



BRIEFING DOCUMENT

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TITLE:

**Briefing Document of
⁹⁰Yttrium Ibritumomab Tiuxetan
Radioimmunotherapy Regimen**

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1. INTRODUCTION

1.A. Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas (NHLs) comprise a heterogeneous group of lymphoid neoplasms that range from predominantly follicular malignancies to highly aggressive lymphomas. The majority of NHLs, 85%, originate from B cells^[1]. More than 54,900 new cases of NHL and 26,100 deaths from NHL were estimated in the United States in the year 2000^[2].

Collectively, the NHLs rank fifth in cancer incidence and mortality. The incidence increases with advancing age; patients' median age at diagnosis is 55 to 60 years^[3,4]. SEER data^a indicate that age-adjusted incidence rates of NHL rose faster than rates for the majority of cancers between 1973 and 1997. During that period, rates increased nearly 80%, with a 3% annual increase; mortality increased 45% overall, with a 1.5% annual percentage increase^[5]. Although largely unexplained, the increase is partially due to the growth of the aging population, AIDS-related NHL, and environmental factors^[6]. Between 1990 and 1997, incidence rates were highest among Caucasians, and age-adjusted rates were higher among men (19.4 and 12.2 per 100,000 men and women, respectively),^b though rates rose significantly in women ($p < 0.05$)^c.

Low-grade or follicular lymphomas account for approximately 65% of lymphoma cases in the population at a given time^[7]. Most of these patients (> 80%) present with advanced disease, and median survival has been estimated at 6.2 years^[7,8]. The incidence of transformation from low-grade or follicular NHL to a more aggressive histology may reach 40% to 70% in patients with progressive disease^[9-11]. Transformation is a major event that changes the course of the disease.

Transformation occurs in 15% to 50% of patients at 5 years, in 60% at 8 years, and may occur in as many as 90% of patients at the time of death^[10,12]. Estimated median survival ranges from 7 to 22 months from the date of transformation^[13,14].

Patients with low-grade or follicular NHL often respond to initial therapy; however, response rates decrease and the duration of remission becomes shorter with repeated therapy^[15] (Figure 1). In time, patients invariably become refractory to treatment.

^aSurveillance, Epidemiology, End Results Program of the National Cancer Institute to provide incidence, mortality, and survival statistics.

^bMiller BA, Kolonel LN, Bernstein L, Young, Jr. JL, Swanson GM, West D, Key CR, Liff JM, Glover CS, Alexander GA, et al. (eds). Racial/Ethnic Patterns of Cancer in the United States 1988 – 1992, National Cancer Institute. NIH Pub. No. 96-4104. Bethesda, MD, 1996; and www.cancernet.nci.nih.gov/seer/Non-Hodgkin's_lymphoma.html.

^cwww.seer.ims.nci.nih.gov.

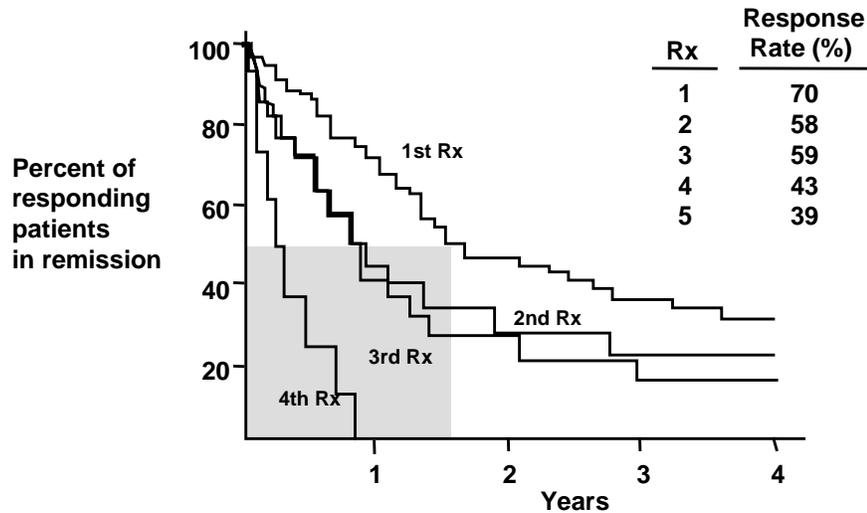


Figure 1. Response rate and duration of remission in patients with Stage III or IV follicular lymphoma

Adapted from Gallagher et al., 1986^[15]

Age has been identified as an important prognostic factor that negatively affects survival^{a[16, 17]} because elderly NHL patients often suffer from other chronic or debilitating conditions, and because adverse events are common in elderly patients who are undergoing chemotherapy. In the U.S., the elderly population (age 65+ years) will comprise 13% of the population in 2000 and 20% in the next 30 years^b.

1.B. NHL Therapy

The only FDA-approved therapy for relapsed or refractory low-grade or follicular NHL is the chimeric anti-CD20 monoclonal antibody, rituximab, given as a single agent. No therapy is currently approved for the treatment of transformed NHL. However, other agents are commonly used, and the risks and benefits of these other treatments must be considered when evaluating the net clinical benefit of ⁹⁰Y ibritumomab tiuxetan therapy.

Overall response rates (ORR) to a variety of single agents used to treat relapsed, low-grade or follicular NHL appear in Table 1. Toxicity data for studies of single-agent and multiagent treatments used to treat NHL are presented below in Table 2 and Table 3.

^aAge ≥ 60 years is one of five variables in the multifactorial International Prognostic Index, which identifies patients with different risks for death based on evaluation of specific baseline characteristics.

^b <http://research.aarp.org/general/profile99.pdf>

Table 1.
ORR of Single-Agent Treatments of Relapsed Low-Grade or Follicular NHL

Agent	Number of Patients	Number of Studies	Mean ORR	ORR Range (% ORR/Number of Patients)
Cyclophosphamide*	-	-	-	-
Chlorambucil†	228	2	51%	39%/18 to 59%/44
Mitoxantrone‡	13	1	54%	N/A
Rituximab§	166	1	48%	N/A
Fludarabine¶	259	8	48%	31%/38 to 62%/13
Cladribine ^b	353	8	48%	32%/28 to 66%/9
Paclitaxel [£]	78	3	17%	0%/12 to 22%/45
Liposomal Daunorubicin ^Δ	19	1	16%	N/A
Liposomal Vincristine ^{**}	10	1	10%	N/A

*Oral alkylating agents are used more commonly as first-line treatments; response rates are unavailable in studies of relapsed or refractory NHL

†Oral alkylating agent^[15, 17], 104 patients were treated with up to 5 courses of chlorambucil or CVP

‡Anthracenedione^[18]

§Chimeric anti-CD20 monoclonal antibody^[19]

¶Purine analog^[20-27]

^bPurine analog^[28-35]

[£]Antimicrotubule drug^[36-38]

^ΔLiposomal encapsulated anthracycline^[39]

^{**}Liposomal encapsulated vinca alkaloid^[40]

N/A = not available (single studies)

Table 2.
Toxicity Incidence for Single-Agent Therapies of
Relapsed Low-Grade or Follicular NHL

	Number of Patients	Neutropenia Grade 3, 4	Thrombocytopenia Grade 3, 4	Infection Grade 3, 4	Neurotoxicity Grade 3, 4	Alopecia	Renal/Hepatic	Related Deaths
Chlorambucil ^[41]	178 (CLL*)	19%	14%	9%	N/A	N/A	N/A	0%
Fludarabine								
Zinzani ^[24]	21	10%, 5%	0%, 0%	14%	N/A	N/A	N/A	5%
Falkson ^[27]	21	N/A	10%, 0%	5%, 5%	N/A	N/A	N/A	5%
Hiddeman ^[23]	45	11%	13%	1%	1%	N/A	N/A	N/A
Hochster ^[21]	62 (27 LG)	N/A	5%, 3%	2%	10%, 0%	N/A	N/A	3%
Package Insert	133 (CLL)	N/A, 59%						
Cladribine								
Tupule ^[35]	28 (23 LG)	43%, 36%	11%, 4%	N/A	N/A	N/A	7%	11%
Rondelli ^[32]	39 (9 LG)	20%	20%	23%	N/A	N/A	N/A	8%
Robak ^[31]	94	0%, 13%	0%, 13%	40%	N/A	N/A	N/A	3%
Kong ^[34]	22	27%	9% [†]	27%	N/A	N/A	N/A	23%
Kay ^[28]	40	18% [‡]	30%	8%	N/A	N/A	N/A	N/A
Rituximab								
Package Insert [‡]	315	2%	1%	6%	N/A	N/A	N/A	N/A
Mitoxantrone								
Angelopoulou ^[18]	13	N/A	31%, 0%	N/A	N/A	N/A	N/A	N/A
Paclitaxel								
Younes ^[36]	54	11%	N/A	N/A	9%	100%	N/A	N/A
Younes ^[38]	96	22% [§]	21%, 23%	N/A	[¶]	100%	N/A	N/A

Continued

	Number of Patients	Neutropenia Grade 3, 4	Thrombocytopenia Grade 3, 4	Infection Grade 3, 4	Neurotoxicity Grade 3, 4	Alopecia	Renal/Hepatic	Related Deaths
Vincristine (Lip) Sarris ^[40]	35 (10 LG)	9%	0%	N/A	31% [‡] , N/A	N/A	N/A	N/A
Daunorubicin (Lip) Richardson ^[39]								
Low Dose	10	10%, 40%	20%, 20%	5% ^Δ , 0%	N/A	N/A	20%	N/A
High Dose	9	33%, 89% [#]	44%, 67%	38% ^Δ , 0%	N/A	11%	11%	N/A

*Previously untreated. Following therapy, 44% had a Grade 3 or 4 toxicity.

[†]32% developed persistent thrombocytopenia after a median of 4 cycles

[‡]43% of neutropenic patients (3 of 7) had sepsis

[§]Grade 4 only

[¶]Neutropenic fever occurred in 8% of paclitaxel courses

[‡]35% Grade ≥ 2 sensory neuropathy

[‡]Required treatment termination in 45% of patients

^ΔFrequency (% episodes)

[#]33% (3 patients) received growth factors

LG = low-grade; CLL = chronic lymphocytic leukemia; HCL = hairy cell leukemia; N/A = not available; Lip = Liposomal

Table 3.
Toxicity Incidence for Multiagent Therapies for NHL

	Number of Patients*	Neutropenia Grade 4	Thrombocytopenia Grade 4	Infection, Febrile Neutropenia Grade 3, 4	Neurotoxicity Grade 3, 4	Alopecia	Renal/Hepatic	Treatment-Related Deaths
ESHAP Velasquez ^[42]	122	50%	†	30%	N/A	100%	18% rev. 4% perm.	16%
DHAP Velasquez ^[43]	90	53+%	39%‡	48%	5%	100%	14% rev. 4% perm.	17%§
CVP Hagenbeek ^[44]	310	11%	< 1%	< 1%	3%	39%	na	< 1%
ICE Moskowitz ^[45]	163	13%	15%	14%	3%	N/A	21% rev	N/A
MACOP-B Sertoli ^[46]	107	20%	3%	13%	10%	100%	9%	9%
ProMACE-MOPP Sertoli ^[46]	114	26%	5%	10%	2%	100%	2%	4%
CHOP Various [¶]	31 - 408	16% - 39%	2% - 12%	3% - 33%	3%	100%	1%	< 1% - 10%
# Studies Reporting	6	5	4	5	1		1	5

*Patients treated with ESHAP, DHAP, and ICE had relapsed or refractory NHL. All others were previously untreated.

†No toxicity grades reported. Median platelet nadir = 70,000/mm³

‡Grade 4 defined as < 20,000 cells/mm³

§10 deaths due to infection, 3 due to tumor lysis syndrome, 2 due to renal failure

¶Miller et al.,^[47], Gordon et al.,^[48], Jones et al.,^[49], Campbell et al.,^[50], Intragumtornchai et al.,^[51], Montserrat et al.,^[52]

N/A = not available; rev. = reversible; perm. = permanent

Note: Most toxicity data are published for first-line therapy; therefore, toxicity is underestimated in the relapsed/refractory lymphoma population. Deaths due to late or long-term toxicity such as MDS and AML are not included in this table.

Conventional chemotherapy is often accompanied by side effects ranging from unpleasant to life-threatening. Approximately 70% to 80% of patients who receive chemotherapy experience nausea and vomiting^[53] which is often persistent. Similarly, alopecia is a significant and distressing side effect and was considered the most bothersome aspect of treatment in 88% of women who received chemotherapy^[54]. Antineoplastic agents used to treat low-grade NHL may also have potential nephrotoxicity^[55]. Toxicity may be compounded in multidrug regimens.

Myelosuppression, the major toxic effect associated with most chemotherapy treatments, is associated primarily with the intensity of the cytotoxic drugs administered^[56]. For example, the duration of marrow recovery has been reported to range from 18 to 40 days for alkylators such as cyclophosphamide and chlorambucil, and 21 to 24 days for anthracyclines. Myelosuppression is cumulative for many chemotherapeutic agents, and repeated courses worsen toxicity. Moreover, the cumulative time at nadir increases four- to six-fold with repeated cycles of chemotherapy. Intensive chemotherapy has no advantage over less intensive treatments in altering the natural history of low-grade NHL^[57-60]. In the absence of survival benefit, prolongation of the time that a patient is in remission and off therapy is clinically meaningful.

Long-term side effects of therapy for NHL include an increased risk of secondary malignancies. High-dose chemotherapy with autologous stem cell support confers a significant risk of myelodysplasia (MDS), with actuarial 5-year incidence rates ranging from 6% to 15%, depending on the series^[61]. Also, a cumulative incidence of MDS of 4% to 8% was reported in NHL patients who had not undergone high-dose therapy but who had been exposed to alkylator-based therapies^[62]. In a series of 602 NHL patients reported by Pedersen-Bjergaard et al, 9 patients developed MDS or leukemia, resulting in a 6.3% estimated cumulative probability seven years after the start of treatment^[63]. These authors quoted a general risk of MDS following alkylator therapy of 1% to 1.5% per year, from 2 to at least 9 years after the initiation of therapy.

1.B.1. Radioimmunotherapy

Radioimmunotherapy (RIT) combines both biologic and radiolytic mechanisms of action to target and destroy tumor cells. The penetrating effect of radiation permits treatment of bulky or poorly vascularized tumors, because malignant cells not directly accessible to the antibody can be killed at a distance by the ionizing radiation. This crossfire effect makes RIT an excellent modality in the treatment of NHL, an inherently radiation-sensitive malignancy. The target antigen, radionuclide emission properties, and chemical stability of radioimmunoconjugates are important factors that contribute to the effectiveness of RIT.

The CD20 B-lymphocyte differentiation antigen provides an attractive target for immunotherapy for the following reasons^[64, 65]:

- expressed by more than 90% of B-cell tumors
- present exclusively on mature B cells and most B-cell lymphomas
- absent from hematopoietic stem cells, pro-B cells, normal plasma cells, or other nonlymphoid normal tissues
- does not circulate as free protein that could block anti-CD20 antibody targeting

- does not shed from the cell surface upon anti-CD20 antibody binding

Rituximab, a chimeric IgG1 kappa monoclonal antibody with mouse variable and human constant regions, was derived from the parent murine antibody, ibritumomab. Both rituximab and ibritumomab specifically recognize the CD20 antigen^[66]. In vitro studies demonstrated that rituximab binds human complement and lyses lymphoid B-cell lines through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity^[66]. Rituximab and ibritumomab have been shown to have antiproliferative effects in tritiated thymidine incorporation assays and to induce apoptosis in vitro^[67, 68].

We and others have studied radiolabeled antibodies to treat B-cell lymphomas using iodinated (¹³¹I) antibodies^[69-74]; however, this use was complicated by several factors. The 8-day half-life of ¹³¹I is significantly longer than that of a murine antibody. Dehalogenation can result in accumulation of the free radionuclide in the patient's thyroid, rapid excretion, or both. It has been reported that 46% to 90% of ¹³¹I is excreted in the urine within 48 hours following administration of ¹³¹I-radiolabeled immunoconjugate^[75, 76]. Since 44 to 72 hours are required for an intact monoclonal antibody to localize optimally to its antigen^[77], clearance of ¹³¹I varies significantly among individuals^[78] and ¹³¹I dosimetry has been necessary to calculate individual administered dose. Penetrating gamma emissions of ¹³¹I irradiate distant organs and increase whole body radiation exposure and exposure to others in close proximity^[79, 80]. Therefore, hospitalization and/or shielding^[71, 76, 81] are required.

Improvement in methods for attaching metal chelating groups to proteins made it possible to study other potentially useful radionuclides such as ⁹⁰Yttrium (⁹⁰Y)^[82]. Compared with ¹³¹I, ⁹⁰Y can deliver a higher beta energy to tumor (2.3 MeV for ⁹⁰Y versus 0.6 MeV for ¹³¹I) resulting in a longer mean path length over which 90% of the emitted energy is absorbed (5 mm for ⁹⁰Y versus 0.8 mm for ¹³¹I)^[80, 83-85]. These characteristics of ⁹⁰Y may be especially advantageous in treating bulky, poorly vascularized tumors and those with heterogeneous antigen expression. The shorter half-life of ⁹⁰Y (64 hours versus 192 hours) approximates the biologic half-life of the radiolabeled antibody. A number of investigators using various radioimmunoconjugates have reported that ⁹⁰Y can deliver radioactivity to tumor more effectively and is associated with a better therapeutic index than ¹³¹I^[86, 87], and that ⁹⁰Y-labeled antibodies appear to demonstrate more clinical activity than ¹³¹I-labeled antibodies in a human xenograft model^[88, 89]. Theoretical optimal tumor size by isotope has been reported as 2.8 – 4.2 cm for ⁹⁰Y and 0.2 – 0.5 cm for ¹³¹I^[90]. As a pure beta emitter, ⁹⁰Y can be given on an outpatient basis without patient restrictions (see Table 4).

Table 4.
Features of Yttrium-[90] Compared with Iodine-[131]

Properties	Yttrium-[90]	Iodine-[131]
Energy	Beta emitter (2.3 MeV)	Gamma (0.36 MeV)/ Beta (0.6 MeV) emitter
Path Length	χ_{90} 5 mm	χ_{90} 0.8 mm
Administration	Outpatient	Inpatient or with restrictions to protect family/environment
Half-Life	64 Hours	192 Hours
Urinary Excretion	Minimal 7% in 7 Days	Extensive/variable 46% to 90% in 2 days
Dosing	Dose based on weight and baseline platelet count	Tracer dose and dosimetry used to customize dose

Chelator-linkers have been developed to attach radioactive metals to antibodies. Improved methods for attaching metal chelating groups have enhanced the properties of ^{90}Y radioimmunoconjugates in vivo by increasing both radionuclide retention time and tumor-to-nontumor ratios. First generation chelates developed for use with radioimaging and RIT include the polyaminocarboxylic acids DTPA and EDTA^[91, 92]. MX-DTPA (tiuxetan), an isothiocyanatobenzyl derivative of DTPA, was developed to increase stability of the chelate without compromising antibody specificity, altering metabolism of antibody conjugates, or allowing measurable elution of ^{90}Y ^[92, 93]. A comparison of the MX-DTPA derivative with other chelates containing DTPA or its cyclic anhydride derivative demonstrated that the MX-DTPA derivative yielded conjugates with increased tumor-to-nontumor ratios, and resulted in greater in vivo retention of ^{90}Y ^[94, 95].

1.B.2. Yttrium-[90] Ibritumomab Tiuxetan

Yttrium-[90] ibritumomab tiuxetan (^{90}Y ZevalinTM) is composed of ibritumomab covalently bound to tiuxetan, which strongly chelates the radionuclide ^{90}Y . The radionuclide indium-[111] (^{111}In) has a similar physical half-life (67 hours) and the biodistribution of ^{111}In -labeled ibritumomab tiuxetan mirrors the ^{90}Y -labeled antibody. When substituted for ^{90}Y , ^{111}In ibritumomab tiuxetan is used as a surrogate for imaging^[96, 97].

The ^{90}Y ibritumomab tiuxetan regimen consists of an initial infusion of rituximab to deplete B cells from the peripheral circulation, and to optimize ibritumomab tiuxetan biodistribution. An imaging dose of ^{111}In ibritumomab tiuxetan (5 mCi [185 MBq]; 1.6 mg) is given following the initial rituximab infusion. The biodistribution of ^{111}In ibritumomab tiuxetan is assessed by a visual evaluation of whole body planar view anterior and posterior gamma images at 2 to 24 hours and 48 to 72 hours. To resolve ambiguities, a third image at 90 to 120 hours can be obtained. One week later, patients receive a second infusion of rituximab followed by a single IV injection of ^{90}Y ibritumomab tiuxetan. The standard ^{90}Y ibritumomab tiuxetan dose, 0.4 mCi/kg body weight (15 MBq/kg; not to exceed 32 mCi [1.2 GBq]), is reduced to 0.3 mCi/kg

(11 MBq/kg not to exceed 32 mCi) in patients with mild thrombocytopenia (100,000 to 149,000 platelets/mm³).

1.C. Clinical Development

Yttrium-[90] ibritumomab tiuxetan clinical development was initiated in 1993. Seven clinical trials (6 complete and 1 ongoing) have been performed (Table 5).

Table 5.
⁹⁰Y Ibritumomab Tiuxetan Clinical Studies

Study	Description	N	Status
106-01/02	Phase I/II	18	Complete
106-03	Phase I/II	58	Complete
106-04	Phase III Controlled Randomized 0.4 mCi/kg	143	Complete
106-05	Phase II Mild Thrombocytopenia 0.3 mCi/kg	30	Complete
106-06	Phase III Rituximab-Refractory Nonrandomized 0.4 mCi/kg	57	Complete
106-98	Open Label	183	Ongoing
	Total	489	

N = number of patients

- **Dose-Finding and Safety Trials.** Dose-escalation studies (106-01/02^a; 106-03) were conducted to optimize the biodistribution of ibritumomab tiuxetan, to determine the maximum tolerated dose (MTD) of ⁹⁰Y ibritumomab tiuxetan under conditions of optimal biodistribution, and to obtain Phase II safety and efficacy data. The study population included low-grade, intermediate-grade, and mantle-cell NHL patients.
- **Randomized, Controlled Comparison Phase III Trial.** Study 106-04 was designed to compare the efficacy and safety of the ⁹⁰Y ibritumomab tiuxetan regimen with the control, rituximab. The study population included relapsed or refractory low-grade, follicular, or CD20+ transformed NHL patients.
- **Supportive Phase II Trial in a Special Population.** Patients in Study 106-05 received a reduced dose of ⁹⁰Y ibritumomab tiuxetan (0.3 mCi/kg) to confirm safety and efficacy in a specific population of mildly thrombocytopenic patients with relapsed or refractory low-grade, follicular, or CD20+ transformed NHL.
- **Phase III Rituximab-refractory Trial.** A Phase III, internally controlled study (106-06) was conducted in relapsed or refractory follicular NHL patients who were refractory to rituximab treatment.

^aStudy 106-02 was designed to test a multiple low-dose treatment scheme for ⁹⁰Y ibritumomab tiuxetan. After enrollment of a single patient, the study was terminated for administrative reasons (investigator relocation to another institution). This study is included for completeness, but provides no relevant information on the efficacy or safety of ⁹⁰Y ibritumomab tiuxetan.

- **Supportive Study.** Study 106-98 is an ongoing open-label trial designed to provide compassionate treatment to patients without other alternatives and to add to the overall safety experience. Histologies include low-grade, follicular, de novo diffuse large cell, transformed including Richter's, and mantle cell NHL.

2. EFFICACY OF ⁹⁰Y IBRITUMOMAB TIUXETAN

Standardized response criteria for the evaluation of NHL therapies did not exist when the ⁹⁰Y ibritumomab tiuxetan protocols were designed. The ⁹⁰Y ibritumomab tiuxetan protocol-defined response criteria (PDRC) were designed in consultation with the FDA. Subsequently, in 1998, an International Workshop was convened at the U.S. National Cancer Institute to define a standardized set of response criteria for NHL patients. The resultant International Workshop Response Criteria (IWRC) for NHL were published^[98] and have been rapidly adopted by the NCI cooperative study groups and academic oncology researchers. Results are presented using both guidelines for response criteria.

The LEXCOR (Lymphoma Experts of Confirmation Response) panel, an independent, third-party panel blinded to patient identity, treatment received, and investigator assessments of response, was utilized to assess response. LEXCOR panel members were radiologists and oncologists expert in lymphoma who were not investigators on the ⁹⁰Y ibritumomab tiuxetan studies. The panel applied a uniform set of criteria to clinical data and CT scans from patients who had received either the study drug or control therapy.

