

COSTART Term	Grade 3	Grade 4	Total #
Insomnia	1	0	1
Intestinal Obstruction	0	2	2
Intracranial Hemorrhage	0	1	1
Ischemia Myocardia	1	0	1
Jaundice	2	0	2
Kidney Failure	0	1	1
LDH Increase	2	0	2
Liver Failure	0	1	1
Malaise	2	0	2
Melena	3	0	3
Migraine	1	0	1
Myalgia	1	0	1
Myasthenia	1	0	1
Nausea	2	0	2
Neuritis	1	0	1
Osteomyelitis	1	0	1
Pain	3	0	3
Pain Back	1	0	1
Pain Eye	1	0	1
Pain Neck	1	0	1
Pain Tumor	3	0	3
Pericarditis	1	0	1
Peripheral Edema	3	0	3
Pleural Effusion	2	0	2
Pneumonia	6	2	8
Prothrombin Increase	1	0	1
Pruritus	1	0	1
Pulmonary Embolism	0	1	1
Rash	1	0	1
Respiratory Disease	1	2	3
Sepsis	3	3	6
SGOT Increase	1	0	1
SGPT Inc	2	0	2
Somnolence	1	0	1
Subdural Hematoma	0	1	1
Supventricular Tachycardia	2	0	2
Tachycardia	1	0	1
Urinary Tract Infection	6	0	6
Urine Frequency	1	0	1
Urticaria	1	0	1
Vaginal Hemorrhage	1	0	1
Venacaval Pressure Increase	1	0	1
Total	162	35	197

SAFETY OF IDEC-IN2B8 (N = 348)

- IDEC-In2B8 administered 1 week prior to IDEC-Y2B8 is associated with an increase in overall frequency of AEs (all grades).
- The incidence of all Grade 3 or 4 non hematologic and hematologic AEs were similar whether or not therapy included IDEC-In2B8

ABDOMINAL AE

The clinical observation of increased GI adverse events in patients treated with the radiolabeled antibody and the imaging findings of localization of the radiolabeled antibody in the bowel are compatible with a second organ radiation toxicity involving the bowel.

- The pre-clinical evaluation of the antibody's human tissue cross-reactivity established that the localization of IDEC-2B8 occurs in the lymphoid aggregates present in the normal submucosa in the bowel.
- Whole body biodistribution images from study participants demonstrates well-defined localization of the radiolabeled antibody in the bowel of many subjects.
- Review of the adverse events with ZEVALIN therapeutic regimen in the controlled clinical trial, 106-04, reveals a two fold increase in adverse events, (grades 1-2 nausea, vomiting, and abdominal pain) related to the bowel in the ZEVALIN arm as compared to the control arm (58% versus 34%).

HOSPITALIZATION

23 of 348 subjects (7%) were hospitalized with infection or febrile neutropenia

- 6 subjects had febrile neutropenia
- 4 subjects had urinary tract infections
- 4 subjects had sepsis (3 foreign-body related)
- 4 subjects had pneumonia
- 3 subjects had cellulitis or abscess
- 2 subjects had gastroenteritis or diarrhea

IMMUNE RECONSTITUTION

- All subjects experienced a depletion of B cells that reverted to baseline with a median of 6 months.
- The median serum IgG and IgA concentrations remained within the normal range for all patients
- A transient decline in serum IgM that returns to normal in 3 months despite a 6-month reversible

HAMA AND HACA

- 3 of 211 subjects (1.4%) and 1/211 (0.5%) developed HAMA and or HACA antibody titers following ZEVALIN therapeutic regimen.

- 2 subjects had pre-existing positive HAMA titers and 3 had pre-existing HACA titers. These subjects went on to receiving ZEVALIN therapeutic regimen. None had unusual toxicity.
- 1 subject enrolled in IDEC 106-01 trial had a positive baseline HAMA titer at the study site. Upon re-testing, HAMA titers were found to be negative. However, the subject was removed from study due to unfavorable biodistribution.

INFECTIONS

Overall, 114 of 358 (32%) subjects developed a total of 183 infections. Subjects may have had more than 1 type of infection in the course of follow-up post ZEVALIN therapeutic regimen. Of all reported events, 43% percent were Grade 1, 35% Grade 2, 16% Grade 3, and 6% Grade 4 by NCI CTC Grade Criteria.