2.A. Phase III Comparison Study (106-04)

This Phase III, randomized, controlled clinical study was designed to compare the RIT ⁹⁰Y ibritumomab tiuxetan (N = 73) with the control rituximab (N = 70), in patients with low-grade, follicular, or transformed NHL. At enrollment, patients were stratified by histology (IWF A versus follicular versus transformed) and were randomized to receive ⁹⁰Y ibritumomab tiuxetan or rituximab. The ⁹⁰Y ibritumomab tiuxetan treatment group received the following:

- An infusion of rituximab (250 mg/m²) followed by an intravenous (IV) injection of an imaging and dosimetry dose of ¹¹¹In ibritumomab tiuxetan (5 mCi).
- One week following the rituximab and ¹¹¹In ibritumomab tiuxetan, patients meeting dosimetry requirements were to receive a second infusion of rituximab (250 mg/m²) followed by a 10-minute IV injection of ⁹⁰Y ibritumomab tiuxetan (0.4 mCi/kg, maximum dose 32 mCi).

Patients randomized to the rituximab treatment group received a course of rituximab:

- Infusions of 375 mg/m², weekly times four.

The prospectively defined primary endpoint was ORR as determined by the blinded, independent LEXCOR panel. Sample size was chosen to provide 80% power to detect a treatment difference of 25% in ORR given an alpha level of 0.05. Secondary efficacy endpoints included time to progression (TTP) in all patients and responders, duration of response (DR), time to next anticancer therapy (TTNT), and quality of life (QOL) assessment. The study was not powered to show a difference in TTP, but was prospectively designed to demonstrate clinical equivalence (\pm 1.5 months). All analyses were calculated from data obtained on the intent-to-treat (ITT) population. Inclusion criteria defined by the protocol required that patients enrolled in Study 106-04 must have:

“histologically confirmed, relapsed or refractory low-grade or follicular, or transformed... B-cell NHL requiring treatment as determined by an increase in overall

tumor size, the presence of B symptoms ($\geq 10\%$ weight loss, fever, night sweats), and or the presence of masses causing ongoing clinical symptomatology (tumor-related pain, organ dysfunction, hepatomegaly, splenomegaly).”

Patients were required to have a bone marrow biopsy and lymph node biopsy within 6 months prior to treatment to confirm disease histology.

Comparisons made throughout this section will list data from ^{90}Y ibritumomab tiuxetan treatment group first followed by data from the rituximab control group.

2.A.1. Demographics and Disease Status at Study Entry

Demographic data are presented in [Table 6](#). Patients were stratified by histology at registration. The sponsor reviewed all pathology report source documents when it was discovered that pathology classifications reported on case report forms for some patients were not internally consistent. As a result, a reassignment of the pathology group was confirmed for four patients in the Comparison Study: two patients in the ^{90}Y ibritumomab tiuxetan group misclassified with follicular NHL were reclassified with transformed NHL, and two patients in the rituximab group were misclassified with transformed NHL and were reclassified with follicular. This reclassification did not affect outcome. Source documents were provided to FDA.

Table 6.
Summary of Demographics at Study Entry:
Phase III Comparison Study

	⁹⁰ Y Ibritumomab Tiuxetan (N = 73)	Rituximab (N = 70)	p-value*
Age (Years)			
Median	60.0	57.0	
Range	29 – 80	36 - 78	
Age Group [N (%)]			0.629
< 65 years	48 (66%)	46 (66%)	
65 - < 75 years	17 (23%)	20 (29%)	
≥ 75 years	8 (11%)	4 (6%)	
Sex [N (%)]			0.868
Female	38 (52%)	35 (50%)	
Male	35 (48%)	35 (50%)	
Ethnicity [N (%)]			0.610
Caucasian	68 (93%)	63 (90%)	
African-American	2 (3%)	3 (4%)	
Hispanic	2 (3%)	2 (3%)	
Asian	1 (1%)	0 (0%)	
Other	0 (0%)	2 (3%)	
Weight (kg)			0.962
Mean	78.0	77.8	
Std	18.3	17.4	
Median	75.0	75.5	
Range	(45.0 - 159.0)	(48.0 - 117.0)	

N = number of patients

*p-values are calculated from Cochran-Mantel-Haenszel test for ordinal variables, Fishers' exact two-tailed test for categorical variables and t-test for continuous variables; does not include unknown category

No statistical differences in disease status were found at study entry between the ⁹⁰Y ibritumomab tiuxetan treatment group and the rituximab control group (Table 7). Patients had advanced stage disease, a median of 2 prior regimens (range 1 to 6), 45% had bulky disease, and 39% had bone marrow involvement. More than 10% of patients in each treatment group were classified as International Prognostic Index (IPI) intermediate-high risk or high risk.

Table 7.
Summary of Disease Status:
Phase III Comparison Study

	⁹⁰ Y Ibritumomab Tiuxetan (N = 73)	Rituximab (N = 70)	p-value*
	N (%)	N (%)	
Disease Stage at Study Entry			
I/II	8 (11.0)	6 (8.6)	0.780
III/IV	65 (89.0)	64 (91.4)	
Histology Type			
A	9 (12.3)	8 (11.4)	0.391
Follicular	55 (75.3)	58 (82.9)	
Transformed	9 (12.3)	4 (5.7)	
Bone Marrow Involvement			
0%	42 (57.5)	46 (65.7)	0.456
0.1 - 5%	3 (4.1)	5 (7.1)	
5 - 20%	20 (27.4)	15 (21.4)	
≥ 20%	8 (11.0)	4 (5.7)	
Splenomegaly			
Yes	7 (9.6)	3 (4.3)	0.327
No	66 (90.4)	67 (95.7)	
Extranodal Disease			
0, 1	60 (82.2)	61 (87.1)	0.490
≥ 2	13 (17.8)	9 (12.9)	
Bulky Disease			
< 5 cm	40 (54.8)	39 (55.7)	0.672
5 - < 7 cm	18 (24.7)	13 (18.6)	
7 - < 10 cm	9 (12.3)	13 (18.6)	
≥ 10 cm	6 (8.2)	5 (7.1)	
WHO Performance Status			
0, 1	72 (98.6)	68 (97.1)	0.614
≥ 2	1 (1.4)	2 (2.9)	
Baseline LDH			
Normal or Low	57 (78.1)	54 (77.1)	0.653
High	14 (19.2)	10 (14.3)	
Unknown	2 (2.7)	6 (8.6)	
Baseline PB B-Cell Counts (× 10³ cells/mm³)			
None [†]	3 (4.1)	2 (2.9)	0.844
Low (< 32)	15 (20.5)	13 (18.6)	
Normal/High (≥ 32)	52 (71.2)	54 (77.1)	
Unknown	3 (4.1)	1 (1.4)	
<i>bcl-2</i> (Peripheral Blood)			
Positive	30 (41.1)	33 (47.1)	0.493
Negative	39 (53.4)	33 (47.1)	
Unknown	4 (5.5)	4 (5.7)	
<i>bcl-2</i> (Bone Marrow)			
Positive	27 (37.0)	30 (42.9)	0.357
Negative	34 (46.6)	26 (37.1)	
Unknown	12 (16.4)	14 (20.0)	

Continued

	⁹⁰ Y Ibritumomab Tiuxetan (N = 73)	Rituximab (N = 70)	p-value*
	N (%)	N (%)	
Number of Prior Regimens			
Median	2.0	2.0	0.803
Range	(1.00 - 6.00)	(1.00 - 5.00)	
Number of Prior Regimens by Category			
1	34 (46.6)	29 (41.4)	0.668
2 - 3	31 (42.5)	35 (50.0)	
≥ 4	8 (11.0)	6 (8.6)	
Type of Prior Regimen[‡]			
Alkylator +/- Prednisone	21 (28.8)	19 (27.1)	N/A
Purine Analogs	7 (9.6)	15 (21.4)	
Steroids	14 (19.2)	15 (21.4)	
CVP or COP	27 (37.0)	19 (27.1)	
CHOP	30 (41.1)	34 (48.6)	
Other Aggressive	18 (24.7)	30 (42.9)	
Prior Radiotherapy			
Yes	21 (28.8)	15 (21.4)	0.341
No	52 (71.2)	55 (78.6)	
IPI Risk Group			
Low	25 (34.2)	32 (45.7)	0.188
Low/Intermediate	38 (52.1)	23 (32.9)	
Intermediate/High	5 (6.8)	7 (10.0)	
High	3 (4.1)	2 (2.9)	
Unknown	2 (2.7)	6 (8.6)	

N = number of patients

N/A = not available

*p-values are calculated from Cochran-Mantel-Haenszel test for ordinal variables, Fishers' exact two-tailed test for categorical variables and t-test for continuous variables; does not include unknown category

[†]None = level below the detectable limit

[‡]Numbers are not additive since a patient can receive more than one type of regimen

2.A.2. Overall Response Rate

The primary efficacy endpoint goal was met: the ORR achieved in the ⁹⁰Y ibritumomab tiuxetan group was statistically higher than that in the rituximab control group regardless of response criteria used (Table 8).

Table 8.
Overall Response Rates:
Phase III Comparison Study
(N = 143)

	Protocol-Defined Response Criteria			International Workshop Response Criteria		
	⁹⁰ Y Ibritumomab Tiuxetan	Rituximab	p-value*	⁹⁰ Y Ibritumomab Tiuxetan	Rituximab	p-value*
ORR	73%	47%	0.002	80%	56%	0.002
CR	18%	11%	0.326	30%	16%	0.040
CCR/CRu	3%	4%	-	4%	4%	-
PR	52%	31%	-	45%	36%	-

N = number of patients

*p-values generated by Cochran-Mantel-Haenszel test adjusted for histology type

CR = complete response

CCR = complete clinical response

CRu = complete response, unconfirmed

Treatment comparisons of ORR are presented by histology type (Table 9). Interaction effect among histology types was not significant (p = 0.252).

Table 9.
LEXCOR Response by Histology:
Phase III Comparison Study

Histology Type	⁹⁰ Y Ibritumomab Tiuxetan (N = 73) N/Total (%)	Rituximab (N = 70) N/Total (%)	p-value*	p-value [†]
All	53/73 (72.6)	33/70 (47.1)	0.002	0.252
A	6/9 (66.7)	3/8 (37.5)		
Follicular	42/55 (76.4)	27/58 (46.6)		
Transformed	5/9 (55.6)	3/4 (75.0)		
95% CI (ORR)	[60.7%, 82.1%]	[35.2%, 59.4%]		

N = number of patients

*p-values are calculated from Cochran-Mantel-Haenszel test, stratified by pathology report histology

[†]p-values are calculated from Breslow-Day test to test interaction effect among different histology types

The reduction in overall tumor burden (sum of the products of the perpendicular diameters of all lesions [SPD]) was greater in the ⁹⁰Y ibritumomab tiuxetan group than in the control (Table 10).

Table 10.
Change in Median SPD:
Phase III Comparison Study

Treatment Group	N	Median Baseline SPD (cm ²)	Median Percent Change in SPD*	p-value [†]
⁹⁰ Y Ibritumomab Tiuxetan	73	21.4	-90.9	0.004
Rituximab	69 [‡]	25.0	-70.5	

N = number of patients

*Measured at tumor nadir

[†]p-value generated by Wilcoxon rank sum test

[‡]Lesion-measurement data for one patient was not available

At the time of progression, for patients who relapsed, the SPD reduction from baseline continued to be greater in the ⁹⁰Y ibritumomab tiuxetan group. See Table 11.

Table 11.
Change in Median SPD in Patients Who Have Progressed:
Phase III Comparison Study

Treatment Group	N	Median Baseline SPD (cm ²)	Median Percent Change in SPD*	Median [†] Percent SPD Change at Progression	p-value [‡]
⁹⁰ Y Ibritumomab Tiuxetan	46	26.2	-76.4	-48.0	0.057
Rituximab	49	28.8	-58.0	-20.0	

N = number of patients

*Measured at tumor nadir

[†]Patients' last SPD percentage change from baseline

[‡]p-value generated by Wilcoxon rank sum test

2.A.3. Duration of Response

Results are summarized in [Table 12](#). The Kaplan-Meier (K-M) estimated median DR was not statistically different between groups. In the subset of patients with follicular NHL, the estimated median DR was 6.4 months longer in the ⁹⁰Y ibritumomab tiuxetan group (18.5+ versus 12.1+ months) and appears clinically meaningful, though not statistically significant.

Table 12.
Summary of Duration of Response* in Months:
Phase III Comparison Study
(N = 143)

Histology Type		⁹⁰ Y Ibritumomab Tiuxetan (N/Total)	Rituximab (N/Total)	p-value
All	N	53/73	33/70	0.644 [†]
	Median	14.2+	12.1+	
	Range	(0.9, 28.9+)	(2.1, 24.5)	
	95% CI	[9.4, .]	[8.0, 24.5]	
	% Censored	47.2%	42.4%	
A	N	6/9	3/8	0.420 [‡]
	Median	9.8	.	
	Range	(5.0, 20.5)	(8.0, 14.5+)	
	95% CI	[7.1, 20.5]	[8.0, .]	
	% Censored	16.7%	66.7%	
Follicular	N	42/55	27/58	0.371 [‡]
	Median	18.5+	12.1+	
	Range	(1.7, 28.9+)	(2.7, 24.5)	
	95% CI	[10.0, .]	[7.9, 24.5]	
	% Censored	52.4%	40.7%	
Transformed	N	5/9	3/4	0.850 [‡]
	Median	6.8	11.7	
	Range	(0.9, 20.3+)	(2.1, 17.0+)	
	95% CI	[0.9, .]	[2.1, .]	
	% Censored	40.0%	33.3%	

N = number of patients

*DR is the interval from onset of response to disease progression.

[†]p-value generated by proportional hazard regression adjusted for histology type

[‡]p-values generated by Log-rank test

Note: “+” for a median value indicates median not yet reached, these values are K-M estimated medians; “+” for a maximum value indicates censored data; dots for a median or 95% CI indicate the value could not be estimated due to the high percentage of censored data

2.A.4. Time to Progression and Time to Next Anticancer Treatment

This study was not designed or powered to demonstrate a difference in TTP for ⁹⁰Y ibritumomab tiuxetan compared with rituximab (FDA agreement, September 30, 1997). Instead, the protocol statistical section prospectively defined a TTP objective, stating that

“the target median TTP for the ⁹⁰Y ibritumomab tiuxetan group will be at least similar to that of the rituximab group. Based on the current clinical experience, a median TTP of 7.5 months is expected for all patients in the rituximab group. A difference of 1.5 months or less in the point estimate of TTP will be considered as clinically equivalent between the two treatment groups”.

Evaluation of TTNT was prospectively defined as a secondary efficacy endpoint.

As defined in the protocol, median TTP was to be compared using the Log-rank test. Estimated median TTP in the ITT population is 11.2+ months in the ^{90}Y ibritumomab tiuxetan group (95% confidence interval [CI]: 7.8, 15.4) and 10.1+ months in the rituximab group (95% CI: 6.8, 12.9). See Figure 2.

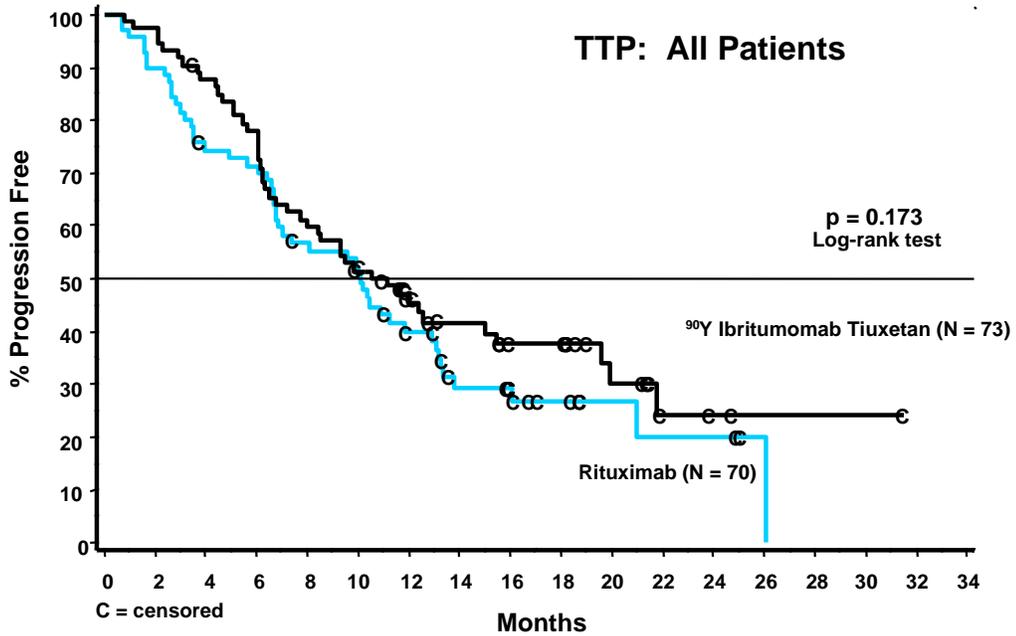


Figure 2. TTP in Phase III Comparison Study: Kaplan-Meier analysis

For the ^{90}Y ibritumomab tiuxetan group, the median time to next therapy (TTNT) has not been reached (range, 1.2 to 31.5+ months) as 56% of patient data are censored. The median TTNT after treatment with rituximab was 13.1+ months (0.8 to 26.1+ months), with 44.0% censored (Figure 3).

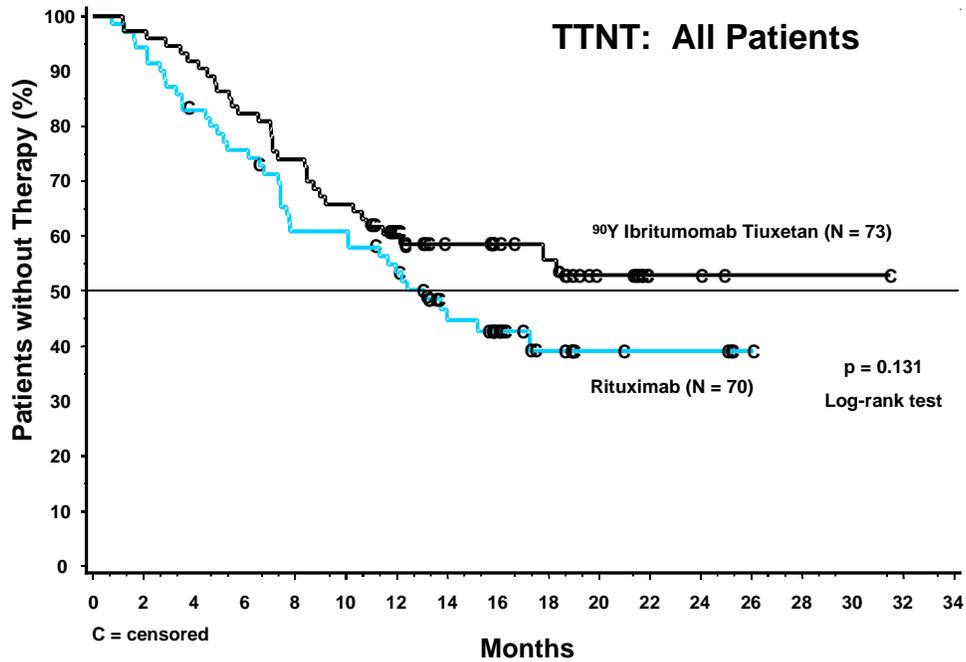


Figure 3. TTNT in Phase III Comparison Study: Kaplan-Meier analysis

2.A.4.a. TTP and TTNT by Histology

The protocol also defined subset analyses by prognostic indicators including histology. In the population of patients with follicular histology, the Kaplan-Meier estimated median TTP was 12.6+ months (range, 2.9 to 31.5+ months; 95% CI: 9.3, 19.9; 21 patients ongoing) for the ^{90}Y ibritumomab tiuxetan group compared with 10.2+ months (range, 0.7 to 22.1+ months, 95% CI: 6.9, 13.1; 14 patients ongoing) for the rituximab control (Figure 4 and Table 13). The difference in TTP values in follicular histology patients receiving ^{90}Y ibritumomab tiuxetan therapy versus control, though not statistically significant, approaches the $\alpha = 0.05$ level.

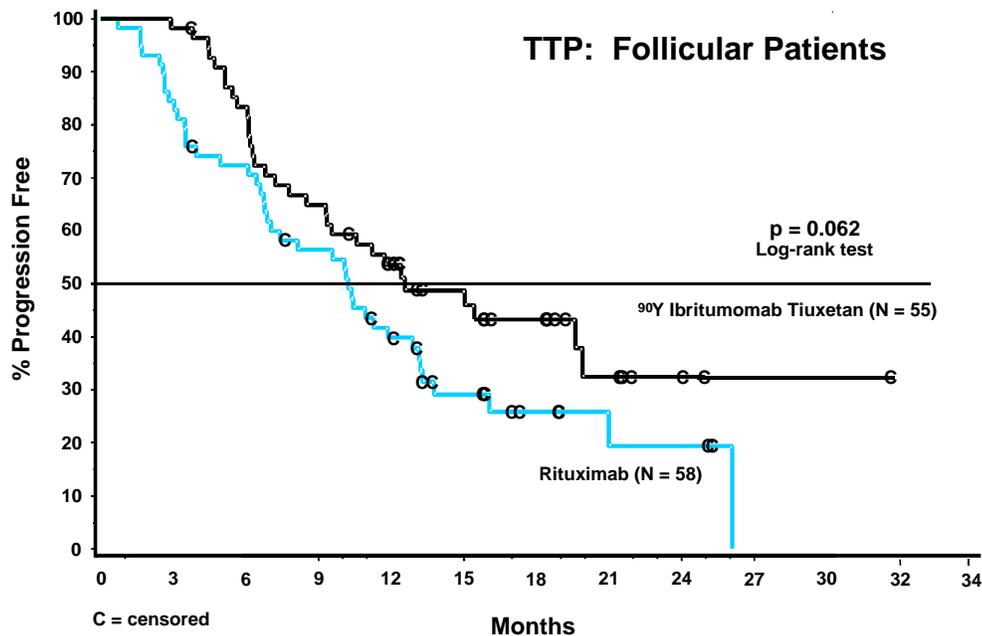


Figure 4. TTP in Phase III Comparison Study: Kaplan-Meier analysis of patients with follicular NHL

For patients with follicular lymphoma, median TTNT for the ^{90}Y ibritumomab tiuxetan group could not be determined as 62% of patient data were censored; the range was 3.5 to 31.5 months. Estimated median TTNT for the rituximab follicular-histology group was 13.8+ months (range, 1.6 to 26.1 months, 47% censored). See Figure 5.

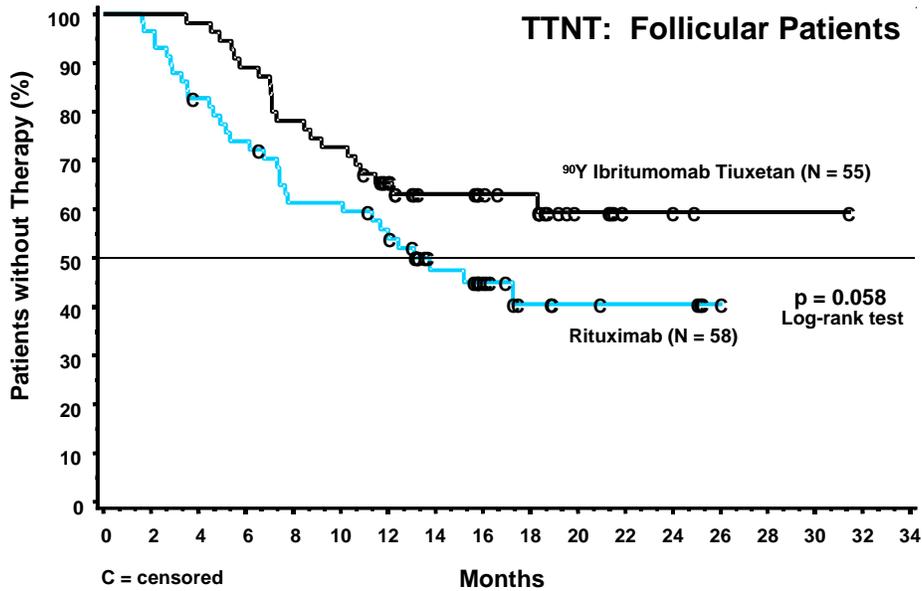


Figure 5. TTNT in Phase III Comparison Study: Kaplan-Meier analysis of patients with follicular NHL

The Kaplan-Meier estimated TTP for nontransformed patients (low-grade and follicular) is presented in Figure 6 and in [Table 13](#).

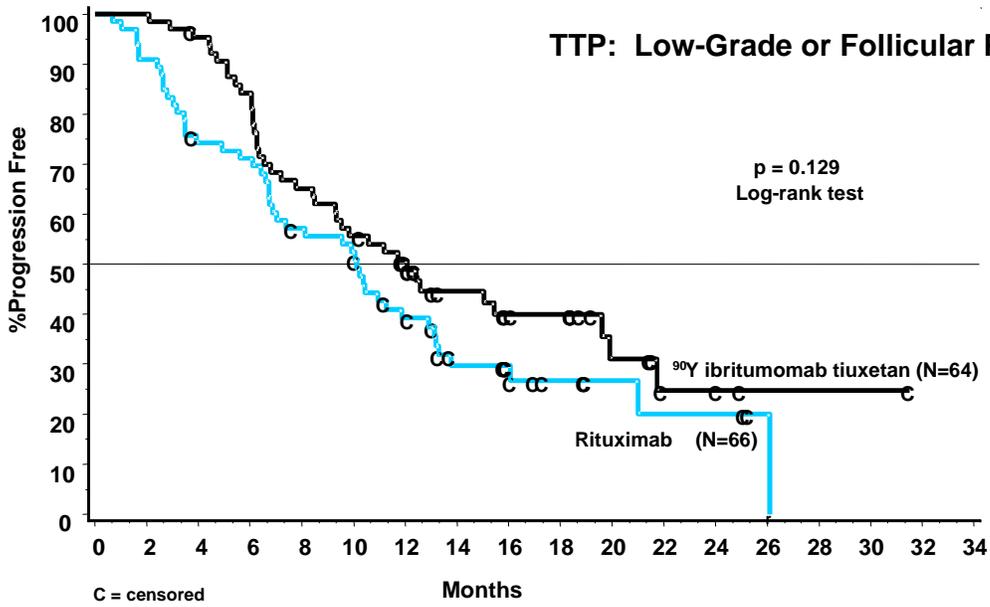


Figure 6. TTP in Phase III Comparison Study: Kaplan-Meier analysis of low-grade or follicular patients

For patients with low-grade and follicular (nontransformed) histology, ⁹⁰Y ibritumomab tiuxetan patients had a significantly longer TTNT (median cannot yet be estimated, range 2.1 - 31.5+ months, 61% censored) when compared with rituximab patients (median 13.1+ months, range 1.3 - 26.1+ months, 46% censored) using the Log-rank test (p = 0.040). See Figure 7.

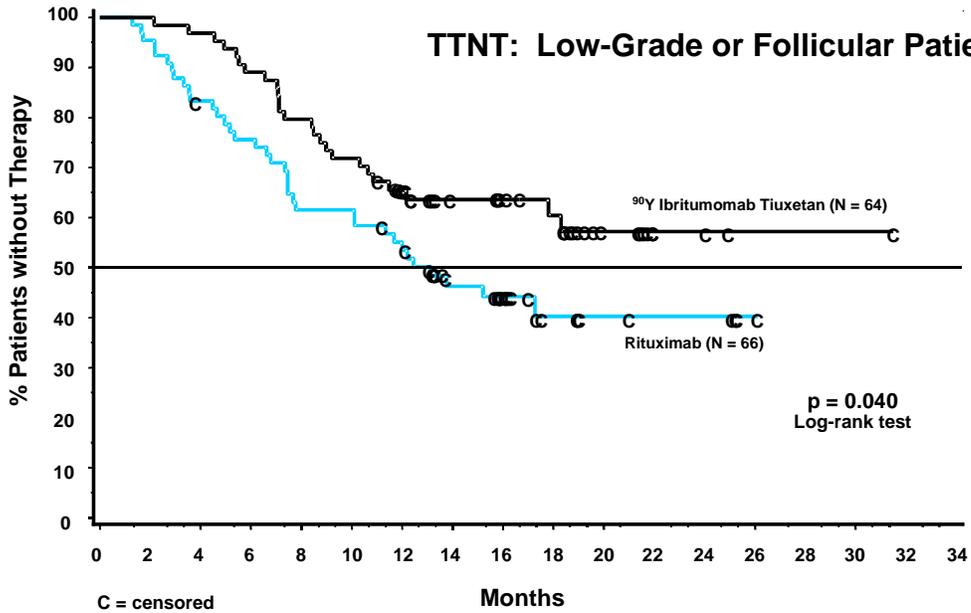


Figure 7. TTNT in Phase III Comparison Study: Kaplan-Meier analysis of low-grade or follicular patients

Table 13.
Time to Progression* in Months by Histology Type:
Phase III Comparison Study
(N = 143)

Histology Type		⁹⁰ Y Ibritumomab Tiuxetan (N = 73)	Rituximab (N = 70)	p-value
All	N	73	70	0.173 [†]
	Median	11.2+	10.1+	
	Range	(0.8, 31.5+)	(0.7, 26.1)	
	95% CI	[7.8, 15.4]	[6.8, 12.9]	
	% Censored	37.0%	28.6%	
A [‡]	N	9	8	0.767 [§]
	Median	8.4	8.3	
	Range	(2.1, 21.7)	(1.0, 16.1+)	
	95% CI	[6.3, 12.1]	[1.7, .]	
	% Censored	11.1%	37.5%	
Follicular	N	55	58	0.062 [§]
	Median	12.6+	10.2+	
	Range	(2.9, 31.5+)	(0.7, 26.1)	
	95% CI	[9.3, 19.9]	[6.9, 13.1]	
	% Censored	43.6%	27.6%	
Transformed	N	9	4	0.576 [§]
	Median	3.1	10.1	
	Range	(0.8, 21.7+)	(0.7, 18.7+)	
	95% CI	[2.1, 8.0]	[0.7, .]	
	% Censored	22.2%	25.0%	

N = number of patients

*TTP of disease is the interval from the first infusion to disease progression. 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.

[†]p-value generated by proportional hazards regression adjusted for histology type.

[‡]Pathology of IWF-A patients included small lymphocytic lymphoma, lymphoplasmocytic lymphoma, nodal and extranodal marginal zone, maltoma, and a single mantle-cell NHL.

[§]p-values generated by Log-rank test.

Note: “+” for a median value indicates median not yet reached, these values are K-M estimated medians; “+” for a maximum value indicates censored data; dots for a 95% CI indicate the value could not be estimated due to the high percentage of censored data.

2.A.4.b. TTP for CR/CCR Patients

For ⁹⁰Y ibritumomab tiuxetan patients who achieved a complete response (CR) or clinical complete response (CCR), the median TTP could not be estimated, as 73% of data are censored; the range of TTP values was 8.4 to 31.5+ months; median follow up is 19.2 months. The Kaplan-Meier estimated median TTP was 13.4 months for rituximab patients who achieved a CR or CCR (range, 6.8 to 25.3+ months; 46% censored data). See [Figure 8](#). This difference in TTP between groups is not statistically significant (note small patient numbers).

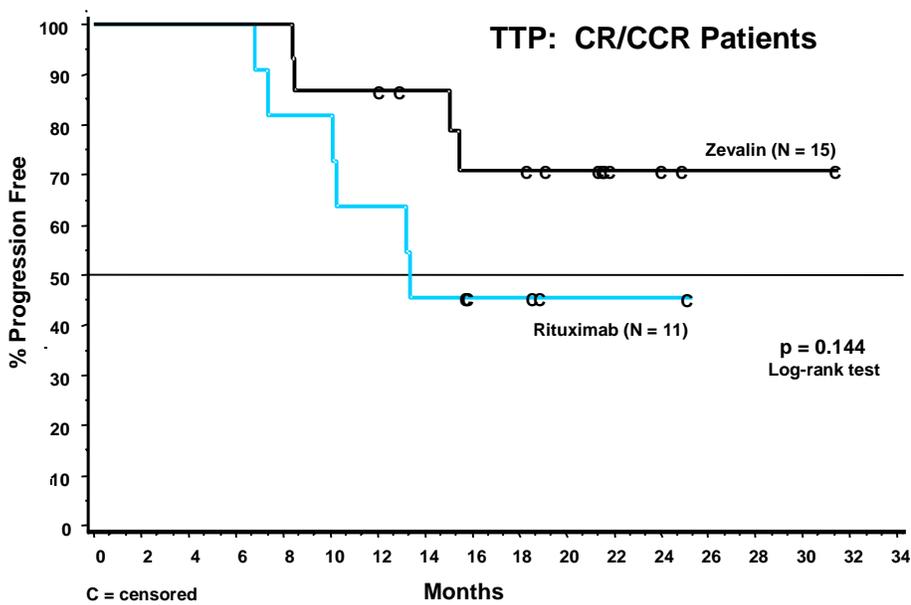


Figure 8. TTP in Phase III Comparison Study: Kaplan-Meier analysis of patients achieving a CR or CCR

2.A.5. Evaluation of Time to Progression and Time to Next Anticancer Therapy

Though TTP and TTNT were both determined by investigators, designation of TTP depended on assessment of disease progression as defined by the protocol-defined response criteria. Patients in the ⁹⁰Y ibritumomab tiuxetan group had greater tumor shrinkage than those in the rituximab group (see Table 10). This difference may have introduced bias because progressive disease (PD) was defined as a 50% increase in SPD from nadir. Thus, the absolute increase in tumor size for a designation of PD is considerably smaller for patients whose tumor burden is low at nadir (Figure 9, Hypothetical Patient A) than for patients whose tumor burden is not as low (Figure 9, Hypothetical Patient B).

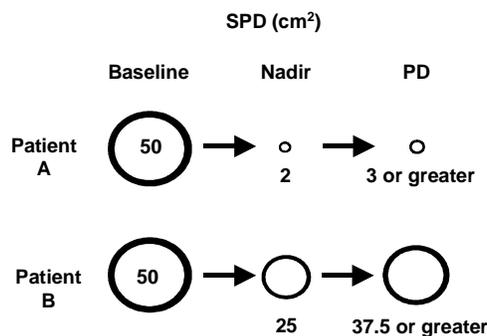


Figure 9. Definition of progressed disease is biased against therapy that results in greater tumor shrinkage

For example, Figure 10 shows lesion SPD values over time for two actual patients from Study 106-04 who progressed without new lesions. The two patients began the study with similar SPD values, but the patient who received ^{90}Y ibritumomab tiuxetan had a much greater decrease in SPD than the patient who received rituximab. The absolute increase in tumor size necessary to assign an outcome of progressive disease was much greater for the rituximab patient than for the ^{90}Y ibritumomab tiuxetan patient.

Thus, evaluations based on TTNT avoid a bias inherent in TTP and may better reflect the clinical decision to treat a patient who has progressed, based on their tumor size and disease-related signs and symptoms.

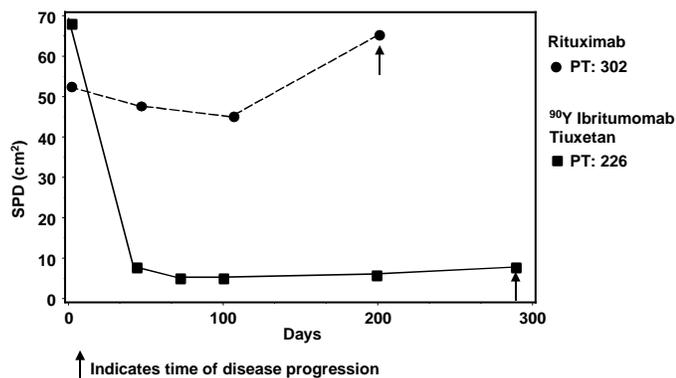


Figure 10. Lesion SPD over time for two patients who progressed without new lesions

2.A.6. Response Rates in Special Populations

2.A.6.a. Treatment-Resistant Patients

Patients with relapsed or refractory NHL who are resistant to treatment, including chemotherapy and rituximab, have few alternatives for further therapy. Remission duration and response rates decline with consecutive courses of chemotherapy^[15, 17].

Resistance to last chemotherapy at baseline was similar in the two groups (49%, ^{90}Y ibritumomab tiuxetan group; 47%, rituximab group). Patients who were resistant to their last chemotherapy at study entry were more likely to respond to ^{90}Y ibritumomab tiuxetan therapy than to rituximab therapy (Table 14).

Table 14.
Response in Chemotherapy-Resistant* Patients:
Phase III Comparison Study

	Response	⁹⁰Y Ibritumomab Tiuxetan (N = 73) N (%)	Rituximab (N = 70) N (%)	p-value[†]
Resistance To Any Chemotherapy	CR, CCR, or PR	24 (63)	18 (43)	0.078
	SD or PD	14 (37)	24 (57)	
Resistance To Last Chemotherapy	CR, CCR, or PR	21 (64)	11 (36)	0.045
	SD or PD	12 (36)	20 (65)	

N = number of patients

*Chemotherapy-resistant: nonresponders or progressed within 6 months

[†]p-value generated by Fisher's Exact two-tailed test

2.A.6.b. Patients with Bulky Disease

The high beta energy (2.4 MeV) and resultant long path length (5 mm) from ⁹⁰Y result in effective therapy of bulky, poorly vascularized tumors. Malignant NHL cells at the center of bulky lymphomatous masses can be killed by radioactive emissions from a radiolabeled antibody that only partially penetrates these bulky masses.

Consistent with this mechanism, response rates in ⁹⁰Y ibritumomab tiuxetan patients with bulky disease were significantly higher than control (Table 15).

Table 15.
Overall Response Rates* in Patients with Bulky Disease:
Phase III Comparison Study

Bulky Disease Category	⁹⁰Y Ibritumomab Tiuxetan (N = 73) N/Total (%)	Rituximab (N = 70) N/Total (%)	p-value[†]
< 5 cm	31/40 (78)	19/39 (49)	0.002
≥ 5 cm	22/33 (67)	14/31 (45)	

N = number of patients

*Protocol-defined response criteria

[†]p-value generated by Cochran-Mantel-Haenszel test over prognostic variables

2.A.7. Univariate Analysis of Response by Baseline Patient Characteristic

A univariate analysis of response by patient characteristic at baseline was performed. Analysis of treatment difference, adjusting for each patient characteristic, was conducted using the Cochran-Mantel-Haenszel test. The response rate was significantly higher in the ⁹⁰Y ibritumomab tiuxetan group regardless of any adjustment for any patient characteristic. The relevance of a baseline patient characteristic to treatment difference was assessed using the Breslow-Day test. No baseline patient characteristic was statistically relevant (Table 16).

Table 16.
Analysis of Treatment Difference by Baseline Patient Characteristic:
Phase III Comparison Study

Variable	Category	⁹⁰ Y Ibritumomab Tiuxetan (N = 73) N/Total (%)	Rituximab (N = 70) N/Total (%)	p-value*	p-value [†]
Age	< 65 years	34/48 (70.8)	20/46 (43.5)	0.002	0.829
	≥ 65 years	19/25 (76.0)	13/24 (54.2)		
Sex	Female	29/38 (76.3)	15/35 (42.9)	0.002	0.302
	Male	24/35 (68.6)	18/35 (51.4)		
Disease Stage at Study Entry	I/II	6/8 (75.0)	3/6 (50.0)	0.002	0.991
	III/IV	47/65 (72.3)	30/64 (46.9)		
Pathology Report Histology	A	6/9 (66.7)	3/8 (37.5)	0.002	0.252
	Follicular	42/55 (76.4)	27/58 (46.6)		
	Transformed	5/9 (55.6)	3/4 (75.0)		
Bone Marrow Involvement	Yes	21/31 (67.7)	10/24 (41.7)	0.002	0.908
	No	32/42 (76.2)	23/46 (50.0)		
Splenomegaly	Yes	6/7 (85.7)	1/3 (33.3)	0.002	0.362
	No	47/66 (71.2)	32/67 (47.8)		
Extranodal Disease	0,1	42/60 (70.0)	30/61 (49.2)	0.002	0.164
	≥ 2	11/13 (84.6)	3/9 (33.3)		
Bulky Disease	< 5 cm	31/40 (77.5)	19/39 (48.7)	0.001	0.273
	5 - < 7 cm	14/18 (77.8)	5/13 (38.5)		
	7 - < 10 cm	7/9 (77.8)	7/13 (53.8)		
	≥ 10 cm	1/6 (16.7)	2/5 (40.0)		
WHO Performance Status	0, 1	53/72 (73.6)	33/68 (48.5)	0.002	N/A
Baseline LDH	Normal or Low	44/57 (77.2)	29/54 (53.7)	0.002	0.562
	High	8/14 (57.1)	2/10 (20.0)		
	Unknown	1/2 (50.0)	2/6 (33.3)		
Baseline IgM	Not Done	2/2 (100.0)	2/6 (33.3)	0.003	0.269
	Normal or Low	49/69 (71.0)	31/64 (48.4)		
	High	2/2 (100.0)	0/0 (0)		
Baseline PB B-Cell Count (x 10 ³ cells/mm ³)	None	0/3 (0)	0/2 (0)	< 0.001	0.698
	Low (< 32)	12/15 (80.0)	6/13 (46.2)		
	Normal/High (≥ 32)	39/52 (75.0)	26/54 (48.1)		
	Unknown	2/3 (66.7)	1/1 (100.0)		
<i>bcl-2</i> (PB)	Positive	23/30 (76.7)	16/33 (48.5)	0.001	0.857
	Negative	27/39 (69.2)	14/33 (42.4)		
	Unknown	3/4 (75.0)	3/4 (75.0)		

Continued

Variable	Category	⁹⁰ Y Ibritumomab Tiuxetan (N = 73) N/Total (%)	Rituximab (N = 70) N/Total (%)	p-value*	p-value [†]
<i>bcl</i> -2 (BM)	Positive	20/27 (74.1)	15/30 (50.0)	0.002	0.723
	Negative	25/34 (73.5)	11/26 (42.3)		
	Unknown	8/12 (66.7)	7/14 (50.0)		
Years Since Diagnosis	< 5 years	36/49 (73.5)	21/50 (42.0)	0.003	0.413
	5 - 10 years	9/14 (64.3)	7/14 (50.0)		
	≥ 10 years	8/10 (80.0)	5/6 (83.3)		
Number of Prior Regimens	1	26/34 (76.5)	14/29 (48.3)	0.002	0.550
	2 - 3	23/31 (74.2)	16/35 (45.7)		
	≥ 4	4/8 (50.0)	3/6 (50.0)		
Prior Radiotherapy	Yes	15/21 (71.4)	7/15 (46.7)	0.002	0.944
	No	38/52 (73.1)	26/55 (47.3)		
IPI Risk Group	Low Risk	18/25 (72.0)	13/32 (40.6)	0.010	0.440
	Low/Intermediate	29/38 (76.3)	16/23 (69.6)		
	Intermediate/High	3/5 (60.0)	2/7 (28.6)		
	High Risk	2/3 (66.7)	0/2 (0.0)		
	Unknown	1/2 (50.0)	2/6 (33.3)		

N = number of patients

*p-values are calculated from Cochran-Mantel-Haenszel test adjusted for patient characteristics

[†]p-values are calculated from Breslow-Day test to test interaction between treatment and patient characteristic

N/A = not available

2.A.8. Multivariate Analysis of Response by Baseline Patient Characteristics

A multivariate analysis of response to treatment by patient characteristics at baseline (including age group, sex, histology type, bone marrow involvement, splenomegaly, hepatomegaly, extranodal disease, tumor bulk, number of prior regimens, IPI index, peripheral blood *bcl*-2 status) revealed that no combination of patient characteristics had a statistically significant influence on treatment differences. Without adjustment of prognostic factors, the odds ratio was 2.89 (95% CI, 1.44 to 5.8; p = 0.003) in favor of ⁹⁰Y ibritumomab tiuxetan.

2.A.9. Quality of Life

The impact of anticancer therapy on QOL is an important consideration for both the patient and the treating physician. The Functional Assessment of Cancer Therapy—General (FACT—G) is a validated QOL survey method that captures the major areas of a patient’s subjective evaluation for the following domains: physical, social, emotional, functional, and relationship with the treating doctor ^[99]. Scores improved in both groups; however, the improvement from baseline to 3 months was statistically significant in the ⁹⁰Y ibritumomab tiuxetan group (p = 0.001) but not in the rituximab group.

While data collection was incomplete, 81 of 143 patients (57%) completed the FACT-G survey prior to treatment at baseline and at 12 weeks: 45 patients (62%) in the ⁹⁰Y ibritumomab tiuxetan group and 36 (51%) in the rituximab group. Although QOL was an analysis variable discussed in the protocol, there were no statistical hypotheses

specified, and no prospective methods were determined for the handling of missing data. For these reasons, QOL data was not used to support clinical benefit.

2.B. Phase III Rituximab-Refractory Study (106-06)

This Phase III, nonrandomized, controlled, open-label, multicenter study was designed to evaluate the ^{90}Y ibritumomab tiuxetan regimen in rituximab-refractory follicular B-cell NHL patients, i.e., patients with follicular NHL treated previously with rituximab (375 mg/m^2 weekly times four), who did not respond or had a TTP < 6 months. The protocol allowed patients with IWF A or transformed lymphoma histology who did not respond to rituximab in the control group of the Phase III Comparison Study (106-04) to be treated on this study for safety assessments only (N = 3).

The primary efficacy endpoint was ORR as determined by the independent, blinded LEXCOR panel and was calculated using both the protocol-derived response criteria (PDRC) and the International Workshop response criteria (IWRC). The target ORR was 35% in patients with follicular histology. Secondary efficacy endpoints were comparisons of ORR and DR to those achieved with prior rituximab treatment and last chemotherapy (Figure 11). The prospectively defined response duration goal was 5 months.

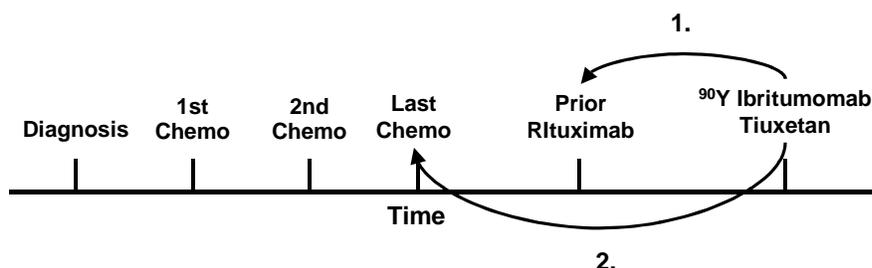


Figure 11. Comparisons of ^{90}Y ibritumomab tiuxetan therapy with: (1.) prior rituximab therapy (ORR data in [Table 21](#)); and (2.) last chemotherapy treatment (ORR data in [Table 22](#))

Demographic and efficacy data are presented from the 54 patients with follicular histology; an additional 3 patients with either nonfollicular, low-grade (IWF A) or transformed lymphoma are included in the safety analyses ([Section 3](#)).

2.B.1. Demographics and Disease Status at Study Entry

Demographic data of the 54 follicular patients are presented in [Table 17](#).

Table 17.
Demographics at Study Entry:
Phase III Rituximab-Refractory Study
(N = 54)

Age (Years)	
Mean	54.2
Std	10.34
Sex [N (%)]	
Female	28 (51.9%)
Male	26 (48.1%)
Ethnicity [N (%)]	
African-American	1 (1.9%)
Caucasian	51 (94.4%)
Hispanic	2 (3.7%)

N = number of patients

Patients were heavily pretreated (median 4 prior regimens, range 1 to 9), had a high incidence of tumor bulk (74% bulky disease; 11.1% splenomegaly, 31.5% bone marrow involvement, and 16.7% with ≥ 2 extranodal sites of disease). See [Table 18](#). Most patients were resistant to at least one course of chemotherapy, and 67% were resistant to their last chemotherapy ([Table 19](#)).

Table 18.
Summary of Disease Status:
Phase III Rituximab-Refractory Study
(N = 54)

	N (%)
Disease Stage at Study Entry	
I/II	3 (5.6%)
III/IV	49 (90.7%)
Unknown	2 (3.7%)
Bone Marrow Involvement	
0%	37 (68.5%)
0.1 - 5%	3 (5.6%)
5 - 20%	12 (22.2%)
≥ 20%	2 (3.7%)
Splenomegaly	
Yes	6 (11.1%)
No	48 (88.9%)
Extranodal Disease	
0, 1	45 (83.3%)
≥ 2	9 (16.7%)
Bulky Disease	
< 5 cm	14 (25.9%)
5 - < 7 cm	17 (31.5%)
7 - < 10 cm	13 (24.1%)
≥ 10 cm	10 (18.5%)
Number of Prior Regimens	
Median	4.0
Range	1 - 9
Prior Radiotherapy	
Yes	16 (29.6%)
No	38 (70.4%)
IPI Risk Group	
Low	25 (46.3%)
Low/Intermediate	10 (18.5%)
Intermediate/High	7 (13.0%)
High	4 (7.4%)
Unknown	8 (14.8%)

N = number of patients

Table 19.
Summary of Prior Chemoresistance:
Phase III Rituximab-Refractory Study
(N = 54)

		Follicular Patients	
		N/Total	(%)
Resistance To Any Chemotherapy	Yes	42/52	(80.8)
	No	10/52	(19.2)
Resistance To Last Chemotherapy	Yes	35/52	(67.3)
	No	17/52	(32.7)

N = number of patients

2.B.2. Overall Response Rate

ORR, CR and PR rates are shown in Table 20. Comparisons of ORR with previous treatment used PDRC.