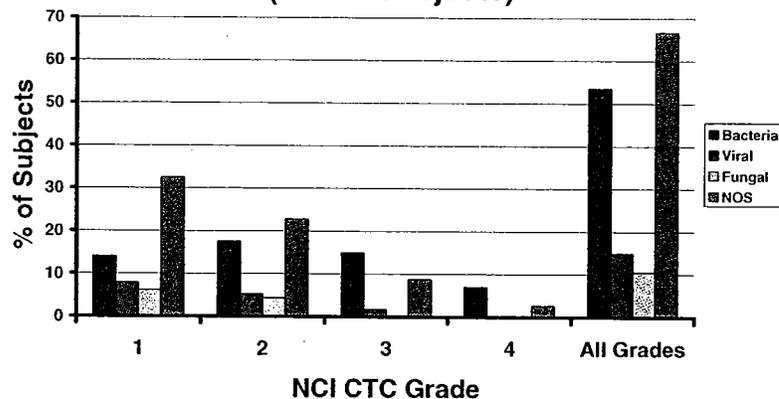
- 28 of 358 (8%) subjects had Grade ≥ 3 infections.

**Grade ≥ 3 Infections
by COSTART Preferred Term (n=41 AEs)**

AE	N
Febrile Neutropenia	9
Pneumonia	8
Urinary Tract Infection	6
Sepsis	6
Respiratory Infection	2
Cellulitis	1
Cholangitis	1
Colitis	1
Diarrhea	1
Fever	1
Hepatitis	1
Infection (NOS)	1
Bacterial Infection (NOS)	1
Osteomyelitis	1
Pericarditis	1

- The majority of infections were not subcategorized in the CRF (n=68). Among those that were subcategorized, bacterial infection occurred in 48 subjects, viral infections in 17, and mucocutaneous fungal in 13 subjects.

**Frequency of Infections
by Type and CTC Grade
(n=114 Subjects)**



SECONDARY MALIGNANCY AND MYELODYSPLASIA

Six of 348 subjects (1.7%) developed secondary malignancies following treatment with ZEVALIN therapeutic regimen

- 3 AML
- 2 MDS
- 1 meningioma
- Onset 8-24 months post ZEVALIN and 4.4 to 11.5 years post NHL diagnosis.

Hematologic Toxicity

The overall hematologic adverse event analyses included a total of 392 subjects for whom hematology data was available (Studies 106-03, 106-04, 106-05, 106-06, and 182 subjects in Study 106-98).

For all hematologic adverse events, duration of Grade ≥ 3 toxicity is defined as end date minus start date, where end date and start date are defined relative to the nadir lab value. A patient's end date is defined as the 1st lab test date after the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit. A patient's start date is defined as the most recent lab test date prior to the nadir visit when the patient's lab test is above the Grade ≥ 3 toxicity limit.

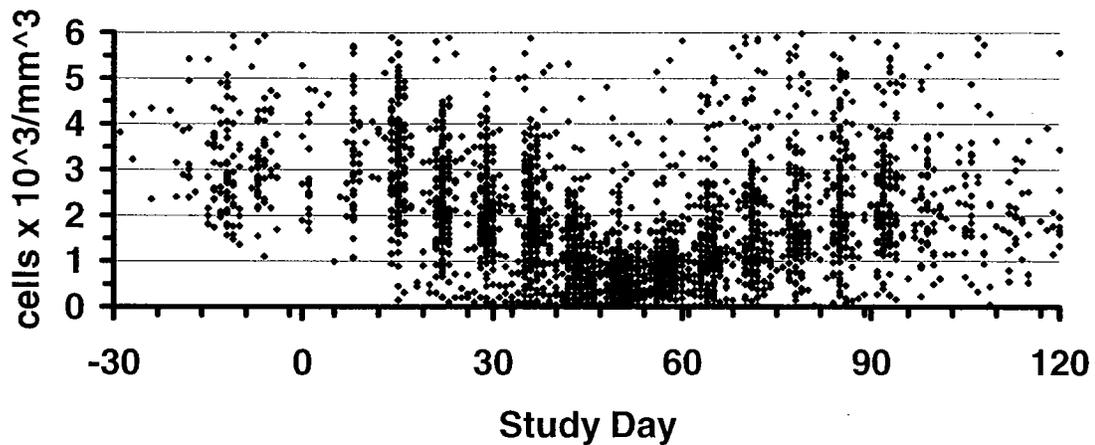
Patients not recovered from Grade ≥ 3 toxicity were censored by one of two rules. If a patient had received next anti-cancer therapy, that patient was censored to the date of the most recent lab test prior to receiving next anti-cancer therapy. If the patient had not received next anti-cancer therapy, that patient was censored to the date of the most recent lab test.

NEUTROPENIA

- 214 of 392 (55%) subjects experienced Grade ≥ 3 neutropenia within 90 days of ZEVALIN therapeutic regimen.

- For the 214 subjects with grade ≥ 3 neutropenia within 90 days of ZEVALIN therapeutic regimen, the median duration was 25 days (range 2-190+ days).

ITT Subjects With Grade 3-4 ANC
n = 214/392 (55%)



Use of hematopoietic growth factors

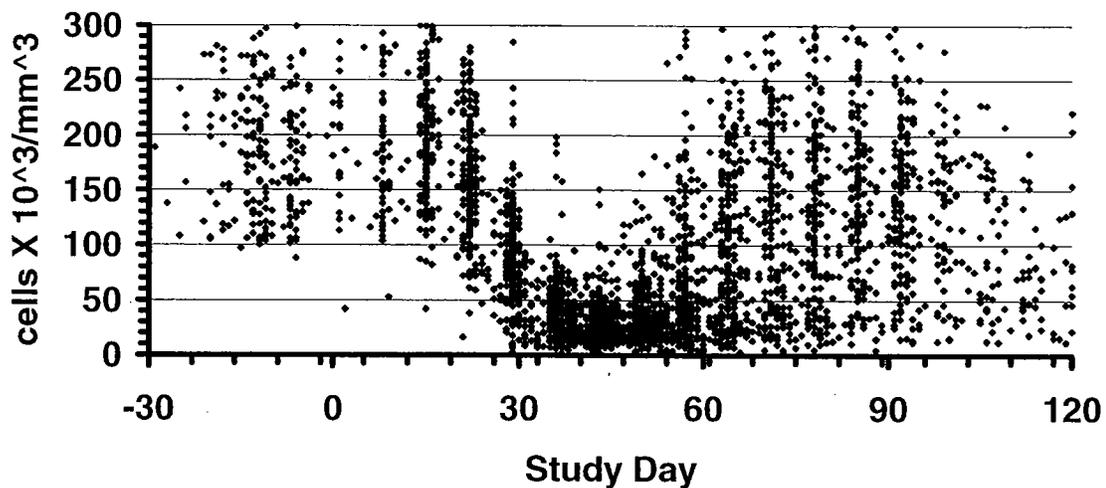
Among 211 patients for whom data were collected,

- 37 (17.5%) received filgrastim
- 22 (10.4%) received prophylactic antibiotics

THROMBOCYTOPENIA

- 224 of 392 (57%) subjects experienced Grade ≥ 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen.
- For the 224 subjects with Grade ≥ 3 thrombocytopenia within 90 days of ZEVALIN therapeutic regimen, the median duration was 27 days (range 7 to 167+ days)

ITT Subjects With Grade 3-4 PLT
n = 224/392 (57%)



Use of hematopoietic growth factors

Of 211 patients for whom data were collected,

- 3 (1%) received oprelvekin
- 47 (22%) received platelet transfusions

ANEMIA

46 of 349 (13%) subjects had Grade 3 anemia

14 of 349 (4%) subjects had Grade 4 anemia

Use of hematopoietic growth factors

Of 211 subjects for whom data were collected,

- 17 (8%) received erythropoietin
- 43 (20%) received red blood cell transfusions

HEMATOLOGIC TOXICITY AND DELAYED HEMATOLOGIC RECOVERY

Exploratory analyses to assess risk factors predictive of hematologic toxicity and delayed hematologic recovery were performed by the sponsor.

Prior Therapy

1. 23 subjects whose platelet counts did not recover to $\geq 100,000$ cells/ mm^3 were compared with 299 subjects whose platelet counts did recover. Non-recovered subjects received significantly more chemotherapy regimens than recovered subjects.
 - 61% of non-recovered subjects received 4 or more prior chemotherapy regimens compared with 26% of recovered subjects.
 - Number of prior chemotherapy regimens was associated with a greater incidence of Grade 3 or 4 anemia, Grade 4 thrombocytopenia.

- Number of prior chemotherapy regimens is not associated with a longer median duration of Grade ≥ 3 or Grade 4 neutropenia, thrombocytopenia, or anemia.