Table 20.
Response Rate:
Phase III Rituximab-Refractory Study

Response Criteria	ORR	CR	PR
	N (%)	N (%)	N (%)
Protocol-Defined	32 (59)	2 (4)	30 (56)
International Workshop	40 (74)	8 (15)	32 (59)

N = number of patients

A reduction in overall tumor burden (SPD) was observed in 94% (51 of 54) of patients following treatment. SPD-change data by patient are summarized in Figure 12.

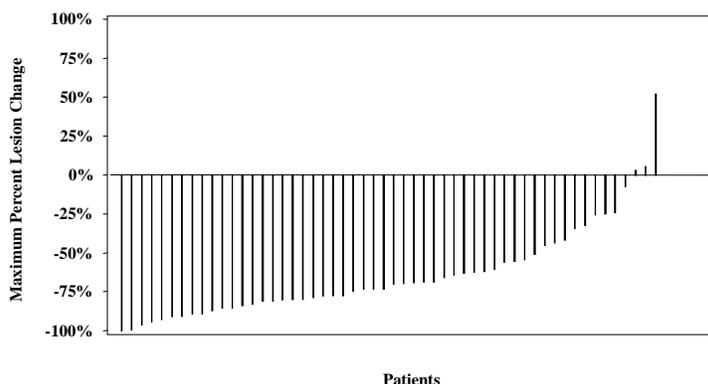


Figure 12. Maximum change from baseline in SPD by patient in the Phase III Rituximab-Refractory Study

2.B.2.a. Comparison of ORR Between ⁹⁰Y Ibritumomab Tiuxetan Therapy and Prior Rituximab Therapy

The ORR of patients treated with ⁹⁰Y ibritumomab tiuxetan therapy was significantly higher than that of the patient’s prior rituximab therapy (Table 21).

Table 21.
Response to ⁹⁰Y Ibritumomab Tiuxetan Therapy Compared with Response to Prior Rituximab Therapy: Phase III Rituximab-Refractory Study (N = 54)

	Total	Responders N (%)	p-value*
Response to ⁹⁰ Y Ibritumomab Tiuxetan	54	32 (59.3)	0.002
Response to Prior Rituximab [†]	54	17 (31.5)	
Response to ⁹⁰ Y Ibritumomab Tiuxetan for Prior Rituximab Responders [†]	17	13 (76.5)	
Response to ⁹⁰ Y Ibritumomab Tiuxetan for Prior Rituximab Nonresponders	37	19 (51.4)	

N = number of patients

*p-value generated by McNemar test

[†]Patients who responded but TTP < 6 months

2.B.2.b. Comparison of ORR Between ⁹⁰Y Ibritumomab Tiuxetan Therapy and Last Chemotherapy

For the 52 patients who received prior chemotherapy, the ORR for patients treated with ⁹⁰Y ibritumomab tiuxetan was not statistically different from the ORR noted for the patients’ last chemotherapy (Table 22). As response rates generally decline with each subsequent therapy (Figure 1), the ORR in the ⁹⁰Y ibritumomab tiuxetan group would be expected to be less than the ORR to the last chemotherapy. In addition, 8 of the 17 patients (47.1%) who did not respond to their last chemotherapy responded to ⁹⁰Y ibritumomab tiuxetan therapy.

Table 22.
Response to ⁹⁰Y Ibritumomab Tiuxetan Therapy Compared with
Response to Last Chemotherapy*:
Phase III Rituximab-Refractory Study

	Responders		
	Total	N (%)	p-value [†]
Response to ⁹⁰ Y Ibritumomab Tiuxetan	51	30 (58.8)	0.371
Response to Last Chemotherapy	51	34 (66.7)	
Response to ⁹⁰ Y Ibritumomab Tiuxetan for Last Chemotherapy Responders	34	22 (64.7)	
Response to ⁹⁰ Y Ibritumomab Tiuxetan for Last Chemotherapy Nonresponders	17	8 (47.1)	

N = number of patients

*Two patients received no prior chemotherapy and data for one additional patient were not available

[†]p-value generated by McNemar test

2.B.3. Time to Progression and Duration of Response

TTP and DR data are presented in Table 23.

Table 23.
Time to Progression* and Duration of Response for Intent-to-Treat Patients
Phase III Rituximab-Refractory Study
(N = 54)

	Time to Progression (Months)	Duration of Response (Months)
Median (K-M)	6.8+	7.7+
Lower (95% CI)	6.1	5.5
Upper (95% CI)	9.3	9.1
Minimum	1.1	2.3
Maximum	25.9+	24.9+
Censored (%)	16	10

*DR is the interval from onset of response to disease progression. TTP of disease is the interval from the first infusion to disease progression. 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.

Note: “+” for a median value indicates median not yet reached; “+” for a maximum value indicates censored data

DR and TTP analyses used PDRC. Time to response, DR, and TTP for responders are shown in [Table 24](#).

Table 24.
Time to Response, Duration of Response, and Time to Progression* in Responders:
Phase III Rituximab-Refractory Study
(N = 32)

	Time to Response (Days)	DR (Months)	TTP (Months)
Median (K-M)	35.0	7.7+	9.1
Lower (95% CI)	35.0	5.5	6.8
Upper (95% CI)	37.0	9.1	10.0
Minimum	27.0	2.3	3.5
Maximum	98	24.9+	25.9+
Censored (%)	0	31.3	31.3

N = number of patients

*DR is the interval from onset of response to disease progression. TTP of disease is the interval from the first infusion to disease progression. 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.

Note: “+” for a median value indicates median not yet reached; “+” for a maximum value indicates censored data

2.B.3.a. Comparison of Duration of Response Between ⁹⁰Y Ibritumomab Tiuxetan Therapy and Prior Rituximab Therapy

Of 54 patients, 32 responded to ⁹⁰Y ibritumomab tiuxetan therapy and 17 responded to their prior rituximab therapy, although to be eligible for the study, the TTP following rituximab had to be less than 6 months. The estimated median DR following ⁹⁰Y ibritumomab tiuxetan therapy was longer than the median DR following the patients’ prior rituximab therapy. The distribution of the DR following ⁹⁰Y ibritumomab tiuxetan therapy was significantly different from the distribution of the DR following the patients’ prior rituximab therapy (Table 25).

Table 25.
Duration of Response Following ⁹⁰Y Ibritumomab Tiuxetan Therapy and
Prior Rituximab Therapy Using the Log-rank Test:
Phase III Rituximab-Refractory Study
(N = 36)

	⁹⁰Y Ibritumomab Tiuxetan Therapy (Months)	Prior Rituximab Therapy (Months)	p-value*
N	32	17	
Median (K-M)	7.7+	4.0	< 0.001
95% CI	[5.5, 9.1]	[3.0, 6.0]	
Censored (%)	31.3	0.0	

N = number of patients

*p-value generated by Log-rank test

Note: “+” for a median value indicates median not yet reached, these values are Kaplan-Meier estimated medians

Data comparing DR for ⁹⁰Y ibritumomab tiuxetan treatment with the same patient's DR from a prior rituximab therapy were available for 13 patients who responded to both therapies. The estimated median DR following ⁹⁰Y ibritumomab tiuxetan therapy is significantly longer than the median DR following the patients' prior rituximab therapy (p = 0.008). See Table 26.

Table 26.
Duration of Response* Following ⁹⁰Y Ibritumomab Tiuxetan Therapy and
Prior Rituximab Therapy Using the Sign and Signed-Rank Tests:
Phase III Rituximab-Refractory Study
(N = 13)

	⁹⁰ Y Ibritumomab Tiuxetan Therapy (Months)	Prior Rituximab Therapy (Months)	p-value [†]	p-value [‡]
N	13	13		
Median (K-M)	8.4+	4.00	0.092	0.008
95% CI	[4.8, .]	[3.00, 6.00]		
Censored (%)	46.2	0.00		

N = number of patients

*DR is the interval from onset of response to disease progression

[†]p-value generated by sign test

[‡]p-value generated by signed-rank test

Note: "+" for a median value indicates the median not yet reached, these values are Kaplan-Meier estimated medians; dots for a 95% CI indicate the value could not be estimated due to the high percentage of censored data

2.B.3.b. Comparison of Duration of Response Between ⁹⁰Y Ibritumomab Tiuxetan Therapy and Last Chemotherapy

The DR following ⁹⁰Y ibritumomab tiuxetan therapy was compared with the DR following the patients' last chemotherapy. Of 54 patients, 32 responded to ⁹⁰Y ibritumomab tiuxetan therapy and 34 responded to their last chemotherapy. The estimated median DR following ⁹⁰Y ibritumomab tiuxetan therapy was longer than the median DR following the patients' last chemotherapy. The distribution of the DR following ⁹⁰Y ibritumomab tiuxetan therapy was not significantly different from the distribution of the DR following the patients' last chemotherapy using the Log-rank test (Table 27).

Table 27.
Duration of Response* Following ⁹⁰Y Ibritumomab Tiuxetan Therapy
and Last Chemotherapy Using the Log-rank Test:
Phase III Rituximab-Refractory Study
(N = 44)

	⁹⁰ Y Ibritumomab Tiuxetan (Months)	Last Chemotherapy (Months)	p-value [†]
N	32	34	
Median (K-M)	7.7+	6.5	0.351
Range	(2.3, 24.9+)	(1.0, 175.0)	
95% CI	[5.5, 9.1]	[4.00, 10.00]	
Censored (%)	31.3	0.00	

N = number of patients

*DR is the interval from onset of response to disease progression

[†]p-value generated by Log-rank test

Note: “+” for a median value indicates median not yet reached, these values are Kaplan-Meier estimated medians; “+” for a maximum value indicates censored data

Data comparing patient response to both ⁹⁰Y ibritumomab tiuxetan and the same patient’s last chemotherapy were available for 19 patients who responded to both therapies. The estimated median DR following ⁹⁰Y ibritumomab tiuxetan therapy was not significantly longer than the median DR following the patients’ last chemotherapy (Table 28).

Table 28.
Duration of Response* Following ⁹⁰Y Ibritumomab Tiuxetan Therapy and
Last Chemotherapy Using the Sign and Signed-Rank Tests:
Phase III Rituximab-Refractory Study
(N = 19)

	⁹⁰ Y Ibritumomab Tiuxetan Therapy (Months)	Last Chemotherapy (Months)	p-value [†]	p-value [‡]
N	19	19		
Median (K-M)	6.1	5.00	0.064	0.294
Range	(2.8, 24.9+)	(1.0, 175.0)		
95% CI	[5.2, 8.4]	[3.00, 8.00]		
Censored (%)	21.1	0.00		

N = number of patients

*DR is the interval from onset of response to disease progression

[†]p-value generated by sign test

[‡]p-value generated by signed-rank test

Note: “+” for a maximum value indicates censored data

2.B.4. Clinical Efficacy Comparison with Prior Therapies

While in review, the following additional exploratory analysis was performed at the request of the FDA.

Methods

A patient is considered as “Favor ⁹⁰Y ibritumomab tiuxetan” if the patient responded to ⁹⁰Y ibritumomab tiuxetan treatment and as “Favor Rituximab” if the patient responded to prior Rituximab treatment but did not respond to ⁹⁰Y ibritumomab tiuxetan therapy or the patient responded to both therapies but the response duration to Rituximab is at least one month longer.

A patient is considered as “Neutral” if the patient did not respond to either therapy or the patient responded to both therapies but the response duration difference is less than one month. If the patient is still in remission and the response duration is shorter than that of the Rituximab therapy, the patient is also considered as “Neutral”.

The response duration data from the “Favor ⁹⁰Y ibritumomab tiuxetan” group were compared with the “Favor Rituximab” group using both sign test and signed ranks test. The level of significance was generated using PROC UNIVARIATE under SAS version 6.12. These analyses were repeated by replacing “one month” with “three months” in the definition of these three categories (“Favor ⁹⁰Y ibritumomab tiuxetan”, “Favor Rituximab” and “Neutral”). A similar comparison against last chemotherapy was also performed ([Table 29](#)).

Results

All 54 patients with follicular histology were included in the analysis.

Table 29.
Response to ⁹⁰Y Ibritumomab Tiuxetan Therapy and Prior Rituximab
or Last Chemotherapy
(N = 54)

	N	%	
⁹⁰Y Ibritumomab Tiuxetan versus Prior Rituximab (one month analysis)			
Favor ⁹⁰ Y Ibritumomab Tiuxetan	29	54%	P < 0.001 (Signed-rank test)
Favor Rituximab	5	9%	P = 0.003 (Sign test)
Neutral	20	37%	
⁹⁰Y Ibritumomab Tiuxetan versus Prior Rituximab (three months analysis)			
Favor ⁹⁰ Y Ibritumomab Tiuxetan	26	48%	P < 0.001 (Signed-rank test)
Favor Rituximab	5	9%	P = 0.011 (Sign test)
Neutral	23	43%	
⁹⁰Y Ibritumomab Tiuxetan versus Last Chemotherapy (one month analysis)			
Favor ⁹⁰ Y Ibritumomab Tiuxetan	18	33%	P = 0.393 (Signed-rank test)
Favor Last Chemotherapy	17	32%	P = 0.499 (Sign test)
Neutral	19	35%	
⁹⁰Y Ibritumomab Tiuxetan versus Last Chemotherapy (three months analysis)			
Favor ⁹⁰ Y Ibritumomab Tiuxetan	16	30%	P = 0.388 (Signed-rank test)
Favor Last Chemotherapy	16	30%	P = 0.377 (Sign test)
Neutral	22	41%	

N = number of patients

2.B.5. Response Rate and Chemoresistance

Resistance to chemotherapy was not predictive of response to ⁹⁰Y ibritumomab tiuxetan therapy. Notably, 24 of 42 patients (57% of patients) resistant to a prior chemotherapy responded to ⁹⁰Y ibritumomab tiuxetan therapy. Additionally, 21 of 35 patients (60%), resistant to their last chemotherapy, responded to ⁹⁰Y ibritumomab tiuxetan therapy.

2.B.6. Univariate Analysis of Response by Baseline Patient Characteristic

Results are presented in [Table 30](#).

Table 30.
Analysis of Response by Baseline Patient Characteristic:
Phase III Rituximab-Refractory Study
(N = 54)

	Responder N (%)	Nonresponder N (%)	p-value*
Age (years)			
< 65	25 (62.5)	15 (37.5)	0.531
≥ 65	7 (50.0)	7 (50.0)	
Sex			
Female	15 (53.6)	13 (46.4)	0.418
Male	17 (65.4)	9 (34.6)	
Disease Stage at Study Entry			
I/II	2 (66.7)	1 (33.3)	1.000
III/IV	29 (59.2)	20 (40.8)	
Unknown	1 (50.0)	1 (50.0)	
Bone Marrow Involvement			
Yes	10 (58.8)	7 (41.2)	1.000
No	22 (59.5)	15 (40.5)	
Splenomegaly			
Yes	4 (66.7)	2 (33.3)	1.000
No	28 (58.3)	20 (41.7)	
Extranodal Disease			
0, 1	29 (64.4)	16 (35.6)	0.136
≥ 2	3 (33.3)	6 (66.7)	
Bulky Disease			
< 5 cm	12 (85.7)	2 (14.3)	0.123
5 - < 7 cm	9 (52.9)	8 (47.1)	
7 - < 10 cm	6 (46.2)	7 (53.8)	
≥ 10 cm	5 (50.0)	5 (50.0)	
WHO Performance Status			
0, 1	31 (60.8)	20 (39.2)	0.560
2	1 (33.3)	2 (66.7)	
LDH			
Low or Normal	23 (74.2)	8 (25.8)	0.004
High	4 (26.7)	11 (73.3)	
Unknown	5 (62.5)	3 (37.5)	
IgM			
Low or Normal	28 (56.0)	22 (44.0)	1.000
High	1 (100.0)	0 (0.0)	
Unknown	3 (100.0)	0 (0.0)	
PB B-Cell Counts (× 10³ cells/mm³)			
None [†]	4 (21.1)	15 (78.9)	< 0.001
Low (< 32)	14 (70.0)	6 (30.0)	
Normal/High (≥ 32)	12 (92.3)	1 (7.7)	
Unknown	2 (100.0)	0 (0.0)	

Continued

	Responder N (%)	Nonresponder N (%)	p-value*
Years from Diagnosis to Treatment			
< 5 years	19 (59.4)	15 (68.2)	0.310
5 - 10 years	10 (31.3)	3 (13.6)	
≥ 10 years	3 (9.4)	4 (18.2)	
Number of Prior Regimens			
1	1 (33.3)	2 (66.7)	0.258
2 - 3	16 (69.6)	7 (30.4)	
≥ 4	15 (53.6)	13 (46.4)	
Prior Radiotherapy			
Yes	10 (62.5)	6 (37.5)	1.000
No	22 (57.9)	16 (42.1)	
IPI Risk Group			
Low	20 (80.0)	5 (20.0)	0.004
Low/Intermediate	4 (40.0)	6 (60.0)	
Intermediate/High	1 (14.3)	6 (85.7)	
High	2 (50.0)	2 (50.0)	
Unknown	5 (62.5)	3 (37.5)	

N = number of patients

*p-values generated by Fisher's exact two-tailed test

†None = level below the detectable limit

2.C. Summary

Evaluation of net clinical benefit of ⁹⁰Y ibritumomab tiuxetan in the population studied must consider that these patients have incurable disease, are symptomatic and in need of therapy, and that no treatment has been shown to prolong survival^[57]. In this context, a clinically meaningful outcome is a significant reduction in tumor burden (as defined by a partial, clinical complete, or complete response) sustained for a period of time during which further treatment is not required.

Two Phase III adequate and well-controlled studies of ⁹⁰Y ibritumomab tiuxetan have been performed. The primary efficacy endpoint goals were met in both studies.

Comparison Study

A significantly greater ORR was achieved in the ⁹⁰Y ibritumomab tiuxetan treatment group compared with the rituximab control in a population of poor prognosis patients, including elderly patients, patients with bulky, extranodal, or chemoresistant disease, splenomegaly, or bone marrow involvement.

- Patients resistant to their last chemotherapy had a significantly higher response rate to ⁹⁰Y ibritumomab tiuxetan than to rituximab.
- Patients with bulky disease had a significantly higher response rate to ⁹⁰Y ibritumomab tiuxetan than to rituximab.
- Although this study was not designed to detect differences in TTP between the treatment groups, K-M curves suggested a longer TTP in the ⁹⁰Y ibritumomab tiuxetan group compared with the rituximab group in the low-grade and follicular patient population.
- The K-M curves for TTNT suggest a longer treatment-free period in the ⁹⁰Y ibritumomab tiuxetan group compared with the rituximab control. For patients

with low-grade or follicular histology, the ^{90}Y ibritumomab tiuxetan group had a significantly longer TTNT when compared with the rituximab control.

Rituximab-Refractory Study

The ORR was 59% in a heavily pretreated rituximab-refractory population.

- The ORR of patients treated with ^{90}Y ibritumomab tiuxetan therapy was significantly higher than that of the patient's prior rituximab therapy
- The ORR for patients treated with ^{90}Y ibritumomab tiuxetan was not statistically different from the ORR noted for the patients' last chemotherapy
- The estimated median DR following ^{90}Y ibritumomab tiuxetan therapy is significantly longer than the median DR following the patients' prior rituximab therapy
- The estimated median DR following ^{90}Y ibritumomab tiuxetan therapy was longer than the median DR following the patients' last chemotherapy

3. SAFETY OF ⁹⁰Y IBRITUMOMAB TIUXETAN

This document presents an integrated summary of the safety of ⁹⁰Y ibritumomab tiuxetan therapy of 349 patients. In the Phase III Randomized Comparison Study (106-04), the 70 patients in the rituximab control group allowed a direct comparison with the 73 patients in the ⁹⁰Y ibritumomab tiuxetan group, and these comparative data follow the overall safety analysis. Additionally, safety results are presented from analyses in a population of 211 patients (representing variables not collected in the current, on-going open-label study), as well as in patients with mild thrombocytopenia and in the elderly.

A total of 489 patients enrolled in 7 clinical trials of ⁹⁰Y ibritumomab tiuxetan therapy in patients with B-cell NHL were included in the submitted BLA (Table 5). Patients not included in the integrated safety analysis were: seven patients who received only ¹¹¹In ibritumomab tiuxetan as part of a dose-finding study of imaging and biodistribution. Another 70 patients received rituximab as part of the control group in the Phase III Randomized Comparison Study (106-04). Patients from Phase I Study 106-01 and Study 106-02 (N = 18) were excluded from the integrated safety analysis because of several important differences between these and subsequent trials:

- The murine monoclonal antibody, ibritumomab, was used as the unlabeled antibody prior to ⁹⁰Y ibritumomab tiuxetan, instead of the chimeric monoclonal antibody, rituximab, which was used in all subsequent studies.
- These studies were conducted prior to the use of the ⁹⁰Y radiolabeling kit.
- ⁹⁰Y ibritumomab tiuxetan dosing was not adjusted for body weight, unlike all subsequent trials.
- These studies were dose escalated to a myeloablative range, requiring stem-cell collection.

Data from 45 patients from the ongoing open-label Study 106-98 were not included in the integrated safety evaluation because the patients were still participating in the protocol-defined 12 weeks of follow up.

3.A. Patient Disposition

Of 349 patients, 345 patients completed treatment (99%). Of the four patients who did not receive ⁹⁰Y ibritumomab tiuxetan, one was withdrawn from Study 106-03 after receiving ¹¹¹In ibritumomab tiuxetan but prior to receiving ⁹⁰Y ibritumomab tiuxetan at the investigator's discretion. This patient was treated with a full course of rituximab (375 mg/m² once weekly times four). Three patients were withdrawn from Study 106-98 after receiving rituximab on Day 1 but prior to receiving ⁹⁰Y ibritumomab tiuxetan. Reasons for withdrawal were disease progression, rituximab-associated toxicity, or investigator judgement. Data from these three patients are included in this ITT safety analysis.

3.B. Overall Extent of Exposure

Yttrium-[90] ibritumomab tiuxetan was administered as a single IV injection at the following intended protocol-defined doses:

- 0.4 mCi/kg, N = 283: Studies 106-03 (N = 30), 106-04 (N = 73), 106-06 (N = 57), and 106-98 (N = 123)
- 0.3 mCi/kg, N = 58: Studies 106-03 (N = 16), 106-05 (N = 30), and 106-98 (N = 12)
- 0.2 mCi/kg Study 106-03, N = 5

The maximum dose permitted was 32 mCi. See Table 31 for a summary of cumulative dose of ⁹⁰Y ibritumomab tiuxetan.

Table 31.
Cumulative Dose of ⁹⁰Y Ibritumomab Tiuxetan

	Dose (mCi/kg)			
	[0-0.25)	[0.25-0.35)	[0.35-0.45)	[0.45+)
N	10	127	205	3
Mean	0.21	0.31	0.40	0.49
Standard Deviation	0.02	0.02	0.02	0.03
Range	0.19 - 0.25	0.26 - 0.35	0.35 - 0.45	0.47 - 0.52

N = number of patients

Infusion data for one patient were not available

Note: Treatment period for patients treated with ⁹⁰Y ibritumomab tiuxetan is the time interval from the first rituximab infusion to 12 weeks following the ⁹⁰Y ibritumomab tiuxetan injection.

3.C. Clinical Adverse Events

3.C.1. Nonhematologic Adverse Events

Overall Safety Analysis (N = 349)

This section summarizes clinical adverse events (AEs), excluding hematologic toxicities, by body system and includes the most common (≥ 5%) events of possible, probable, or unknown relationship to study treatment (related events) in [Table 32](#). Nonhematologic AEs of the Comparison Study are summarized in [Table 33](#).

Table 32.
Nonhematologic Adverse Events of $\geq 5\%$ Incidence*
(N = 349)

	N (%)
Any Adverse Event	279 (79.9)
Body as a Whole	222 (63.6)
Asthenia	123 (35.2)
Chills	73 (20.9)
Fever	46 (13.2)
Headache	31 (8.9)
Throat Irritation	31 (8.9)
Abdominal Pain	27 (7.7)
Flushing	19 (5.4)
Digestive System	118 (33.8)
Nausea	86 (24.6)
Vomiting	25 (7.2)
Hemic and Lymphatic System	45 (12.9)
Echymosis	21 (6.0)
Nervous System	57 (16.3)
Dizziness	27 (7.7)
Respiratory System	82 (23.5)
Dyspnea	26 (7.4)
Increased Cough	20 (5.7)
Skin and Appendages	69 (19.8)
Pruritus	26 (7.4)
Rash	23 (6.6)

N = number of patients

*AEs possibly, probably, or of unknown relationship to treatment; excludes neutropenia, leukopenia, thrombocytopenia, and anemia.

Note: Treatment period for patients treated with ^{90}Y ibritumomab tiuxetan is the time interval from the first rituximab infusion to 12 weeks following the ^{90}Y ibritumomab tiuxetan injection.