Prior Fludarabine Therapy

1. Subjects treated with fludarabine had significantly lower platelet count and hemoglobin concentration at baseline.
2. Fludarabine-treated subjects were more likely than patients not previously treated with fludarabine to develop Grade ≥ 3 neutropenia, thrombocytopenia, and anemia.
3. Prior fludarabine treatment was associated with a significantly longer median duration of Grade 3 or 4 thrombocytopenia;
4. Median duration of Grade 3 or 4 neutropenia and anemia was longer in fludarabine-treated patients; however, this difference was not significant

Bone Marrow Involvement

1. The presence of bone marrow involvement at baseline was associated with a significantly greater incidence of:
 - Grade 4 neutropenia,
 - Grade 4 thrombocytopenia,
 - Grade 4 anemia
2. The incidence of Grade 4 hematologic toxicity increased with increasing bone marrow involvement at baseline

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GERIATRIC USE:

Of 211 patients treated with ZEVALIN in clinical studies, 33.6% (71 patients) were age 65 years and over, and 9.0% (19 patients) were age 75 years and over. The safety and effectiveness of ZEVALIN were similar in elderly and younger adult patients. Other reported clinical experience has not identified differences in response between elderly and younger adults.

PEDIATRIC USE:

There is no experience using ZEVALIN therapeutic regimen in the pediatric population. Indolent NHL is extremely rare in the pediatric population.

DEATHS

70 of 349 (20%) subjects have died.

58 of 70 (83%) deaths were reported to be secondary to disease progression. 43 of the 58 subjects received additional anticancer treatment following ZEVALIN.

Non Lymphoma Related Causes Of Death

Among the 12 subjects who did not die of progressive disease, the cause of death is listed as follows:

- 2 subjects (10606001031, 10698019028) with pancytopenia died of intracranial hemorrhage. Both had traumatic head injury; one was taking oral anti-coagulants. One died on Study Day 62, the other on Study Day 144.
- 5 subjects (106-03-002-305, 106-03-003-211, 106-04-001-252, 106-05-002-011, 106-06-018-036) died of MDS/AML (41, 30, 19, 14, and 13 months post ZEVALIN therapeutic regimen).
- 3 subjects (106-03-007-336, 106-98-041-084, and 106-98-003-089) died of pulmonary complications and/or respiratory failure in the setting of pre-existing pulmonary disease (COPD and idiopathic pulmonary fibrosis) on Study Day 12, 80, and 873.
- 1 subject (106-98-003-121) died of cardiac arrest in the setting of pre-existing coronary artery disease on Study Day 471.
- 1 subject (106-05-017-021) died of complications related to a pneumonia following additional chemotherapy for progressive disease on Study Day 71.

SUMMARY OF DOSIMETRY DATA**Biodistribution Imaging**

CBER has reviewed the biodistribution imaging of In-111-2B8 performed at five time points prior to the administration of Y-90-2B8.

CBER has found the In-111-2B8 whole body biodistribution imaging provides diagnostic quality whole body images at the five time points. Excellent definition of the liver,

spleen, testes, bone marrow, kidneys, urinary bladder, large bowel, heart and major vascular structures has been demonstrated in the submitted whole body images from the controlled clinical trials.

The biodistribution imaging with In-111-2B8 provides supportive information for the safe administration of Y-90-2B8 as follows:

The biodistribution images confirm the presence of the expected pattern of In-111-2B8 in the normal organs. An alteration in the biodistribution in normal organs suggests the presence of one or more of the following conditions:

- Immune response, e.g., HAMA, HACA.
- Organ dysfunction, e.g., urinary tract obstruction.
- Improper preparation of the In-111-2B8 imaging agent.
- Presence of occult NHL.

The biodistribution images establish the “normal structures at risk” due to the radiation absorbed dose exposures from adjacent tumor sites.

In addition, the performance of the biodistribution imaging allows the following:

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

Normal Organ Dosimetry

FDA has confirmed that the normal organ dosimetry submitted by IDEC is based on the appropriate MIRDOSE software and methodology for the estimation of the radiation absorbed doses.

CBER's review supports the normal organ dosimetry results submitted by IDEC. The normal organ dosimetry results are remarkable for the radiation absorbed dose to the testes and the gastrointestinal tract. The long term evaluation of these organs for the effects of the radiation absorbed dose is indicated.