Comparison Study (N = 143)

A higher incidence of nonhematologic adverse events were noted in the ^{90}Y ibritumomab tiuxetan group for the following systems:

- Respiratory system; the difference consisted of a higher incidence of Grade 1 or 2 cough, bronchospasm, and respiratory infections; no long-term pulmonary toxicity reported (Table 33).
- Digestive system; the difference consisted of a higher incidence of Grade 1 and 2 nausea, vomiting, and anorexia that were not associated with increased bowel uptake on gamma camera images (Table 33).
- Infection and febrile neutropenia; see Section 3.C.3.

Table 33.
Nonhematologic Adverse Events of $\geq 5\%$ Incidence:*
Phase III Comparison Study
(N = 143)

	⁹⁰ Y Ibritumomab Tiuxetan N = 73 N (%)	Rituximab N = 70 N (%)	p-value
Any Adverse Event	64 (87.7)	62 (88.6)	1.000
Body as a Whole	51 (69.9)	51 (72.9)	0.715
Asthenia	29 (39.7)	23 (32.9)	
Chills	14 (19.2)	20 (28.6)	
Throat Irritation	13 (17.8)	10 (14.3)	
Fever	11 (15.1)	11 (15.7)	
Headache	9 (12.3)	11 (15.7)	
Pain	7 (9.6)	5 (7.1)	
Flushing	6 (8.2)	4 (5.7)	
Infection [†]	6 (8.2)	1 (1.4)	
Abdominal Pain	6 (8.2)	3 (4.3)	
Back Pain	1 (1.4)	4 (5.7)	
Cardiovascular System	10 (13.7)	11 (15.7)	0.815
Hypotension	6 (8.2)	7 (10.0)	
Digestive System	28 (38.4)	17 (24.3)	0.075
Nausea	24 (32.9)	10 (14.3)	
Vomiting	10 (13.7)	4 (5.7)	
Anorexia	6 (8.2)	1 (1.4)	
Diarrhea	2 (2.7)	4 (5.7)	
Hemic and Lymphatic System	11 (15.1)	3 (4.3)	0.046
Ecchymosis	5 (6.8)	0 (0.0)	
Metabolic and Nutritional Disorders	12 (16.4)	12 (17.1)	1.000
Angioedema	6 (8.2)	11 (15.7)	
Peripheral Edema	5 (6.8)	0 (0.0)	
Musculoskeletal System	12 (16.4)	7 (10.0)	0.327
Arthralgia	8 (11.0)	3 (4.3)	
Myalgia	4 (5.5)	5 (7.1)	
Nervous System	14 (19.2)	10 (14.3)	0.505
Dizziness	8 (11.0)	3 (4.3)	
Respiratory System	20 (27.4)	10 (14.3)	0.066
Increased Cough	8 (11.0)	1 (1.4)	
Bronchospasm	4 (5.5)	1 (1.4)	
Rhinitis	3 (4.1)	5 (7.1)	
Skin and Appendages	19 (26.0)	19 (27.1)	1.000
Rash	8 (11.0)	7 (10.0)	
Pruritus	6 (8.2)	10 (14.3)	

N = number of patients

*AEs possibly, probably, or of unknown relationship to treatment; excludes neutropenia, leukopenia, thrombocytopenia, and anemia.

[†]Includes only infections coded by COSTART as "Body as a Whole". Information on infection is presented in [Section 3.C.3](#)

Note: Treatment period for patients treated with ⁹⁰Y ibritumomab tiuxetan is the time interval from the first rituximab infusion to 12 weeks following the ⁹⁰Y ibritumomab tiuxetan injection. Treatment period for patients receiving rituximab is the 13-week time interval following the first rituximab infusion.

3.C.1.a. Nonhematologic Adverse Events Occurring on a Treatment Day Overall Safety Analysis (N = 349)

AEs occurring on a treatment day were predominantly Grade 1 or 2, on either Day 1 (rituximab for all patients and ¹¹¹In ibritumomab tiuxetan in those who underwent dosimetry) or Day 8 (rituximab and ⁹⁰Y ibritumomab tiuxetan). A total of 174 patients (49.9% of patients) experienced AEs on Day 1. Events included chills in 62 patients (17.8% of patients), nausea in 32 (9.2%), fever in 24 (6.9%), throat irritation in 23 (6.6%), and pruritus in 22 (6.3%). These symptoms are well described for patients receiving rituximab and, in that setting, decrease with subsequent infusions. A total of 79 patients (22.6%) experienced AEs on Day 8. The most common events included nausea in 12 patients (3.4%) and chills in 10 (2.9%).

Comparison Study (N = 143)

Patients in both treatment groups received rituximab on the first treatment day and experienced similar AEs. AEs occurring in either treatment group were predominantly Grade 1 or 2 and included chills (17.8% of ⁹⁰Y ibritumomab tiuxetan patients; 24.3% of rituximab patients), throat irritation (13.7%; 11.4%), fever (6.8%; 11.4%), nausea (11.0%; 10.0%), angioedema (6.8%; 12.9%), pruritus (6.8%; 14.3%), and asthenia (2.7%; 10.0%).

A total of 22 patients treated with ⁹⁰Y ibritumomab tiuxetan (30.1%) experienced AEs on the ⁹⁰Y ibritumomab tiuxetan treatment day. Most events were Grade 1 or 2 and included nausea (4.1%) and conjunctivitis (4.1%). In patients receiving rituximab, the only frequent AE (≥ 5% of patients) on subsequent infusion days was asthenia: 8.6% with the second infusion and 8.6% with the fourth infusion.

3.C.2. Hematologic Toxicity

Laboratory nadir analyses of hematology variables during the treatment period included data for absolute neutrophil count (ANC), platelets, and hemoglobin, as well as growth factor use. The duration of Grade 3 or 4 hematologic toxicity was defined as the date from the last value prior to development of Grade 3 toxicity to the date of the next value that was less than Grade 3 toxicity. Bleeding AEs and risk factors for hematologic toxicity are also presented.

3.C.2.a. Laboratory Hematologic Variables and Growth Factor Use or Blood Transfusions

Severity and duration data are summarized in [Table 34](#). Growth factor use and blood transfusion data are summarized in [Table 35](#).

Table 34.
Severity and Duration of Hematologic Toxicity: Overall Safety Analysis

Toxicity	Incidence of Grade 3 Toxicity N (%)	Incidence of Grade 4 Toxicity N (%)	Duration* All Patients (Days)	Duration* Patients with Grade 3 or 4 (Days)
Overall Safety Analysis N = 349				
Neutropenia	103 (29.5)	105 (30.1)	15	23
Thrombocytopenia	185 (53.0)	35 (10.0)	17	28
Anemia	46 (13.2)	14 (4.0)	0	14
0.4mCi/kg Dose Group N = 270				
Neutropenia	75 (27.8)	80 (29.6)	14	22
Thrombocytopenia	139 (51.5)	26 (9.6)	15	24
Anemia	38 (14.1)	9 (3.3)	0	14
0.3mCi/kg Dose Group N = 65				
Neutropenia	26 (40.0)	23 (35.4)	23	29
Thrombocytopenia	43 (66.2)	9 (13.8)	29	34.5
Anemia	8 (12.3)	5 (7.7)	0	14

N = number of patients

*Median duration of Grade 3 or 4 toxicity

Table 35.
Growth Factor Use and Blood Transfusions: Overall Safety Analysis

Growth Factor	Overall Safety Analysis N = 211* N (%)	0.4 mCi/kg Dose Group N = 160 [†] N (%)	0.3 mCi/kg Dose Group N = 40 [‡] N (%)
Filgrastim	27 (12.8)	23 (14.4)	4 (10.0)
Oprelvekin	3 (1.4)	2 (1.2)	1 (2.5)
Platelet Transfusion	47 (22.3)	35 (21.9)	12 (30.0)
Erythropoietin	17 (8.1)	14 (8.8)	3 (7.5)
RBC Transfusion	43 (20.4)	31 (19.4)	12 (30.0)

N = number of patients

*Data collected for 211 of 349 patients

[†]Data collected for 160 of 270 patients

[‡]Data collected for 40 of 65 patients

A total of 37 patients (17.5%) received growth factors. In the population of 211 patients, 129 (61%) had Grade 3 or 4 neutropenia. Of these 129 patients, 26 received filgrastim and the median duration of Grade 3 or 4 neutropenia was 8 days shorter than the duration in patients not treated with filgrastim; this difference was not statistically different (Table 36).

Table 36.
Effect of Filgrastim on Duration of Grade 3 or 4 Neutropenia

	Filgrastim	No Filgrastim	p-value*
N	26	103	
Median Duration (days)	19.0+	27.0+	0.060
Range (days)	(3.0, 53.0)	(5.0, 173.0)	

N = number of patients

*p-value generated by Log-rank test

In the population of 211 patients, 38 (18%) had Grade 3 or 4 anemia. Of these 38 patients, 10 received erythropoietin and the median duration of Grade 3 or 4 anemia was shorter than the duration in patients not treated with erythropoietin; this difference was not statistically significant (Table 37).

Table 37.
Effect of Erythropoietin on Duration of Grade 3 or 4 Hematologic Toxicity

	Erythropoietin	No Erythropoietin	p-value*
N	10	28	
Median Duration(days)	12.5	14.0+	0.463
Range (days)	(5.0, 41.0+)	(2.0+, 59.0+)	

N = number of patients

*p-value generated by Log-rank test

3.C.2.b. Recovery of Blood Counts

Blood counts in all patients who experienced Grade 3 or greater neutropenia or thrombocytopenia recovered to Grade ≤ 2 levels during the observation period, with the following exceptions:

- Patients who had progressive disease and received subsequent anticancer therapy or died of lymphoma prior to recovery: Study 10603: 203, 215, 323; Study 10604: 404, 407; Study 10605: 010; 10606: 021, 054; Study 10698: 040, 063, 067, 068, 073, 083, 088, 120, 121, 131, 135
- One patient had greater than 25% bone marrow involvement at study entry (Study 10605: 013); repeat review of bone marrow showed 37% involvement of bone marrow by lymphoma
- Two patients died from intracranial hemorrhage from traumatic head injuries while at platelet nadir (Study 10606: 031; Study 10698: 028); 1 of these patients was receiving therapeutic oral anticoagulants and ibuprofen
- One patient (10698: 057) did not recover to Grade ≤ 2 levels during the observation period. This patient has a history of multiple aggressive chemotherapy regimens, including CHOP, DHAP, and fludarabine.

3.C.2.c. Bleeding Events

During the treatment period, bleeding AEs were reported for 62 patients (18%). Most events were Grade 1 or 2 (Table 38).

Table 38.
Incidence of Bleeding Events during Treatment*:
Overall Safety Analysis
(N = 349)

Adverse Event [‡]	Grade [†]				Total N (%)
	1	2	3	4	
Any Event	39	17	5	1	62 (17.8)
Ecchymosis	16	8	1	0	25 (7.2)
Gastrointestinal Hemorrhage	8	3	4	0	15 (4.3)
Petechia	8	4	0	0	12 (3.4)
Epistaxis	9	1	0	0	10 (2.9)
Gum Hemorrhage	4	0	0	0	4 (1.1)
Hematuria	2	1	0	0	3 (0.9)
Injection Site Hemorrhage	2	0	0	0	2 (0.6)
Vaginal Hemorrhage	1	0	1	0	2 (0.6)
Easy Bruisability	0	0	1	0	1 (0.3)
Hemorrhage [§]	1	0	0	0	1 (0.3)
Retinal Hemorrhage	1	0	0	0	1 (0.3)
Subdural Hematoma [¥]	0	0	0	1	1 (0.3)

*Treatment period is the time interval from first infusion to 12 weeks after ⁹⁰Y ibritumomab tiuxetan treatment

[†]Patient is counted only under the worst grade experienced

[‡]Excludes neutropenia, leukopenia, thrombocytopenia, or anemia

[§]Superficial facial cut

[¥]A second patient reported during follow-up period

3.C.2.d. Risk Factors for Hematologic Toxicity

3.C.2.d.1. Bone Marrow Involvement (N = 349)

- The presence of bone marrow involvement at baseline was associated with a significantly greater incidence of Grade 4 neutropenia (p = 0.001), thrombocytopenia (p = 0.013), and anemia (p = 0.040)
- The incidence of Grade 4 hematologic toxicity increased with increasing bone marrow involvement at baseline

3.C.2.d.2. Relationship of Prior Anticancer Therapy to Hematologic Toxicity (N = 349)

Number of Prior Regimens

- Number of prior chemotherapy regimens is associated with a greater incidence of Grade 3 or 4 anemia (p = 0.002), but not Grade 3 or 4 neutropenia (p = 0.812) or thrombocytopenia (p = 0.332)
- Number of prior chemotherapy regimens is associated with a greater incidence of Grade 4 thrombocytopenia (p = 0.019), but not Grade 4 neutropenia (p = 0.800) or anemia (p = 0.373)

- Number of prior chemotherapy regimens is not associated with a longer median duration of Grade 3 or 4 neutropenia, thrombocytopenia, or anemia.
- Disease status of the patients whose platelet counts did not recover to 100,000 cells/mm³ (Nonrecovered Patients) was compared with patients whose platelet counts recovered above 100,000 cells/mm³ (Recovered Patients). Nonrecovered Patients received significantly more chemotherapy regimens than Recovered Patients ($p < 0.001$); 60.9% of Nonrecovered Patients received 4 or more prior chemotherapy regimens compared with 26.1% of Recovered Patients.

Prior Fludarabine Therapy

- Patients treated with fludarabine had a significantly longer duration from diagnosis to treatment with ⁹⁰Y ibritumomab tiuxetan (4.5 years versus 3.3 years; $p = 0.005$) and received a significantly higher number of prior chemotherapy regimens (4 versus 2; $p < 0.001$) than patients not previously treated with fludarabine
- Patients treated with fludarabine had significantly lower platelet count ($p = 0.001$) and hemoglobin concentration ($p = 0.020$) at baseline
- Fludarabine-treated patients are more likely than patients not previously treated with fludarabine to develop Grade 3 or 4 neutropenia ($p = 0.050$), thrombocytopenia ($p = 0.025$), and anemia ($p < 0.001$)
- Association between prior fludarabine treatment and risk of Grade 3 or 4 anemia persisted even after stratification for number of prior chemotherapy treatments ($p = 0.033$ for 2 or fewer prior regimens and $p = 0.008$ for more than 2 prior regimens); association between prior fludarabine treatment and risk of Grade 3 or 4 neutropenia or thrombocytopenia did not persist after stratification for number of prior chemotherapy treatments
- Patients previously treated with fludarabine were significantly more likely than patients not previously treated with fludarabine to develop Grade 3 or 4 hematologic toxicity with duration greater than the median

3.C.3. Infection and Febrile Neutropenia

Overall Safety Analysis (N = 349)

During the treatment period (period from the first rituximab infusion to 12 weeks after the ⁹⁰Y ibritumomab tiuxetan injection), infection or febrile neutropenia was reported in 100 patients (28.7%; see [Table 39](#)). Prophylactic antibiotic use was monitored in 4 trials (N = 211) and 17 patients (8.1%) received prophylactic antibiotics during the treatment period.

- Most common infections: nonspecific (mainly upper respiratory tract infections in 26 patients, 7.4%), bacterial urinary tract (19, 5.4%), and febrile neutropenia (8, 2.3%)
- 23 patients (6.6%) were hospitalized (febrile neutropenia in 6; urinary tract infections, sepsis, or pneumonia in 4; cellulitis/abscess in 3; and gastroenteritis/diarrhea in 2)

During the follow-up period (remainder of the study up to 4 years or progression of disease), infection occurred in 21 patients (6.0%).

- Most common infections: nonspecific (mainly upper respiratory tract infections in 4 patients; 1.1%)
- 12 patients (3.4%) hospitalized (pneumonia in 4, urinary tract infection in 2, febrile neutropenia and urinary tract infection in 1, and in 1 patient each: sepsis, pericarditis, respiratory infection, hepatitis, and perihilar infiltrate)

Comparison Study (N = 143)

During the treatment period, a greater incidence of infection occurred in patients treated with ⁹⁰Y ibritumomab tiuxetan than in patients receiving rituximab (see Table 39).

- Most common infections: nonspecific (16.4%; 4.3%), urinary tract infections (8.2%; 1.4%), sinusitis (4.1%; 0%), cold syndrome (2.7%; 4.3%), flu syndrome (1.4%; 2.9%)
- 5 patients (6.8%) receiving ⁹⁰Y ibritumomab tiuxetan hospitalized (febrile neutropenia and urinary tract infection in 2, and in 1 patient each: febrile neutropenia, sepsis, and gastroenteritis)
- 1 patient (1.4%) receiving rituximab hospitalized (gastroenteritis)

During follow up, the incidence of infection was similar between treatment groups (see Table 39).

- Most common infections: nonspecific (2.7%; 4.3%)
- 3 patients (4.1%) receiving ⁹⁰Y ibritumomab tiuxetan hospitalized (hepatitis, perihilar infiltrate, and respiratory infection)
- 1 patient (1.4%) receiving rituximab hospitalized (febrile neutropenia, pneumonia, and sinusitis)

Table 39.
Incidence of Infection (%)

	Overall Safety Analysis		Comparison Study Treatment Period		Comparison Study Follow-up Period	
	Treatment Period (N = 349)	Follow-up Period (N = 349)	⁹⁰ Y Ibritumomab Tiuxetan (N = 73)	Rituximab (N = 70)	⁹⁰ Y Ibritumomab Tiuxetan (N = 73)	Rituximab (N = 70)
Any Grade (%)	28.7	6.0	42.5	20.0	9.6	10.0
Grade 3 or 4 (%)	4.6	2.6	6.9	0	4.1	1.4
Hospitalization (%)	6.6	3.4	6.8	1.4	4.1	1.4

N = number of patients

Note: Treatment period for patients treated with ⁹⁰Y ibritumomab tiuxetan is the time interval from the first rituximab infusion to 12 weeks following the ⁹⁰Y ibritumomab tiuxetan injection. Follow-up period is the remainder of the study up to 4 years or progression of disease.

3.C.4. Secondary Malignancies

Overall Safety Analysis (N = 349)

Six patients (2.3%) developed noncutaneous secondary malignancies following treatment with ⁹⁰Y ibritumomab tiuxetan: 5 patients (1.9%) developed myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML), diagnosed 8 to 34 months after

⁹⁰Y ibritumomab tiuxetan therapy, and 1 was diagnosed with a meningioma. It was the opinion of both the investigators and the sponsor that the cases of MDS/AML could be related to the extensive history of exposure to the alkylator therapy; nevertheless, a relationship to ⁹⁰Y ibritumomab tiuxetan therapy could not be ruled out.

Treatment-related MDS among patients with NHL has been described previously following chemotherapy and radiation therapy [100]. The annualized rate for MDS and AML based on ⁹⁰Y ibritumomab tiuxetan patients known to be alive and in continuing follow up was determined by two methods: calculation of the number of events per person-year and estimation by the Kaplan-Meier method (Table 40). Kaplan-Meier estimations of percentage of cumulative risk for MDS/AML for ⁹⁰Y ibritumomab tiuxetan and historical studies (Greene[101]; Pedersen-Bjergaard[63]), calculated either from the date of diagnosis or from the date of first treatment, are shown in Figure 13.

Table 40.
Annualized Rate for Time to Development of MDS or AML

Estimate	From Date of Diagnosis	From Date of First Infusion
Kaplan-Meier Estimate (%)	0.6	1.1
Number of Events – person-years (%)	0.3	1.2

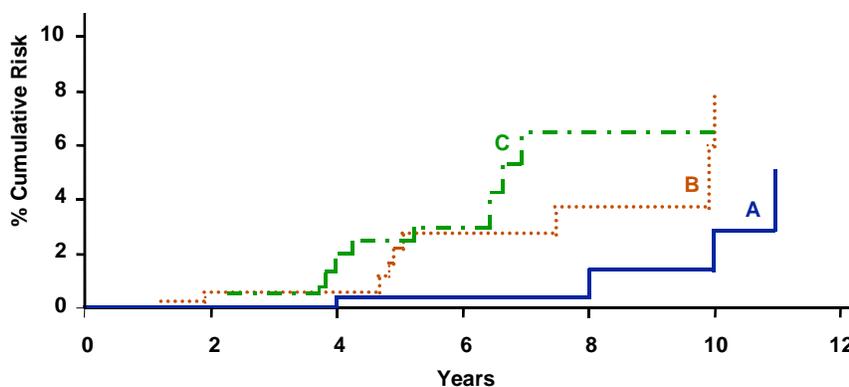


Figure 13. K-M curves of cumulative risk of MDS/AML from date of diagnosis, (A) ⁹⁰Y ibritumomab tiuxetan RIT and (B) Greene[101]; and from date of first treatment, (C) Pedersen-Bjergaard[63]

Published reports cite a cumulative incidence of MDS in NHL patients who have not undergone dose-intensive therapy of about 4% to 8% [62], a general risk of about 1% to 1.5% per year from 2 to at least 9 years after the start of therapy [63]. In view of the number of prior treatments received by patients enrolled in the ⁹⁰Y ibritumomab tiuxetan RIT and of the general risk of MDS in this patient population, these results provide insufficient data for an assessment of the risk of developing MDS following ⁹⁰Y ibritumomab tiuxetan therapy at this time.

3.C.5. Nonhematologic Grade 3 and 4 Adverse Events

Nonhematologic Grade 3 and 4 adverse events are summarized in Table 41 (Overall Safety Analysis) and in Table 42 (Comparison Study).

Table 41.
Nonhematologic Grade 3 and 4 Adverse Events*
(N = 349)

	Total N (%)
Body as a Whole	22 (6.3)
Asthenia	6 (1.7)
Abdominal Pain	4 (1.1)
Allergic Reaction	3 (0.9)
Sepsis	3 (0.9)
Fever	2 (0.6)
Tumor Pain	2 (0.6)
Cellulitis	1 (0.3)
Chills	1 (0.3)
Infection	1 (0.3)
Malaise	1 (0.3)
Pain	1 (0.3)
Back Pain	1 (0.3)
Neck Pain	1 (0.3)
Cardiovascular System	3 (0.9)
Hypotension	1 (0.3)
Tachycardia	1 (0.3)
Deep Thrombophlebitis	1 (0.3)
Digestive System	3 (0.9)
Melena	2 (0.6)
Colitis	1 (0.3)
Diarrhea	1 (0.3)
GI Hemorrhage	1 (0.3)
Nausea	1 (0.3)
Metabolic and Nutritional Disorders	1 (0.3)
Angioedema	1 (0.3)
Musculoskeletal System	2 (0.6)
Arthralgia	1 (0.3)
Myalgia	1 (0.3)
Osteomyelitis	1 (0.3)
Nervous System	3 (0.9)
Depression	1 (0.3)
Dizziness	1 (0.3)
Subdural Hematoma [†]	1 (0.3)

Continued

	Total N (%)
Respiratory System	6 (1.7)
Pneumonia	3 (0.9)
Dyspnea	2 (0.6)
Pleural Effusion	1 (0.3)
Hypoxia	1 (0.3)
Skin and Appendages	2 (0.6)
Pruritus	1 (0.3)
Rash	1 (0.3)
Urticaria	1 (0.3)
Urogenital System	4 (1.1)
Urinary Tract Infection	3 (0.9)
Vaginal Hemorrhage	1 (0.3)

N = number of patients

*AEs possibly, probably, or of unknown relationship to treatment; excludes hemic and lymphatic system.

†A second patient had a subdural hematoma in the follow-up period, Day 139.

Note: Treatment period for patients treated with ⁹⁰Y ibritumomab tiuxetan is the time interval from the first rituximab infusion to 12 weeks following the ⁹⁰Y ibritumomab tiuxetan injection.

Table 42.
Nonhematologic Grade 3 and 4 Adverse Events:*
Phase III Comparison Study
(N = 143)

	⁹⁰ Y Ibritumomab Tiuxetan N = 73 (N/%)	Rituximab N = 70 (N/%)	p-value
Any Adverse Event	9 (12.3)	4 (5.7)	0.245
Body as a Whole	4 (5.5)	1 (1.4)	0.367
Asthenia	3 (4.1)	0 (0.0)	
Infection [†]	1 (1.4)	0 (0.0)	
Pain	1 (1.4)	0 (0.0)	
Back Pain	0 (0.0)	1 (1.4)	
Cardiovascular System	0 (0.0)	1 (1.4)	0.490
Atrial Fibrillation	0 (0.0)	1 (1.4)	
Syncope	0 (0.0)	1 (1.4)	
Hemic and Lymphatic System	2 (2.7)	0 (0.0)	0.497
Easy Bruisability	1 (1.4)	0 (0.0)	
Febrile Neutropenia	1 (1.4)	0 (0.0)	
Metabolic and Nutritional Disorders	0 (0.0)	1 (1.4)	0.490
Dehydration	0 (0.0)	1 (1.4)	
Musculoskeletal System	1 (1.4)	0 (0.0)	1.000
Arthralgia	1 (1.4)	0 (0.0)	
Myalgia	1 (1.4)	0 (0.0)	
Respiratory System	1 (1.4)	0 (0.0)	1.000
Hypoxia	1 (1.4)	0 (0.0)	
Skin and Appendages	1 (1.4)	1 (1.4)	1.000
Rash	1 (1.4)	0 (0.0)	
Pruritus	0 (0.0)	1 (1.4)	
Urogenital System	2 (2.7)	0 (0.0)	0.497
Urinary Tract Infection	2 (2.7)	0 (0.0)	

N = number of patients

*AEs possibly, probably, or of unknown relationship to treatment; excludes neutropenia, leukopenia, thrombocytopenia, and anemia.