The gastrointestinal tract has not been evaluated as a route of clearance for $^{111}\text{In}/^{90}\text{Y}$ -2B8.

Tumor Dosimetry

CBER's review of the tumor dosimetry confirms 57 tumor sites have been evaluated from 38 patients. The information from these tumor sites is considered supportive to the BLA, but the 57 tumor sites cannot be considered as necessarily representative of all tumor sites. Further investigational studies should be performed to characterize the tumor site uptake and the tumor site response to Y-90-2B8 therapy.

Radiation Absorbed Dose Estimates for "Worst Case Scenarios"

CBER's review of theoretical models has established a potential risk for radiation absorbed doses to normal structures in the following worst case scenarios:

- Normal structures adjacent to tumor sites with significant radiation absorbed doses.
- An altered biodistribution (e.g., immune response due to HACA, HAMA) of Y-90-2B8.
- Renal obstruction.

**Appears This Way
On Original**

ONCOLOGY DRUG ADVISORY COMMITTEE DISCUSSIONS

On September 11, 2001, the Oncology Drug Advisory Committee (ODAC) discussed the biologics license application (BLA) 125019 for Zevalin™ (ibritumomab tiuxetan) manufactured by IDEC Pharmaceuticals Corporation.

QUESTIONS TO THE COMMITTEE

In two clinical trials, ZEVALIN™ therapy was associated with durable objective tumor responses as well as a high proportion of serious and life-threatening hematologic toxicity of prolonged duration. ZEVALIN™ is a combination product, consisting of both RITUXAN (an approved product) and radiolabeled Ibritumomab. Approval for this product requires demonstration that both components contribute to benefit. Therefore, there should be a determination that ZEVALIN™ provides benefits beyond those provided by RITUXAN alone.

1. In the setting of treating chemotherapy and RITUXAN refractory patients:

- a. Do the data support a determination that the clinical benefits associated with ZEVALIN™ extend beyond those that could have been realized by retreatment with RITUXAN?

YES – 15 NO – 0 Abstain – 1

- b. Do the benefits associated with ZEVALIN use (clinically significant tumor shrinkage) considered together with the toxicity (hematologic and other) support a determination that ZEVALIN is safe and effective in this setting?

YES – 15 NO – 0 Abstain – 1

2. In patients who have not failed RITUXAN:

- a. Has ZEVALIN™ been demonstrated to provide benefits beyond those attributable to RITUXAN alone?

YES – 9 NO – 7

- b. Is the net clinical benefit of ZEVALIN™, as compared with RITUXAN [higher overall response rate, absence of a clear difference on time-to-progression or overall survival, and higher toxicity], sufficient to recommend approval for this patient population?

YES – 6 NO – 10

In general, the Committee did not feel that the data was sufficient to support conventional approval for patients who have not failed rituximab.

3. In the randomized, active-controlled study, 106-04, a small number of subjects with low grade, non-follicular NHL or CD20+ NHL that had undergone transformation to a more aggressive histology were enrolled. The clinical behavior and level of CD20 expression in low-grade, non-follicular lymphoma and low-grade lymphoma that has undergone transformation may be sufficiently different from that observed in low-grade follicular NHL to preclude extrapolation of the clinical results. The data obtained in these subgroups across other studies have not been as rigorously confirmed for histologic diagnosis or documentation of tumor response and duration.

The following table summarizes the response outcomes in 106-04 by subgroup:

Histology Type	Response	ZEVALIN™ Resp/Total (%)	RITUXAN Resp/Total (%)
Follicular	ORR	42/55 (76)	27/58 (47)
	CR	11/55 (20)	5/58 (9)
IWF A	ORR	6/9 (67)	3/8 (38)
	CR	1/9 (11)	1/8 (13)
Transformed	ORR	5/9 (56)	3/4 (75)
	CR	1/9 (11)	2/4 (50)

- a. RITUXAN is approved for the treatment of chemotherapy-refractory low-grade, non-follicular NHL (IWF A). Although the data for ZEVALIN™ in this group are quite limited, the overall response rate was higher and duration of response similar for the 9 patients who received ZEVALIN™ as compared to the 8 patients who received RITUXAN, a similar pattern to that observed in the follicular subgroup. Please discuss whether the data are sufficient to determine that ZEVALIN™ has benefits beyond those of RITUXAN and that there is net clinical benefit of ZEVALIN™ for patients with chemotherapy-refractory low-grade, non-follicular NHL. In particular, does this subpopulation require independent data or do the data from patients with follicular disease together the limited numbers of patients with IWF A, support a determination of regarding IWF A? If the data are insufficient, please discuss the design of additional studies that would be acceptable if the sponsor wishes to pursue this claim.
- b. RITUXAN is not approved for the treatment of CD20+ low-grade NHL with transformation. The CD20+, transformed B-cell NHL subset [in ZEVALIN study 106-04] included subjects with transformation to diffuse small cleaved cell (IWF E), diffuse mixed cell (IWF F), or diffuse large cell (IWF G) histology at study entry.

The overall response rate, the complete response rate, and the duration of response were lower in 9 ZEVALIN™-treated patients with low-grade lymphoma that had undergone transformation as compared to the 4 subjects who received RITUXAN. Please discuss whether the data are sufficient to determine that the data are sufficient to determine that ZEVALIN™ has benefits beyond those of RITUXAN and that ZEVALIN™ offers net clinical benefit for patients with chemotherapy-refractory CD20, low-grade NHL with transformation. If the data are insufficient, please discuss the design of additional studies that would be acceptable if the sponsor wishes to pursue this claim.

3 a & b.

The Committee felt that it is possible to group the IWF A and follicular subgroups together, but that the transformed subgroup represents a different group that warrants additional consideration. The numbers are too small and the data are insufficient to make any determinations about the comparison of rituximab and Zevalin in the transformed subgroup. It was suggested that based on the CD20 histology and that the presumed mode of action of Zevalin involves CD20 targeting that it is OK to include transformed NHL in the overall indication despite the low numbers and differences in clinical disease. This comment was in response to discussion cautioning that transformed lymphoma behave very differently than indolent histology. The Committee noted that the transformed NHL have additional molecular and chromosomal aberrations. After much discussion, the Committee felt that separating transformed histology was not warranted if the product is approved under accelerated approval regulations and confirmatory trials will be performed as part of a post marketing commitment.

4. The initial step (step 1-administration of RITUXAN and ¹¹¹In-labeled ibritumomab) is an essential component of the ZEVALIN™ therapy. There are no data on the safety and effectiveness of ZEVALIN™ using only one dose of RITUXAN (elimination of step 1) and an inadequate safety database in patients who received RITUXAN alone without radiolabeled material in step 1. Based on experience observed with other murine monoclonal antibodies, the safety profile and efficacy of administration of ZEVALIN™ in patients who have a pre-existing anti-murine antibody immune response is highly likely to be different from that observed in clinical studies. No other screening test, e.g., HAMA, has been adequately evaluated to identify patients at increased risk of altered biodistribution.

In addition, assessment of biodistribution aids in identification of normal tissues that would be exposed to unusually high doses of radiation due to alteration of clearance for mechanical reasons (ureteral obstruction) or based on proximity to tumor masses and may provide information on radiation dosimetry to assist in assessing cumulative doses for future planned radiotherapy.

The Agency seeks advice on additional post-marketing studies to better assess the utility of using ¹¹¹In-labeled ibritumomab for determination of biodistribution, as a component of Step 1, in optimizing the safety and effectiveness of ZEVALIN™. What types of studies and other data should be collected to determine the safety and

effectiveness of deletion of the biodistribution assessment while retaining the first dose of RITUXAN?

The imaging dose is used for qualitative assessment of biodistribution and could be used for dosimetry purposes should this be needed. The Committee agreed that imaging is a necessary component of the therapy.

5. Low grade NHL is rare in the pediatric population. The Biological Response Modifiers Advisory Committee and the pediatric subcommittee to the ODAC have advised that studies in pediatric patients should not be required under the Pediatric Rule because the disease (follicular NHL) does not occur with sufficient frequency in children. The Agency seeks the Committee's advice regarding the waiver of studies in pediatric patients.

Additional studies are necessary to determine the long-term effects of this treatment on children. However, there will be difficulty accruing enough patients for a study. The drug will be used by pediatric oncologists and a risk/benefit analysis is needed.

6. A. Do the data presented support Accelerated Approval for the total population of the large Phase III study?

Yes – 13 No – 2 Abstain – 1

- B. Should the patients in the transformed subgroup be taken out of the indication for Accelerated Approval?

Yes – 3 No – 11 Abstain – 2

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