[†]Includes only infections coded by COSTART in “Body as a Whole.” Information on infections is presented in [Section 3.C.3](#).

Note: Treatment period for patients treated with ⁹⁰Y ibritumomab tiuxetan is the time interval from the first rituximab infusion to 12 weeks following the ⁹⁰Y ibritumomab tiuxetan injection. Treatment period for patients receiving rituximab is the 13-week time interval following the first rituximab infusion.

3.C.6. Serious Adverse Events (SAEs) and Premature Discontinuations Due to Adverse Events

SAEs, defined as events that are fatal, life-threatening, or permanently disabling, or those that require or prolong hospitalization whether or not related to the study drug, are summarized in [Table 43](#) and [Table 44](#).

Overall Safety Analysis (N = 349)

In the Overall Safety Analysis (N = 349), 56 patients (16.0%) experienced a SAE and 13 of these subsequently died. Nonfatal SAEs are presented in Table 43 and deaths are discussed in [Section 3.C.7](#).

Table 43.
Nonfatal Serious Adverse Events
(N = 349)

Study	Site	Patient Number	Study Day	Preferred Term	Grade	Relation To Study Drug	Outcome
106-03	002	210	52	Fever	4	Not Related	Recovered
		314	74	Arthritis	3	Not Related	Recovered
		327	58	Sepsis	4	Not Related	Recovered
	007	215	11	Supraventricular Tachycardia	3	Not Related	Recovered
			21	Venacava Pressure Increase	3	Not Related	Recovered
		304	16	Bacterial Infection	4	Not Related	Recovered
		317	94	Pericarditis	3	Not Related	Controlled
		332	52	Pneumonia	3	Not Related	Recovered
		336	187	Pneumonia	3	Not Related	Recovered
	008	302	24	Syncope	2	Not Related	Recovered
318		36	Pulmonary Embolus	4	Not Related	Recovered	
106-04	001	116	9	Sepsis	3	Not Related	Recovered
		230	59	Deep Vein Thrombophlebitis	2	Not Related	Recovered
		232	65	Gastroenteritis	2	Not Related	Recovered
	002	117	27	Abdominal Aortic Occlusion	3	Not Related	Recovered
	003	215	298	Hepatitis C*	3	Not Related	Recovered
	011	115	5	Hypertension	2	Not Related	Recovered
			32	Myocardial Ischemia	3	Not Related	Ongoing
	020	109	39	Urinary Tract Infection	2	Possibly Related	Recovered
			289	53	Diarrhea	3	Not Related
		53	53	Urinary Tract Infection	3	Probably Related	Recovered
411			39	Febrile Neutropenia	3	Probably Related	Recovered
022	224	116	Perihilar Infiltrate	3	Not Related	Recovered	
106-05	001	008	199	Convulsions	3	Not Related	Controlled
	002	002	20	Diarrhea	1	Possibly Related	Recovered
		011	54	Ecchymosis	2	Probably Related	Recovered
			79	Urinary Tract Infection	2	Not Related	Recovered

Continued

Study	Site	Patient Number	Study Day	Preferred Term	Grade	Relation To Study Drug	Outcome			
106-05		023	46	Thrombocytopenia	3	Probably Related	Recovered			
			70	Abdominal Pain	3	Not Related	Recovered			
			197	Urinary Tract Infection	2	Not Related	Recovered			
	005	013	37	Thrombocytopenia	4	Probably Related	Recovered			
106-06	014	019	54	Thrombocytopenia	4	Probably Related	Recovered			
			143	Pneumonia	2	Not Related	Recovered			
106-06	017	005	43	Febrile Neutropenia	3	Probably Related	Recovered			
			014	019	37	Deep Thrombophlebitis	3	Unknown	Recovered	
			017	022	57	Cellulitis	2	Probably Related	Recovered	
			042	38	Urinary Tract Infection	1	Not Related	Recovered		
			054	36	Chills	2	Not Related	Recovered		
106-98	011	073	27	Chest Pain	2	Possibly Related	Recovered			
			096	89	Fever	2	Not Related	Recovered		
	012	104	21	Thrombocytopenia	4	Probably Related	Ongoing			
	017	060	45	45	Febrile Neutropenia	2	Not Related	Recovered		
				019	049	21	Pancytopenia	4	Probably Related	Ongoing
				69	Sepsis	3	Probably Related	Recovered		
				077	8	Pancytopenia	4	Probably Related	Ongoing	
				39	Sepsis	3	Probably Related	Recovered		
	097	11	Diarrhea	3	Unknown	Recovered				
	111	33	Febrile Neutropenia	3	Probably Related	Recovered				
021	066	2	Lung Edema	1	Probably Related	Recovered				
033	094	36	Dehydration	2	Probably Related	Controlled				

N = number of patients
 *Associated with IV drug abuse

Comparison Study (N = 143)

In the Comparison Study, 17 patients experienced a SAE; 11 patients received ⁹⁰Y ibritumomab tiuxetan (15.1%) and 6 patients received rituximab (8.6%). There were no premature discontinuations from the study due to AEs.

Table 44.
Serious Adverse Events:
Phase III Comparison Study
(N = 143)

Site	Patient Number	Study Day	Preferred Term	Grade	Relation to Study Drug	Outcome
⁹⁰Y Ibritumomab Tiuxetan						
001	116	9	Sepsis	3	Not Related	Recovered
	230	59	Deep Vein Thrombophlebitis	2	Not Related	Recovered
	232	65	Gastroenteritis	2	Not Related	Recovered
	252	347	Myelodysplastic Syndrome	4	Possibly Related	Death [†]
002	117	27	Abdominal Aortic Occlusion	3	Not Related	Recovered
003	215	298	Hepatitis C*	3	Not Related	Recovered
011	115	5	Hypertension	2	Not Related	Recovered
		32	Myocardial Ischemia	3	Not Related	Recovered
020	109	39	Urinary Tract Infection	2	Possibly Related	Recovered
			Diarrhea	3	Not Related	Recovered
	289	53	Urinary Tract Infection	3	Probably Related	Recovered
		411	39	Febrile Neutropenia	3	Probably Related
022	224	116	Perihilar Infiltrate	3	Not Related	Recovered
Rituximab						
003	298	57	Back Pain	3	Possibly Related	Recovered
007	302	1	Atrial Fibrillation	4	Possibly Related	Recovered
013	221	85	Gastroenteritis	2	Not Related	Recovered
016	270	140	Hypoplastic Anemia	4	Possibly Related	Ongoing
		273	Febrile Neutropenia	3	Possibly Related	Recovered
		312	Pneumonia	3	Possibly Related	Recovered
		481	Fever	3	Possibly Related	Controlled
		521	Pneumonia	Unknown	Possibly Related	Recovered
023	401	148	Gastrointestinal Hemorrhage	3	Not Related	Recovered
031	231	70	Pancreatic Cancer	4	Not Related	Death [†]

*Associated with IV drug abuse

[†]Unresolved at death

3.C.7. Deaths

Overall Safety Analysis (N = 349)

All patients were followed for survival. A total of 70 patient deaths (20.1%) were reported:

- 58 deaths were secondary to NHL or subsequent to chemotherapy-induced toxicity; 43 of 58 patients had post-treatment antilymphoma therapy
- 5 deaths were due to unrelated concurrent or pre-existing illness (respiratory failure due to pre-existing chronic obstructive pulmonary disease [COPD] or pulmonary fibrosis, cardiac arrest due to coronary artery disease, and COPD or pneumonia following other anticancer therapy)
- 5 patients had MDS/AML
- 2 patients experienced intracranial hemorrhage following traumatic injury; 1 patient was receiving oral anticoagulant therapy

Comparison Study (N = 143)

In patients treated with ⁹⁰Y ibritumomab tiuxetan, 12 patient deaths (16.4% of patients) were reported; 10 of whom received additional antilymphoma therapy.

- 11 patients died from disease progression 2.0 to 21.9 months following ⁹⁰Y ibritumomab tiuxetan treatment
- 1 patient died from MDS, after a prolonged postoperative course from an emergency abdominal aortic aneurysm repair

In patients receiving rituximab, 10 patient deaths (14.3%) were reported, 9 of whom received additional antilymphoma therapy.

- 8 patients (11.4%) died from disease progression 1.2 to 21.9 months following rituximab treatment
- 1 patient died from pancreatic cancer (concurrent illness) 3.8 months following rituximab treatment
- 1 patient progressed on Study Day 49, received additional antilymphoma therapy, and died of infectious complications 6.1 months following rituximab treatment

3.D. Clinical Laboratory Results

3.D.1. Chemistry

Chemistry values were monitored in 211 patients and the majority (≥ 93%) had unchanged or improved chemistry laboratory values throughout treatment and follow up. No clinically significant shifts in chemistry laboratory values (2-grade shift or greater) were causally attributed to treatment with ⁹⁰Y ibritumomab tiuxetan by investigators. Reasons for shifts included disease-related events or concurrent illnesses (e.g., IV drug-abuse associated hepatitis C, sepsis, Gilbert's disease).

All patients who experienced clinically significant shifts in chemistry variables were exposed to radiation absorbed dose levels similar to those who did not experience clinically significant shifts. Of the 179 patients analyzed for dosimetry (see [Section 5.A.](#)), six (3%) had a clinically significant shift from baseline in liver chemistry values. Median

radiation-absorbed dose to the liver for these six patients was 415 cGy (range: 268 cGy - 975 cGy). Median radiation-absorbed dose to the liver for all patients was 450 cGy (range: 64 – 1856 cGy). None of the patients who received > 1200 cGy radiation-absorbed dose to liver developed liver toxicity.

In the Comparison Study, the majority of patients in both treatment groups ($\geq 93\%$ of ^{90}Y ibritumomab tiuxetan patients; $\geq 87\%$ of rituximab patients) had unchanged or improved chemistry laboratory values throughout the treatment and follow-up periods. No shifts in chemistry laboratory values (2-grade shift or higher) were causally attributed to either study treatment. See Table 45 for chemistry results in the Comparison Study (N = 143).

Table 45.
Shift Table Analysis of Chemistry Variables:
Phase III Comparison Study
(N = 143)

Treatment Group	Laboratory Test	2*		3 [†]		4 [‡]	
		N	(%)	N	(%)	N	(%)
^{90}Y Ibritumomab Tiuxetan	Creatinine	0	(0)	0	(0)	0	(0)
	SGOT	0	(0)	1	(1)	0	(0)
	SGPT	0	(0)	0	(0)	1	(1)
	Alkaline Phosphatase	1	(1)	0	(0)	0	(0)
	Total Bilirubin	2	(2)	2	(2)	2	(2)
Rituximab	Creatinine	0	(0)	0	(0)	0	(0)
	SGOT	2	(2)	0	(0)	0	(0)
	SGPT	0	(0)	1	(2)	0	(0)
	Alkaline Phosphatase	1	(1)	0	(0)	0	(0)
	Total Bilirubin	0	(0)	1	(1)	2	(2)

N = number of patients
 *2 = Two-grade increase
[†]3 = Three-grade increase
[‡]4 = Four-grade increase

3.D.2. Peripheral Blood B and T cells

Peripheral blood B and T cells were monitored in 211 patients. The median absolute B-cell count declined after treatment onset. Recovery started by Study Month 6, and median counts returned to the normal range by Study Month 9. In patients treated with ^{90}Y ibritumomab tiuxetan, B-cell count recovered between Study Month 6 and 9. In patients receiving rituximab, recovery occurred between Study Month 9 and 12.

Median absolute CD3+/CD4+ and CD3+/CD8+ T-cell subset counts remained within normal ranges throughout the treatment and follow-up periods.

In the Comparison Study, B-cell levels in peripheral blood samples (CD19 [pan-B]) are shown in [Figure 14](#) and T-cell levels in [Figure 15](#).

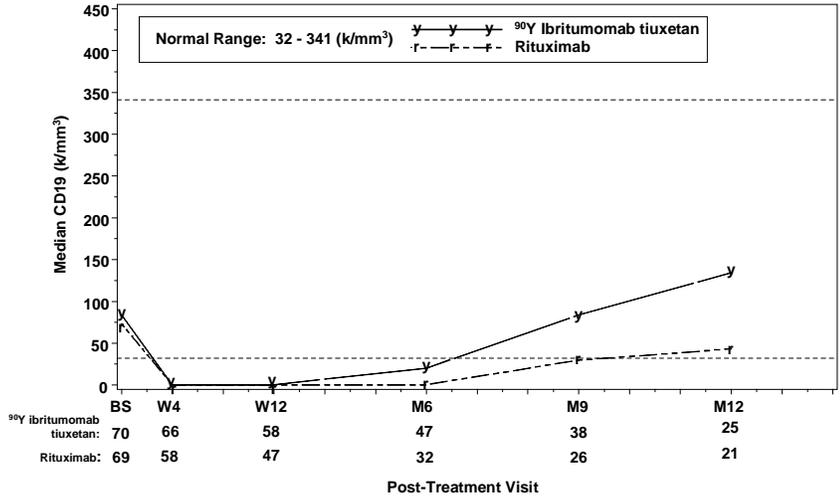


Figure 14. Summary of median CD19 count in peripheral blood by visit and treatment group in the Phase III Comparison Study (N = 143)

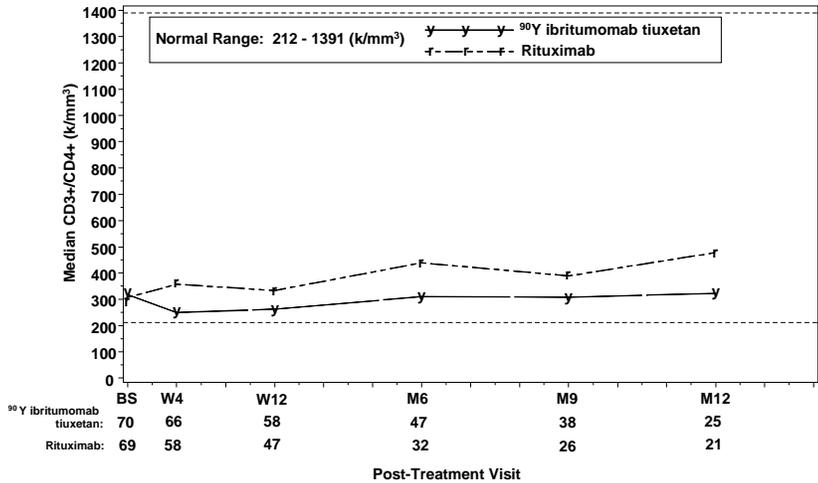


Figure 15. Summary of median CD3+/CD4+ counts in peripheral blood by visit and treatment group in the Phase III Comparison Study (N = 143)

3.D.3. Quantitative Serum Immunoglobulins

Overall Safety Analysis (N = 349)

Median IgG and IgA serum levels remained within normal ranges throughout the treatment and follow-up periods (data available for 211 patients). Median IgM serum level dropped just below normal after treatment onset and recovered by Study Month 6 (Figure 16).

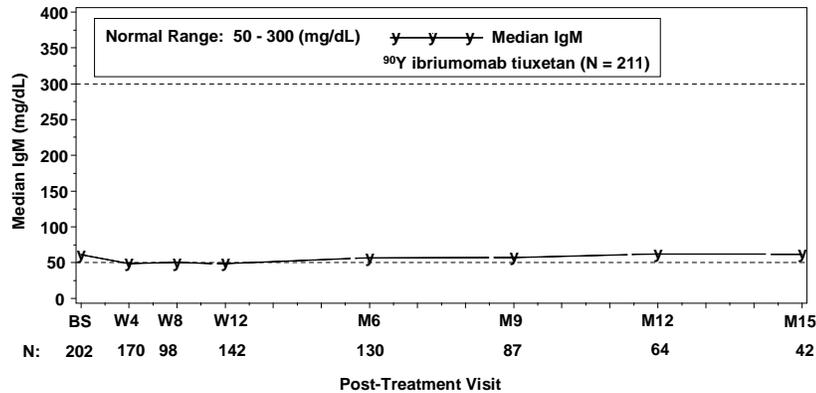


Figure 16. Summary of median IgM by visit (N = 211)

Comparison Study (N = 143)

In both groups, median immunoglobulin levels remained within the normal range.

3.D.4. Human Antimurine Antibody (HAMA) or Human Antichimeric Antibody (HACA) Response (N = 349)

- Three patients (1.4%) developed HAMA following treatment on Day 64, 42, and 39 (peak levels: 14, 25, 33 $\mu\text{g/mL}$), one of whom (0.5%) also developed HACA on Day 92 (peak level, 1.2 $\mu\text{g/mL}$).
- No unusual AEs or laboratory abnormalities were noted in these patients.
- All 3 patients who developed HAMA responded to ^{90}Y ibritumomab tiuxetan therapy.

3.E. Lymphoma Therapy Following ^{90}Y Ibritumomab Tiuxetan Treatment

Treatment with ^{90}Y ibritumomab tiuxetan did not preclude patients from receiving other antilymphoma therapies after relapse. (Numbers are not additive as patients may have received more than one therapy).

- 71 patients received subsequent conventional dose chemotherapy
- 36 patients received bioimmunotherapy (e.g., rituximab, interferon)
- 30 patients received external beam radiation therapy
- 2 patients underwent autologous bone marrow transplantation (ABMT) as first therapy following ^{90}Y ibritumomab tiuxetan RIT

3.E.1. Response to First Subsequent Lymphoma Therapy

Overall (N = 349)

A total of 139 patients (40%) have received subsequent treatment following ⁹⁰Y ibritumomab tiuxetan. Response to treatment is available for 84 patients, 49 of whom were responders (58%). See Table 46.

Comparison Study (N =143)

A total of 74 patients (52%) have received subsequent treatment following treatment in the Comparison Study. Response to treatment is available for 48 patients. In the ⁹⁰Y ibritumomab tiuxetan group, 70% (14/20) responded to subsequent therapy and 47% (13/28) responded in the Rituximab control group (Table 46).

Table 46.
Response to First Subsequent Lymphoma Therapy Following
⁹⁰Y Ibritumomab Tiuxetan

	Overall	Phase III Comparison Study	
	N = 349 N/Total (%)	⁹⁰ Y Ibritumomab tiuxetan N/Total (%)	Rituximab N/Total (%)
All Therapies	49/84 (58)	14/20 (70)	13/28 (46)
Chemotherapy	20/40 (50)	6/9 (67)	5/9 (56)
Alkylator +/- Prednisone	2/3 (67)	1/1 (100)	1/1 (100)
CHOP	3/6 (50)	1/1 (100)	0/1 (0)
CVP or COP	2/3 (67)	-	-
Purine Analogs	3/10 (30)	1/2 (50)	1/1 (100)
Other Aggressive*	10/18 (56)	3/5 (60)	3/6 (50)
Bioimmunotherapy	11/21 (52)	5/8 (63)	4/15 (27)
Radiotherapy	18/23 (78)	3/3 (100)	4/4 (100)

N = number of patients

*Includes ESHAP, DHAP, ICE, PROMACE, CYTOBOM, CHOP-Bleo, and fludarabine-containing combinations, and autologous and allogeneic transplantations

3.E.2. High-dose Therapy

A total of 10 patients (4.7%) who underwent high-dose therapy (HDT) after RIT with ⁹⁰Y ibritumomab tiuxetan (median, 13.3 months) received stem-cell support with bone marrow transplantation (BMT): 9 patients with ABMT (3, peripheral-blood stem-cells collected prior to RIT) and 1 patient with allogeneic BMT. In 2 patients, HDT was the first therapy administered following ⁹⁰Y ibritumomab tiuxetan treatment and, in 8 patients, HDT was preceded by other therapies.

At the time of ⁹⁰Y ibritumomab tiuxetan therapy, the median age of these 10 patients was 55 years (range 35 to 63 years), and histology was 7 follicular, 1 transformed, 1 diffuse large-cell, and 1 diffuse mixed-cell NHL. Patients had a range of 1 to 3 prior regimens,

5 patients had bone marrow involvement, and 8 patients were < 5 years from initial diagnosis of NHL.

Six of these 10 patients had responded to ⁹⁰Y ibritumomab tiuxetan therapy (2 CR and 4 PR), with an estimated median TTP of 10+ months. Successful establishment of the graft in bone marrow occurred in 9 patients, and 1 patient died from infection, during HDT, when hematologic values were at nadir.

3.F. Safety in Patients with Mild Thrombocytopenia

Dose-reduced ⁹⁰Y ibritumomab tiuxetan therapy (0.3 mCi/kg, maximum dose 32 mCi) in patients with mild thrombocytopenia was evaluated in Study 106-05. The incidence of Grade 3 or 4 neutropenia and thrombocytopenia was 20% to 25% higher (absolute) and the median duration was approximately 5 days longer for patients with mild baseline thrombocytopenia compared with patients having no thrombocytopenia. These data must be evaluated in the context of slightly more platelet transfusions in Study 106-05 (30% versus 20% in the two Phase III studies, Study 106-04 and 106-06) and slightly lower filgrastim use (7% versus 15%). The incidence and median duration of Grade 3 or 4 anemia was similar for all patients, which may reflect the use of red blood cell transfusions (27% versus 19% in Studies 106-04 and 106-06). The nonhematologic toxicity profile is similar to that seen with the 0.4 mCi/kg dose in patients with normal platelet counts. Despite the risk of increased hematologic toxicity, ⁹⁰Y ibritumomab tiuxetan treatment was well tolerated by patients with mild thrombocytopenia. The incidence of overall infection, Grade 3 and 4 infection, hospitalization, and treatment-related death (none in Study 106-05) was similar for all patients suggesting that the higher incidence of hematologic toxicity did not translate into a greater number of clinically significant events.

3.G. Safety in the Geriatric Population

To evaluate the safety of ⁹⁰Y ibritumomab tiuxetan therapy in patients over 65 years of age, data from 211 patients were sorted into groups based on the following categories of age:

- < 65 years of age: N = 140
- ≥ 65 years of age: N = 71
- 65 to < 75 years of age: N = 52
- ≥ 75 years of age: N = 19

The analysis of safety in the geriatric subset revealed no clinically significant age-related effects compared with younger patients.

3.H. Summary

- In the overall safety population, AEs were primarily hematologic
- Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 30%, 10%, and 4% of patients, respectively
- Duration of hematologic toxicity:
 - Median duration below an ANC of 1000 cells/mm³ for all patients was 15 days, and for patients with a Grade 3 or 4 nadir was 23 days

- Median duration below a platelet count of 50,000 cells/mm³ for all patients was 17 days and for patients with a Grade 3 or 4 nadir was 28 days
- Median duration below a hemoglobin concentration of 8 g/dL for all patients was 0 days and for patients with a Grade 3 or 4 nadir was 14 days
- Nonhematologic AEs were generally Grade 1 and 2 and the incidence parallels that of rituximab therapy
- No major acute organ dysfunction
- Median serum immunoglobulins remained largely within the normal range despite a 6-month reversible depletion of B cells
- 1.4% incidence of HAMA/HACA
- 6.6% incidence of febrile neutropenia or infection requiring hospitalization
- No observable age-dependent differences in the safety profile
- Specific targeting of tumor cells allows systemic therapy without hair loss or persistent nausea and vomiting.
- Yttrium-[90] ibritumomab tiuxetan RIT has an acceptable safety profile for patients with mild thrombocytopenia, who are at risk for treatment-related hematologic toxicity
- Patients who progress after ⁹⁰Y ibritumomab tiuxetan RIT can subsequently receive a broad range of anticancer therapies, including ESHAP, DHAP, and ProMACE-CytaBOM
- Stem-cell mobilization and high-dose chemotherapy can be performed safely in patients after receiving ⁹⁰Y ibritumomab tiuxetan RIT
- Rare cases of MDS were well within the expected background rate for this heavily pretreated patient population

4. RATIONALE FOR DOSE SELECTION OF RITUXIMAB AND ⁹⁰Y IBRITUMOMAB TIUXETAN

4.A. Dose Selection of Pretreatment Antibody

Results of the Phase I dose-escalation trial, Study 106-01, demonstrated that in the absence of unlabeled antibody, only 18% of known disease sites visible with CT scans had bound sufficient ¹¹¹In ibritumomab tiuxetan to generate a positive gamma camera image. However, when unlabeled ibritumomab was injected prior to ⁹⁰Y ibritumomab tiuxetan at 1 mg/kg (70 mg) or 2.5 mg/kg (175 mg), 56% and 92% of known disease sites, respectively, were imaged.

The Phase I/II Study, 106-03, evaluated pretreatment with unlabeled rituximab at 100 or 250 mg/m² (approximately 170 mg and 425 mg, respectively). No differences were observed in biodistribution, imaging, or dosimetry between 100 and 250 mg/m² pretreatment antibody doses. Based upon the potential for greater clinical activity with the higher dose of rituximab, the 250 mg/m² dose was selected and was given prior to ⁹⁰Y ibritumomab tiuxetan in all subsequent patients.

4.B. Dose Selection of ⁹⁰Y Ibritumomab Tiuxetan

In the Phase I dose-escalation trial, Study 106-01, patients received ⁹⁰Y ibritumomab tiuxetan at fixed single doses of 10 to 50 mCi, with three patients receiving multiple doses leading to a cumulative 70 mCi exposure. Doses ≤ 40 mCi were not myeloablative. The duration of thrombocytopenia (less than 100,000 platelets/mm³) and of nadir platelet count correlated with the ⁹⁰Y ibritumomab tiuxetan dose. Calculation of Pearson correlation coefficients demonstrated a significant correlation between the duration of thrombocytopenia and weight-adjusted doses of ⁹⁰Y ibritumomab tiuxetan (p = 0.038) but the correlation was not significant for doses adjusted to body surface area (p = 0.081) or for unadjusted doses (p = 0.328).

In the subsequent Phase I/II trial, Study 106-03, weight-adjusted doses of 0.2 to 0.4 mCi/kg were evaluated. A separate analysis by dose group revealed that this mixed population of low- and intermediate-grade and mantle cell NHL patients receiving 0.2 mCi/kg, 0.3 mCi/kg, or 0.4 mCi/kg ⁹⁰Y ibritumomab tiuxetan achieved response rates of 40%, 75%, and 67%, respectively. TTP and DR were longer in the higher dose groups (Table 47). The nonmyeloablative maximum tolerated dose of ⁹⁰Y ibritumomab tiuxetan was identified as 0.4 mCi/kg (maximum 32 mCi).

Table 47.
Median Time to Progression and Duration of Response* by Dose in Months

	Responders			Complete Responders		
	N	TTP (months)	DR (months)	N	TTP (months)	DR (months)
0.2 mCi/kg	2/5	12.5	10.8	1/5	12.6	10.3
0.3 mCi/kg	12/16	13.3	11.7	8/16	14.4	13.1
0.4 mCi/kg	20/30	15.4	14.4	4/30	28.3 - 36.4+	27.1 – 35.2+

N = number of patients

*By Kaplan-Meier analysis

“+” indicates median not yet reached, these values are Kaplan-Meier estimated medians; three patients remain in remission

4.B.1. Reduced Dose for Thrombocytopenic Patients

Thrombocytopenia at baseline is a recognized surrogate for reduced marrow reserves and for potentially severe cytopenia in oncology patients undergoing treatment with chemotherapy^[56, 102]. While patients with moderate or severe thrombocytopenia (platelets < 100,000 cells/mm³) were excluded from the studies, patients with mild thrombocytopenia (platelets 100,000 to 149,000 cells/mm³) were enrolled. During Phase I Study 106-03, two patients with thrombocytopenia at baseline developed nadir platelet counts < 25,000 cells/mm³ (one patient received 0.2 mCi/kg and one patient received 0.3 mCi/kg), whereas this did not occur in eight of eight patients with normal baseline platelet counts^[103]. For this reason, patients with baseline thrombocytopenia were not dose-escalated beyond 0.3 mCi/kg. Results from the Phase II Study, 106-05, confirmed the safety and efficacy of ⁹⁰Y ibritumomab tiuxetan at the 0.3 mCi/kg dose level in 30 patients with mild thrombocytopenia: ORR was 67% using the PDRC and the safety profile was acceptable (see [Section 3.F](#)).

5. SUMMARY OF DOSIMETRY AND PHARMACOKINETIC RESULTS

5.A. Dosimetry Analysis

During clinical development, radiation dosimetry was performed at the investigative site on 205 patients in 6 trials prior to treatment with ^{90}Y ibritumomab tiuxetan. All 205 patients studied with dosimetry met protocol-defined criteria for proceeding with ^{90}Y ibritumomab tiuxetan treatment, with estimated radiation-absorbed doses below the maximum allowable of 2000 cGy for uninvolved major organs and 300 cGy for red marrow.

5.A.1. Dosimetry Methods

Investigative Site

- Following 250 mg/m² rituximab, a tracer dose of 5 mCi ^{111}In ibritumomab tiuxetan was administered on Day 1
- Organ ^{111}In activity was measured from anterior and posterior gamma scans obtained at 5 to 8 time points over 1 week
- Region-of-interest (ROI) method used to calculate radiation-absorbed dose for 4 organs (liver, lungs, kidney, spleen); remainder method used for all other organs
- Blood ^{111}In activity was measured at similar time points
- ^{111}In activity was decay-corrected to ^{90}Y activity and converted to fraction of injected activity (FIA)
- Residence times were calculated from the area under the FIA-versus-time curve (AUC) and analyzed with the MIRDOSE3.1 computer software program

Central Laboratory

- Following ^{90}Y ibritumomab tiuxetan treatment, gamma images and blood samples were transferred to a central laboratory (Mayo Clinic and Oak Ridge Associated Universities) for a uniform review of the data
- For 179 patients, ROI method was used to calculate radiation-absorbed dose for 5 organs (lungs, kidneys, liver, spleen, sacral marrow) and the remainder method was used for all other organs
- For a subset of 15 patients, ROI method was used for 10 organs: heart wall, small intestine, upper and lower large intestine, testes, liver, lungs, kidney, spleen, sacral marrow. The remainder method was used for all other organs

5.B. Central Dosimetry using Ten Regions of Interest (N = 15)

Central radiation dosimetry analysis was performed on data from 15 randomly selected patients from the Comparison Study to estimate radiation-absorbed dose factors (cGy/mCi) from ^{111}In and ^{90}Y to all organs and total body (Table 48). A total of 10 organs were measured with the ROI method. The remainder method was used for all other organs. Median radiation-absorbed doses (cGy) from ^{90}Y ibritumomab tiuxetan to all organs and total body are shown in Figure 17.

Table 48.
Median Radiation-Absorbed Dose Factors from
¹¹¹In and ⁹⁰Y Ibritumomab Tiuxetan
 (N = 15)

Organ*	Dose Factor (cGy/mCi)			
	¹¹¹ In Ibritumomab Tiuxetan		⁹⁰ Y Ibritumomab Tiuxetan	
	Median	Range	Median	Range
Adrenals	0.8	0.4 – 1.0	1.2	0.2 – 1.8
Bone Surfaces	0.6	0.2 – 0.8	1.6	0.7 – 2.4
Brain	0.2	0.03 – 0.3	1.2	0.2 – 1.8
Breasts	0.3	0.1 – 0.4	1.2	0.2 – 1.8
Gallbladder Wall	1.1	0.5 – 1.4	1.2	0.2 – 1.8
Heart Wall	1.5	0.9 – 1.7	10.7	5.6 – 12.0
Kidneys	0.6	0.3 – 0.7	0.4	0.0 – 0.8
Liver [†]	2.5	1.2 – 4.0	17.8	8.4 – 29.9
Lower Large Intestine Wall	1.1	0.7 – 1.7	10.6	6.9 – 18.4
Lungs	0.9	0.5 – 1.4	7.4	4.3 – 12.4
Muscle	0.4	0.1 – 0.5	1.2	0.2 – 1.8
Ovaries	0.7	0.6 – 0.8	1.6	1.4 – 1.8
Pancreas	0.8	0.5 – 1.1	1.2	0.2 – 1.8
Red Marrow, sacral-derived	0.4	0.2 – 0.6	1.8	0.9 – 2.9
Skin	0.2	0.1 – 0.3	1.2	0.2 – 1.8
Small Intestine	0.8	0.4 – 1.1	4.3	2.4 – 6.4
Spleen [†]	3.2	0.8 – 4.6	34.8	6.7 – 53.3
Stomach	0.5	0.3 – 0.8	1.2	0.2 – 1.8
Testes	2.3	1.4 – 3.0	33.6	19.9 – 42.2
Thymus	0.5	0.3 – 0.6	1.2	0.2 – 1.8
Thyroid	0.3	0.1 – 0.4	1.2	0.2 – 1.8
Upper Large Intestine Wall	1.0	0.7 – 1.6	6.9	3.7 – 12.2
Urinary Bladder Wall	0.6	0.5 – 0.8	3.5	2.7 – 7.8
Uterus	0.6	0.5 – 0.7	1.6	1.4 – 1.8
Total Body	0.5	0.2 – 0.6	1.9	0.7 – 2.6

*5 women, 10 men for sex-specific organs

[†]Spleen and liver doses were adjusted for organ mass

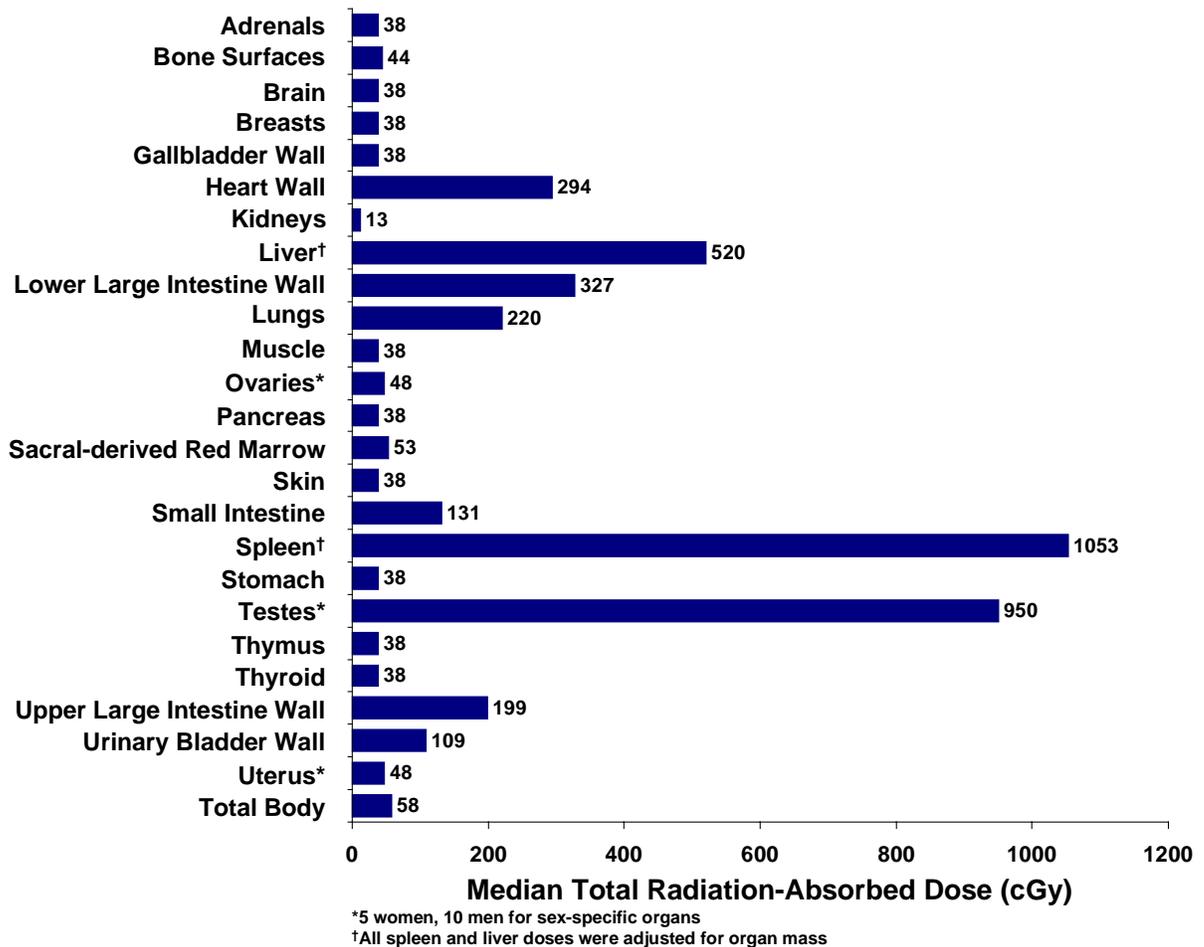


Figure 17. Median total radiation-absorbed dose from ⁹⁰Y Ibritumomab tiuxetan to all organs and total body (N = 15)

The highest median radiation-absorbed dose was to the spleen, an organ often involved with NHL. The second highest median radiation-absorbed dose was to the testes. For testes, with reduced overlying tissue compared with the adjacent abdominal region, these dosimetry methods may overestimate radiation-absorbed dose.

5.C. Central Dosimetry Analysis Using Five Regions of Interest (N = 179)

Central dosimetry was performed in 179 of the 205 patients receiving the following ⁹⁰Y ibritumomab tiuxetan doses:

- 0.2 mCi/kg in Study 106-03 (N = 4)
- 0.3 mCi/kg in Studies 106-03 and 106-05 (N = 46)
- 0.4 mCi/kg in Studies 106-03, 106-04, and 106-06 (N = 129)

Twenty six patients were not included in the integrated central dosimetry for the following reasons:

- Methods in early trials differed substantially from current methods (Studies 106-01 and 106-02, N = 18). See [Section 3](#), Safety of ^{90}Y Ibritumomab Tiuxetan
- Patients received dosimetry twice to assess two different doses of rituximab pretreatment but did not receive ^{90}Y ibritumomab tiuxetan (Study 106-03, N = 6)
- Dosimetry data were irretrievably lost/corrupted during transfer from the clinical site for central analysis (Studies 106-03 and 106-06, N = 2)

For these 179 patients, median radiation-absorbed doses from ^{90}Y ibritumomab tiuxetan were: lungs, 211 cGy (range 41 cGy - 527 cGy); kidneys, 23 cGy (0 cGy - 76 cGy); liver, 450 cGy (64 cGy - 1856 cGy); spleen, 742 cGy (24 cGy - 2448 cGy); blood derived red marrow, 62 cGy (7 cGy - 221 cGy); sacral-derived red marrow, 97 cGy (6 cGy - 257 cGy); total body, 57 cGy (23 cGy - 80 cGy).

5.C.1. Tumor Dosimetry (N = 39)

Radiation-absorbed dose to tumor from ^{90}Y ibritumomab tiuxetan was determined for 57 tumors in 38 patients. The median radiation-absorbed dose factor to tumor from ^{90}Y ibritumomab tiuxetan was 60 cGy/mCi (range 3 cGy/mCi to 778 cGy/mCi). The median total radiation-absorbed dose to tumor was 1480 cGy (range 61 cGy to 24,274 cGy). The median radiation-absorbed dose was 2352 cGy for tumors < 15 g (N = 29) and 873 cGy for tumors \geq 15 g (N = 28). No adverse event was attributed to radiation from an adjacent tumor, including 4 cases where radiation-absorbed dose to tumor was > 10,000 cGy.

5.D. Pharmacokinetic Analysis

Pharmacokinetic data were derived from ^{111}In activity measured in whole blood and plasma rather than from direct measurement of antibody in serum since, at the ibritumomab tiuxetan dose (approximately 2.0 mg), serum levels were not detectable using currently available assays. Estimates of median effective ^{90}Y half-life, biologic half-life, and area under the curve (AUC) of fraction of injected activity (FIA) versus time are presented in [Table 49](#). Whole blood results are presented; plasma results are similar.

Table 49.
⁹⁰Y Effective Half-Life, Biologic Half-Life, and ⁹⁰Y AUC
Derived from ¹¹¹In Activity in Blood (Hours)

Dose Group (mCi/kg)	Parameter	N	Mean (Hours)	Standard Deviation
0.2	AUC	4	16	8
	Biologic T _{1/2} *	4	37	19
	Effective T _{1/2} †	4	23	8
0.3	AUC	43	23	11
	Biologic T _{1/2} *	43	42	13
	Effective T _{1/2} †	43	25	5
0.4	AUC	98	28	13
	Biologic T _{1/2} *	98	50	16
	Effective T _{1/2} †	98	28	5
All	AUC	145	26	12
	Biologic T _{1/2} *	145	47	16
	Effective T _{1/2} †	145	27	5

N = number of patients

*T_{1/2} Biologic: half-life of antibody in blood

†T_{1/2} Effective: half-life of blood activity

5.E. Urinary Excretion of ⁹⁰Y Activity

A consecutive 7-day, total urine collection was obtained from patients during the week following treatment with ¹¹¹In ibritumomab tiuxetan or ⁹⁰Y ibritumomab tiuxetan. The mean percentage of injected ⁹⁰Y activity excreted in urine over 7 days ranged from 5.8% to 11.5% (Table 50).

Table 50.
Mean Percentage of Urinary Excretion of ⁹⁰Y Activity

	106-03			106-04			106-98			All Patients		
	N	Mean	STD	N	Mean	STD	N	Mean	STD	N	Mean	STD
Estimated from ¹¹¹ In Activity	48	11.5%	4.5%	10	9.2%	3.2%	-	-	-	58	11.1%	4.4%
Directly Measured ⁹⁰ Y Activity	-	-	-	10	5.8%	1.6%	27	7.9%	3.5%	37	7.3%	3.2%

N = number of patients

STD = Standard Deviation

5.F. Correlation Analyses of Dosimetry and Pharmacokinetics Versus Clinical Variables

5.F.1. Dosimetric Parameters Versus Hematologic Nadir

Dosimetric data did not correlate with measures of hematologic nadir. No significant correlation was noted between blood- or sacral-image derived estimates of red marrow radiation-absorbed dose or total body radiation-absorbed dose and hematologic nadir grade or nadir value for ANC or platelet level. These data are summarized in Table 51, Table 52, Figure 18, Figure 19, and Figure 20.

Table 51.
Radiation-absorbed dose (cGy) versus ANC Nadir Grade

ANC Nadir Grade	Median Red Marrow Dose [Blood-Derived]	Median Red Marrow Dose [Sacral-Derived]	Median Total Body Dose
0 - 2	62	99	57
3	64	88	58
4	58	107	58
	p = 0.482	p = 0.108	p = 0.958

p-value generated by Kruskal-Wallis test

Table 52.
Radiation-absorbed dose (cGy) versus Platelet Count Nadir Grade

Platelet Count Nadir Grade	Median Red Marrow Dose [Blood-Derived]	Median Red Marrow Dose [Sacral-Derived]	Median Total Body Dose
0 - 2	62	92	56
3	65	96	58
4	49	106	54
	p = 0.066	p = 0.398	p = 0.382

p-value generated by Kruskal-Wallis test

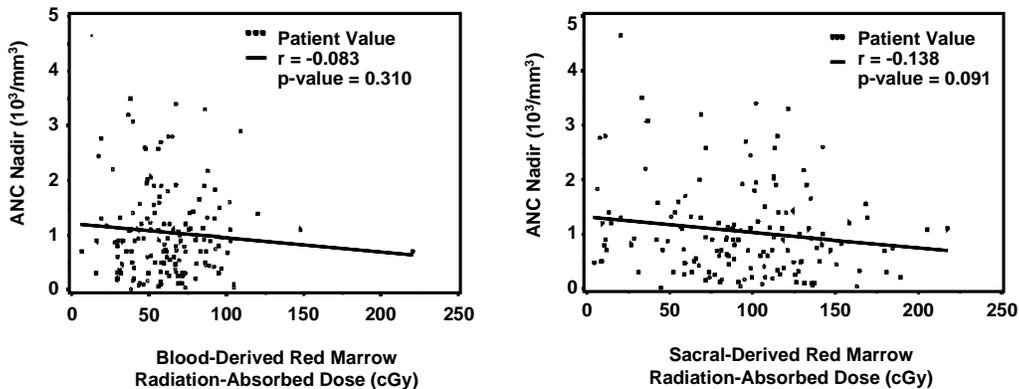


Figure 18. ANC nadir and radiation-absorbed dose

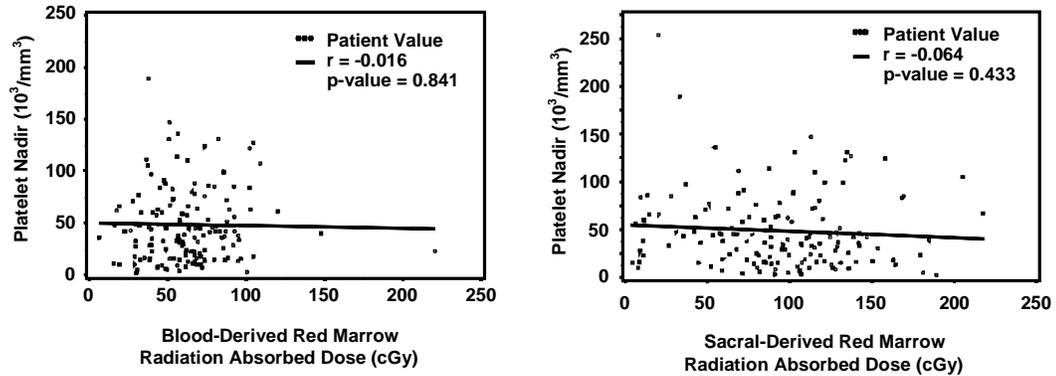


Figure 19. Platelet-count nadir and radiation-absorbed dose

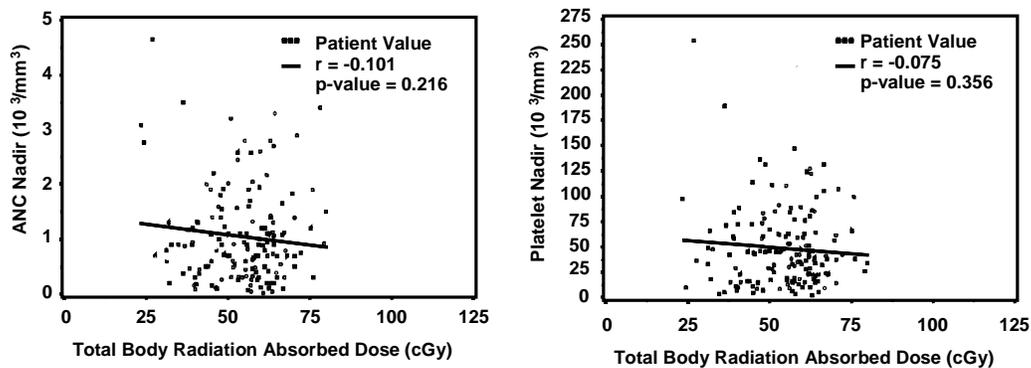


Figure 20. ANC nadir and platelet nadir and total body radiation-absorbed dose

5.F.2. Dosimetric Parameters Versus Days to Hematologic Recovery

In Table 53, Table 54, Figure 21, and Figure 22, results of red marrow and total body radiation-absorbed dose studies are summarized. No clinically meaningful correlation was noted between total body radiation-absorbed dose and time to recovery for ANC or platelet counts.

**Table 53.
 Radiation-absorbed dose (cGy) versus Days to ANC Recovery**

Days to Recovery	Median Red Marrow Dose [Blood-Derived]	Median Red Marrow Dose [Sacral-Derived]	Median Total Body Dose
1 - 14	63	91	57
15 - 28	62	109	58
> 28	46	85	55
	p = 0.694	p = 0.090	p = 0.354

p-values generated by Kruskal-Wallis test

Table 54.
Radiation-absorbed dose (cGy) versus Days to Platelet Count Recovery

Days to Recovery	Median Red Marrow Dose [Blood-Derived]	Median Red Marrow Dose [Sacral-Derived]	Median Total Body Dose
0*	83	150	60
1 - 14	63	93	59
15 - 28	64	112	58
> 28	44	98	46
	p = 0.607	p = 0.227	p = 0.040

*Two tests on the same day
p-values generated by Kruskal-Wallis test

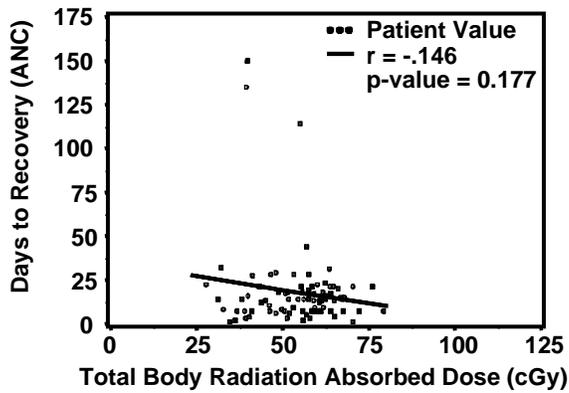
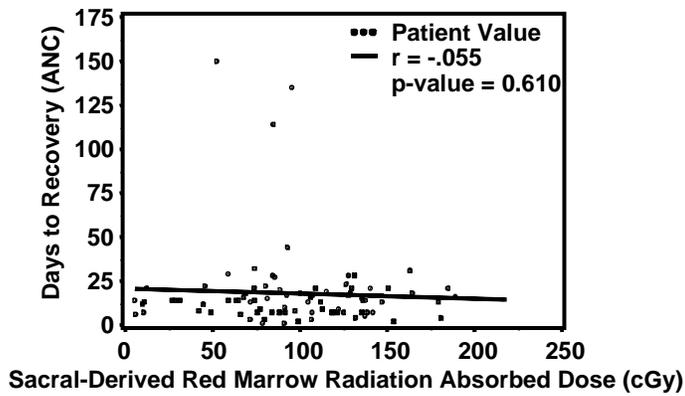
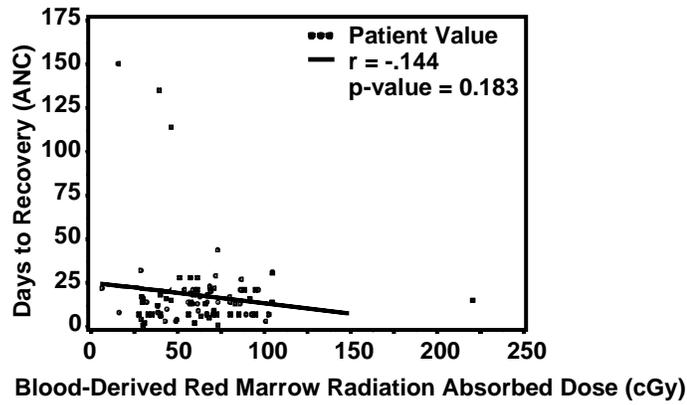


Figure 21. Radiation-absorbed dose and days to ANC recovery

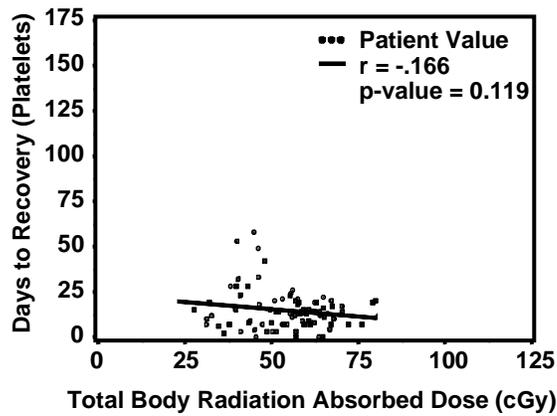
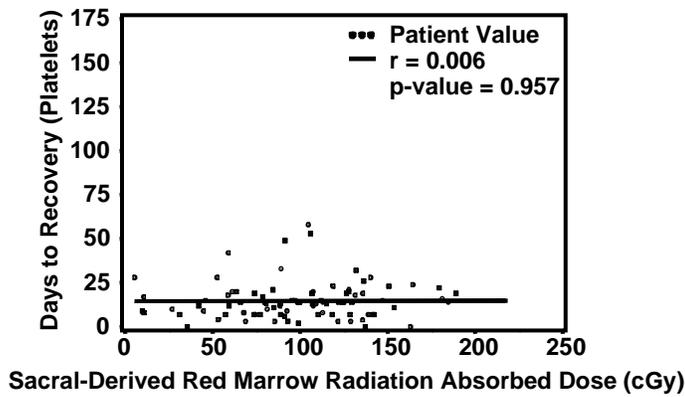
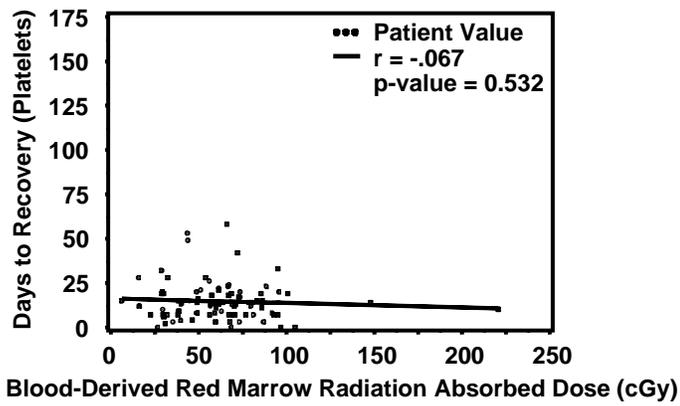


Figure 22. Radiation-absorbed dose and days to platelet count recovery

5.F.3. Pharmacokinetic Parameters Versus Hematologic Nadir

No statistically significant correlation was noted between hematologic nadir and the pharmacokinetic parameters of whole blood ⁹⁰Y effective half-life and AUC. Effective ⁹⁰Y half-life and AUC versus ANC nadir grade is shown in Table 55, and versus platelet-count nadir grade is shown in Table 56. Scatter plots show no correlation between ANC or platelet-count nadir values and whole blood effective T_{1/2} or AUC (Figure 23 and Figure 24).

Table 55.
Whole Blood ⁹⁰Y Effective T_{1/2} and AUC Versus ANC Nadir Grade

ANC Nadir Grade	N	Median T _{1/2} (Hours)	Median AUC (Hours)
0 - 2	63	27	25
3	40	29	24
4	42	27	24
		p = 0.050	p = 0.898

N = number of patients
 p-values generated by Kruskal-Wallis test

Table 56.
Whole Blood ⁹⁰Y Effective T_{1/2} and AUC Versus Platelet-Count Nadir Grade

Platelet Nadir Grade	N	Median T _{1/2} (Hours)	Median AUC (Hours)
0 - 2	53	27	26
3	81	27	24
4	11	27	20
		p = 0.547	p = 0.594

N = number of patients
 p-values generated by Kruskal-Wallis test

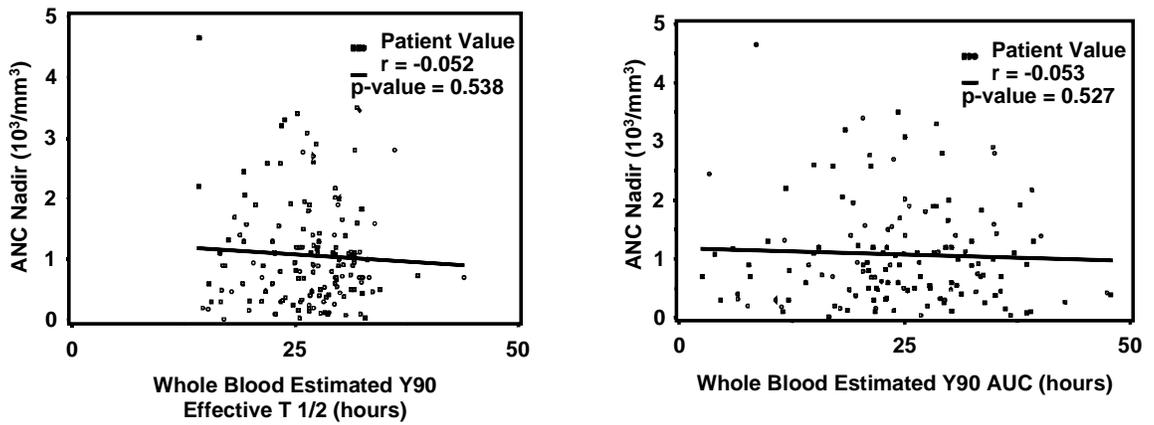


Figure 23. ANC nadir and whole-blood estimated ⁹⁰Y half-life and AUC

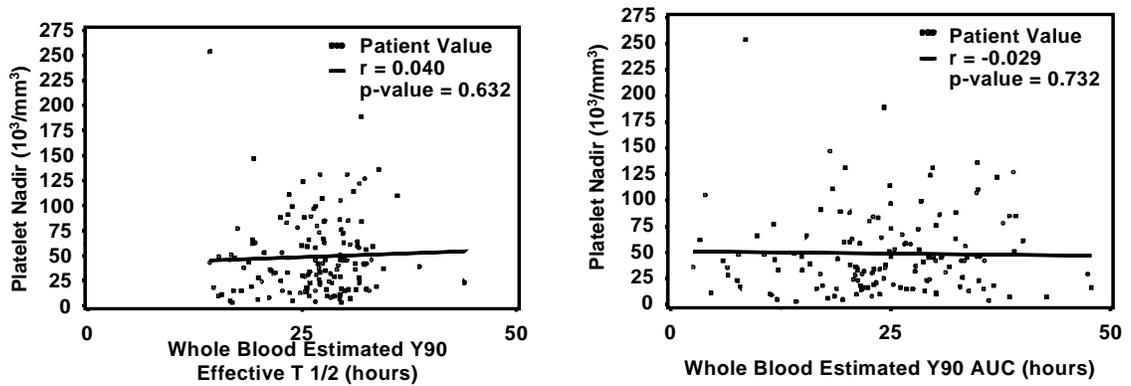


Figure 24. Platelet-count nadir and whole-blood estimated ⁹⁰Y half-life and AUC

5.F.4. Pharmacokinetic Parameters Versus Days to Hematologic Recovery

No correlation of ^{90}Y effective half-life or AUC and days to recovery of ANC or platelet levels was noted as shown in Figure 25 and Figure 26.

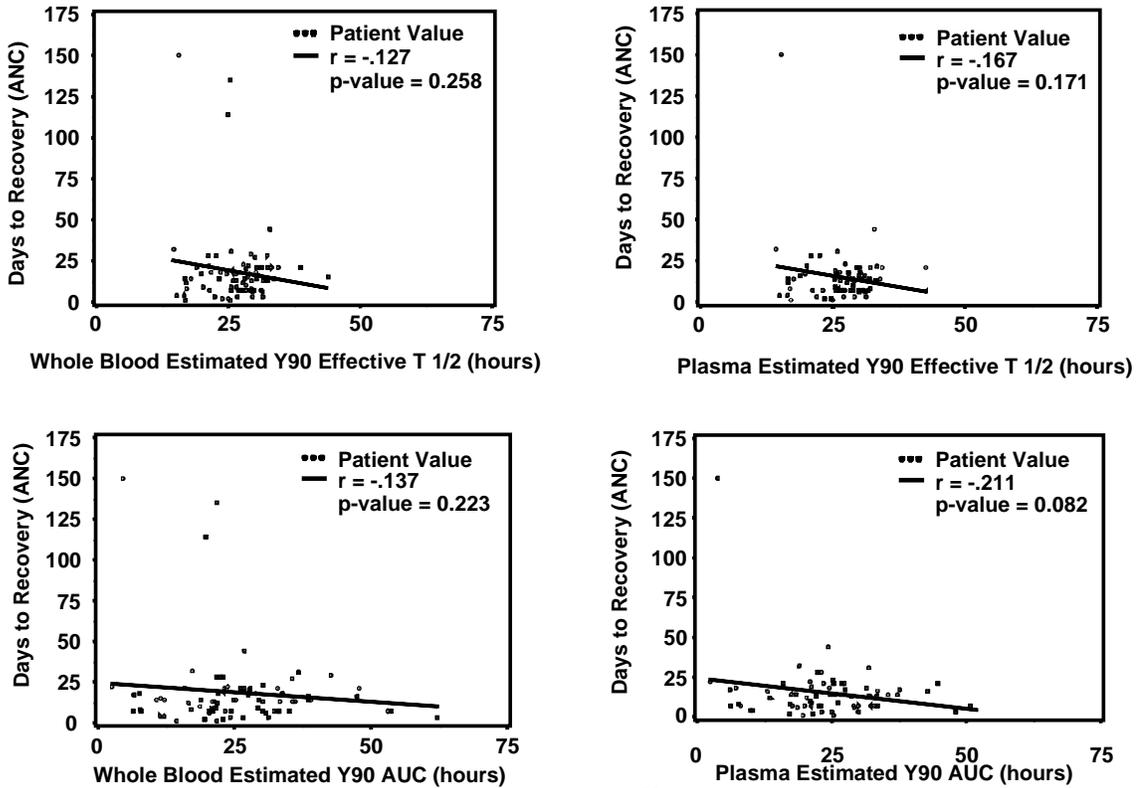


Figure 25. Whole blood and plasma estimated ^{90}Y effective half-life and AUC and days to ANC recovery

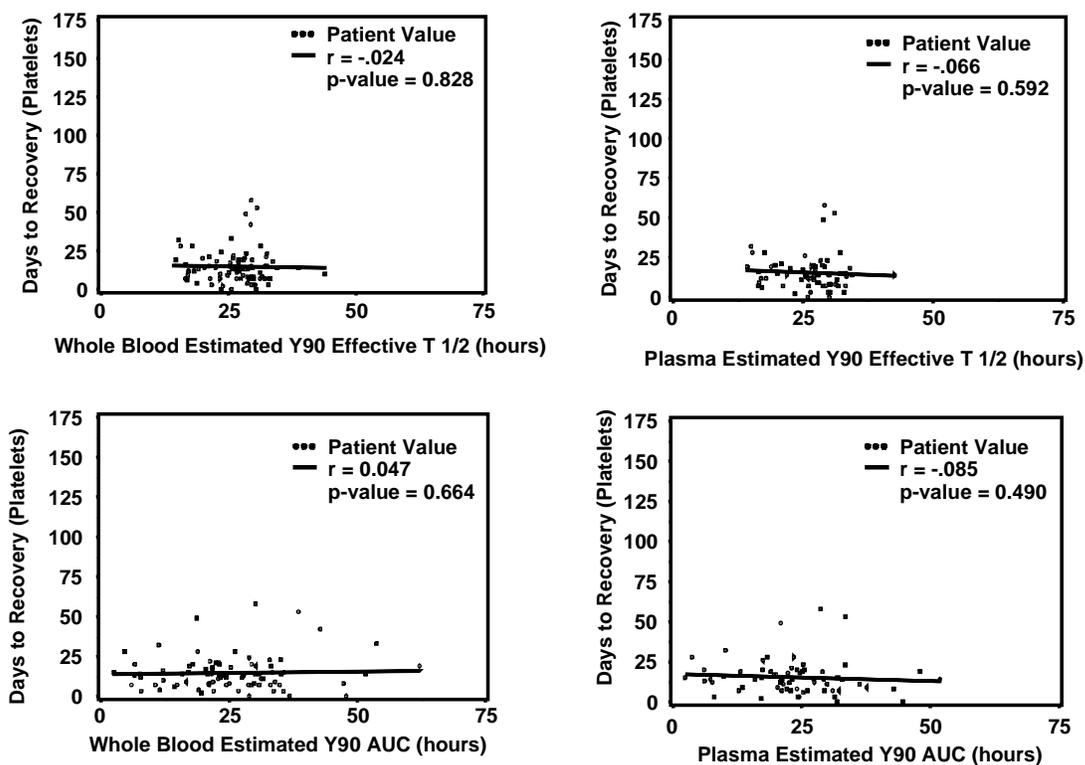


Figure 26. Whole blood and plasma estimated ^{90}Y effective half-life and AUC and days to platelet count recovery

Several factors can explain the failure of red marrow dosimetry, total body dosimetry, or pharmacokinetics to predict hematologic toxicity following ^{90}Y ibritumomab tiuxetan therapy. The predictive value of these parameters does not account for interpatient variability in bone marrow reserve. In this patient population, loss of marrow reserve is common as a result of bone marrow damage from prior chemotherapy, external beam radiation therapy, or from marrow involvement with NHL.

Blood-derived red marrow dosimetry is based on blood activity levels and does not account for secondary irradiation of hematopoietic cells from radiopharmaceutical targeting of NHL within the marrow. In these studies, 49% of patients had bone marrow involvement with NHL.

5.F.5. Absence of Radiation-related Nonhematologic Toxicity

Although mild abnormalities in liver function tests occurred in a few patients, most could be attributed to other causes (i.e., lymphoma, IV drug abuse-associated viral hepatitis, Gilbert's syndrome), and radiation-absorbed doses to the liver in these patients were in the same range as that of the overall patient population. No pulmonary or renal toxicity related to ^{90}Y ibritumomab tiuxetan was observed.

5.G. Imaging with ¹¹¹Indium Ibritumomab Tiuxetan

The usefulness of dosimetry is limited if the radiation-absorbed dose to the dose-limiting organ does not correlate with toxicity. Results from studies of ⁹⁰Y ibritumomab tiuxetan indicate that radiation-absorbed dose does not exceed safe levels and does not correlate with hematologic toxicity. Therefore, dosimetry has been eliminated from the ⁹⁰Y ibritumomab tiuxetan RIT. However, ¹¹¹In ibritumomab tiuxetan imaging will continue as a safety measure.

As part of the ⁹⁰Y ibritumomab tiuxetan regimen, imaging is performed using ¹¹¹In ibritumomab tiuxetan (5 mCi [185 MBq]) immediately following an infusion of rituximab at 250 mg/kg. The biodistribution of ¹¹¹In ibritumomab tiuxetan is assessed by a visual evaluation of whole-body, planar view, anterior and posterior gamma images at 2 to 24 hours and 48 to 72 hours after injection. To resolve ambiguities, a third image at 90 to 120 hours can be obtained.

The radiopharmaceutical is expected to be easily detectable in the blood pool areas at the first time point, with less activity in the blood pool on later images. Moderately high to high uptake is expected in the normal liver and spleen, with low uptake in the lungs, kidneys, and urinary bladder. Localization to lymphoid aggregates in the bowel wall has been reported. Tumor uptake may be visualized as areas of increased intensity.

If visual inspection of the gamma images reveals an altered biodistribution, the patient does not proceed to the therapeutic dose of ⁹⁰Y ibritumomab tiuxetan. The patient may be considered to have an altered biodistribution if the blood pool is not visualized on the first image, indicating rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver, spleen, and/or marrow. Other potential examples of altered biodistribution may include diffuse uptake in the normal lungs or kidneys more intense than in the liver on the second or third image. Altered biodistribution has not been observed in ⁹⁰Y ibritumomab tiuxetan clinical trials.

5.H. Summary

Dosimetry was conducted in a total of 205 patients across four ⁹⁰Y ibritumomab tiuxetan studies and produced radiation-absorbed dose estimates well within the protocol-defined safety limits of 2000 cGy for normal organs and 300 cGy for red marrow. The ⁹⁰Y ibritumomab tiuxetan regimen delivers a safe range of radiation-absorbed dose for the defined group of relapsed or refractory NHL patients with baseline platelet counts > 100,000 cells/mm³, no prior myeloablative or RIT, and < 25% bone marrow involvement with lymphoma. Dosimetric and pharmacokinetic parameters do not correlate with toxicity.

6. CONCLUSIONS

Net clinical benefit was defined in the 1991 publication by the FDA and NCI Division of Cancer Treatment, Board of Scientific Counselors working group^[104]. As O'Shaughnessy, et al., noted in that publication, "the primary aim of cancer treatment is prolongation of life, but the demonstration that a new agent causes tumor regression and improves patients' clinical condition also supports approval of a new agent, even in the absence of improved survival". The benefits of ⁹⁰Y ibritumomab tiuxetan outweigh the toxicity observed in the relapsed or refractory, low-grade, follicular, or CD20+ transformed NHL patient population.

Evaluation of net clinical benefit of ⁹⁰Y ibritumomab tiuxetan in the population studied must consider that these patients have incurable disease, are symptomatic and in need of therapy, and that no treatment has been shown to prolong survival^[57]. In this context, a clinically meaningful outcome is a significant reduction in tumor burden (as evidenced by a partial, clinical complete, or complete response) and resolution of disease-related symptoms sustained for a period of time during which further treatment is not required.

Two Phase III adequate and well-controlled studies of ⁹⁰Y ibritumomab tiuxetan have been performed. The primary efficacy endpoint goals were met in both studies and safety was acceptable.

The ⁹⁰Y ibritumomab tiuxetan treatment regimen is completed in one week with no requirement for hospitalization, isolation, or shielding. The high energy and long path length of the pure beta emission from ⁹⁰Y allow effective treatment of bulky or poorly vascularized tumors. The specific targeting of tumor cells allows systemic therapy without side effects of hair loss, nephrotoxicity, or neurotoxicity. The response rate (57% to 64%) in chemotherapy-resistant and rituximab-refractory (59% to 74%) patients is noteworthy. TTNT (time off therapy) is prolonged.

Yttrium-[90] ibritumomab tiuxetan therapy represents a clinically meaningful advance in therapy for patients with relapsed or refractory, low-grade, follicular, or CD20+ transformed and Rituximab-refractory follicular NHL.

6.A. Efficacy

Phase I/II Dose-finding Study

A separate analysis by dose group revealed that this mixed population of low- and intermediate-grade and mantle cell NHL patients receiving 0.2 mCi/kg, 0.3 mCi/kg, or 0.4 mCi/kg ⁹⁰Y ibritumomab tiuxetan achieved response rates of 40%, 75%, and 67%, respectively.

Phase III Randomized Comparison Study

The net clinical benefit of ⁹⁰Y ibritumomab tiuxetan as observed in this Phase III randomized controlled study is summarized as follows:

- A significantly greater ORR was achieved in the ⁹⁰Y ibritumomab tiuxetan treatment group compared with rituximab control group in a population of poor prognosis patients, including elderly patients, patients with bulky, extranodal, or chemoresistant disease, splenomegaly, or bone marrow involvement.
 - Response was evaluated by an independent blinded panel.

- Tumor burden was reduced to a greater degree by ⁹⁰Y ibritumomab tiuxetan therapy compared with rituximab.
- Patients resistant to their last chemotherapy had a significantly higher response rate to ⁹⁰Y ibritumomab tiuxetan than to rituximab.
- Patients with bulky disease had a significantly higher response rate to ⁹⁰Y ibritumomab tiuxetan than to rituximab.
- PDRC^a: 73% ORR (⁹⁰Y ibritumomab tiuxetan) versus 47% (rituximab), p = 0.002.
- IWRC^b: 80% ORR (⁹⁰Y ibritumomab tiuxetan) versus 56% (rituximab), p = 0.002.
- IWRC: 30% CR (⁹⁰Y ibritumomab tiuxetan) versus 16% (rituximab), p = 0.040.
- Kaplan-Meier (KM) estimated median DR is 14.2+ months for ⁹⁰Y ibritumomab tiuxetan group and 12.1+ months for rituximab group.
- DR in follicular patients is 18.5+ months for the ⁹⁰Y ibritumomab tiuxetan group and 12.1+ months for the rituximab group.
- K-M estimated median TTP for CR/CCR has not been reached for the ⁹⁰Y ibritumomab tiuxetan group (range 8.4 to 31.5+ months) and median TTP for CR/CCR in the rituximab group is 13.4 months (range 6.8 to 25.3+ months).
- This study was not designed to detect differences in TTP between the treatment groups. K-M curves demonstrate a longer TTP in the ⁹⁰Y ibritumomab tiuxetan group compared with the rituximab group in the follicular patient population.
- K-M curves for TTNT suggest a longer treatment-free period in the ⁹⁰Y ibritumomab tiuxetan group compared with the rituximab group. For patients with nontransformed histology, the ⁹⁰Y ibritumomab tiuxetan group had a significantly longer TTNT when compared with the rituximab group.

Phase III Rituximab-Refractory Study

- PDRC: 59% ORR; IWRC: 74% ORR.
- Significantly higher ORR compared with prior rituximab therapy: 59% (⁹⁰Y ibritumomab tiuxetan), 32% (prior rituximab).
- ORR for ⁹⁰Y ibritumomab tiuxetan (median fifth therapy) is similar to that achieved with prior chemotherapy (median third therapy). This result was better than anticipated given the successively lower response rates usually associated with subsequent therapies.
- K-M estimated median DR of 7.7+ months exceeds the prospectively defined 5-month goal, is significantly longer than the 4-month median DR achieved with prior rituximab treatment, and compares favorably with the 6.5-month median DR achieved with prior chemotherapy.

^a PDRC: protocol-defined response criteria

^b IWRC: International Workshop Response Criteria

6.B. Safety

- AEs are primarily hematologic.
- Severity of hematologic toxicity is related to baseline platelet count and percent bone marrow involvement: Grade 4 neutropenia (30% of patients), thrombocytopenia (10%), and anemia (4%).
- Nonhematologic AEs are generally Grade 1 or 2, and the incidence parallels that of rituximab therapy.
- No major acute organ dysfunction.
- B-cell levels recover by 6 to 9 months after therapy. T cells are not depleted.
- Median serum immunoglobulins remained largely within the normal range despite a 6-month reversible depletion of B cells.
- Mildly thrombocytopenic patients can be treated with a reduced dose.
- Low incidence of HAMA/HACA (< 2% of patients).
- No observable age-dependent differences in the safety profile.
- Specific targeting of tumor cells allows systemic therapy without hair loss or persistent nausea and vomiting.

6.C. Dosimetry and Pharmacokinetics

- Radiation-absorbed doses to normal organs acceptable in all patients.
- No correlation of pharmacokinetic or dosimetric parameters with hematologic toxicity.
- No clinically significant variation in whole body clearance; minimal urinary excretion.
- Dosimetry has been safely eliminated for the defined patient population of relapsed or refractory low-grade, follicular, or transformed NHL patients with < 25% bone marrow involvement and acceptable bone marrow reserve, characterized by (1) baseline platelet counts > 100,000 cells/mm³ and (2) no prior myeloablative or RIT.
- Imaging with ¹¹¹In ibritumomab tiuxetan will continue as a safety measure.

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