ONCOLOGIC DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

IODINE I 131 TOSITUMOMAB

(Tositumomab and Iodine I 131 Tositumomab)

BLA 125011

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. EXECUTIVE SUMMARY

Proposed Indication: *BEXXAR® therapy (iodine I 131 tositumomab) is indicated for the treatment of patients with relapsed or refractory low-grade or transformed low-grade, B-cell non-Hodgkin's lymphoma (NHL), including patients with rituximab-refractory non-Hodgkin's lymphoma. Determination of the effectiveness of the BEXXAR therapeutic regimen in a relapsed or refractory low-grade or transformed low-grade patient population is based on the existence of long-term durable responses in multiple clinical studies*.

Corixa Corporation (Corixa) and partner GlaxoSmithKline (GSK) have requested approval of Bexxar therapy, referred to in this document as iodine I 131 tositumomab, based on the following:

1. Accelerated approval of iodine I 131 tositumomab based on demonstrated efficacy in inducing long-term durable responses (time to progression [TTP] of at least 1 year) in patients with relapsed or refractory low-grade or transformed low-grade, B-cell non-Hodgkin's lymphoma in 5 clinical studies.
2. Conventional approval of iodine I 131 tositumomab based on demonstrated efficacy in patients with rituximab-refractory non-Hodgkin's lymphoma.

1.1 REQUEST FOR ACCELERATED APPROVAL

The Food and Drug Administration's (FDA) Accelerated Approval procedure is available for products treating serious or life-threatening illnesses. FDA may grant accelerated approval for a biological product if the product provides a meaningful benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy [21 CFR 314.500 and 601.40]). The approval must be on the basis of adequate and well-controlled clinical trials. These trials may establish that the biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval requires that the sponsor conduct additional clinical research to further verify and define the clinical benefit.

Corixa Corporation has requested accelerated approval for iodine I 131 tositumomab based on the existence of long-term durable responses in multiple clinical studies. In brief, Accelerated Approval is justified based on the following:

1. **Adequate and well-controlled pivotal trial (Study RIT-II-004):** Iodine I 131 tositumomab therapy resulted in more patients having significantly longer durations of response when compared to durations for the patient's previous response to chemotherapy ($p<0.001$). Supportive results (with more patients having a longer duration of response after iodine I 131 tositumomab than after their previous therapy) were achieved in 4 additional trials.
2. **Effect on a surrogate endpoint:** Iodine I 131 tositumomab induced a substantial number of durable responses (TTP of 1 year or more) in patients with relapsed or refractory low-grade or transformed low-grade NHL. Long-term durable responses were demonstrated in the pivotal trial and in each of 4 additional supportive trials. Long-term durable responses produce a meaningful clinical benefit to this relapsed/refractory patient population for whom a single treatment lasting 1–2 weeks gives long-term progression-free survival for up to 8 years without the need for further therapy.

3. **Meaningful benefit over existing treatments:** Treatment with iodine I 131 tositumomab has been shown to provide (a) an improved response (measured in duration of response) when compared to the patient's immediate prior therapy; (b) an improved response (measured in the incidence of durable responders with demonstrably longer durations of response) compared to data reported for Zevalin® or Rituxan®; and (c) a better defined benefit (based on substantially more data) in patients with transformed low-grade NHL than reported for Zevalin.
4. **Further studies to verify clinical benefit: Summary of proposed post-approval commitments:** Corixa, as the sponsor, has committed to conduct additional clinical trials to confirm and further define the clinical benefits. One of the studies is presently ongoing. The study is being conducted by SWOG and compares progression-free survival of patients with newly diagnosed, previously untreated CD20+ follicular lymphoma randomized to CHOP vs. CHOP + rituximab vs. CHOP + iodine I 131 tositumomab. The second randomized trial under final review by the FDA is a 440-patient efficacy evaluation of Bexxar therapy versus Rituxan therapy.

1.2 REQUEST FOR CONVENTIONAL APPROVAL

Regular or conventional marketing approval of oncology drugs requires substantial evidence of efficacy with acceptable safety demonstrated in adequate and well-controlled trials. Unless pre-specified by FDA, there is no requirement to demonstrate an additional clinical benefit in comparison to other approved products. Corixa is requesting Conventional Approval based on demonstrated efficacy in patients with rituximab-refractory low-grade B-cell NHL. Conventional Approval is justified based on results from study CP-97-012. This study examined the safety and efficacy of iodine I 131 tositumomab in patients who did not respond or relapsed following rituximab therapy. The analysis of efficacy in this refractory population compared each patient's duration of response following iodine I 131 tositumomab to the duration of response following prior rituximab. Significantly more patients had a longer duration of response following iodine I 131 tositumomab than that following prior rituximab ($p<0.001$, McNemar's test).

On 11 September 2001, ODAC recommended full approval of Zevalin for the treatment of rituximab-refractory patients with follicular lymphoma. FDA later granted full approval for this indication. The basis of approval was a single-arm study of 54 patients. The primary efficacy endpoint was the overall response rate (ORR). ODAC's recommendation and subsequent FDA approval were based on a secondary analysis that compared the duration of response after Zevalin to the duration of response to prior rituximab, using patients as their own control. Study CP-97-012, evaluating the efficacy of Bexxar therapy, is essentially identical to the study supporting approval of Zevalin.

1.3 RADIOIMMUNOTHERAPY WITH TOSITUMOMAB

Iodine I 131 tositumomab is a novel radioimmunotherapeutic agent developed for the treatment of patients with relapsed/refractory, CD20-positive B-cell, low-grade non-Hodgkin's lymphoma, with or without transformation. Iodine I 131 tositumomab includes an unlabeled and a radiolabeled antibody, commonly known as Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody, respectively. The approved USAN names are tositumomab for the unlabeled antibody and iodine I 131 tositumomab for the labeled antibody.

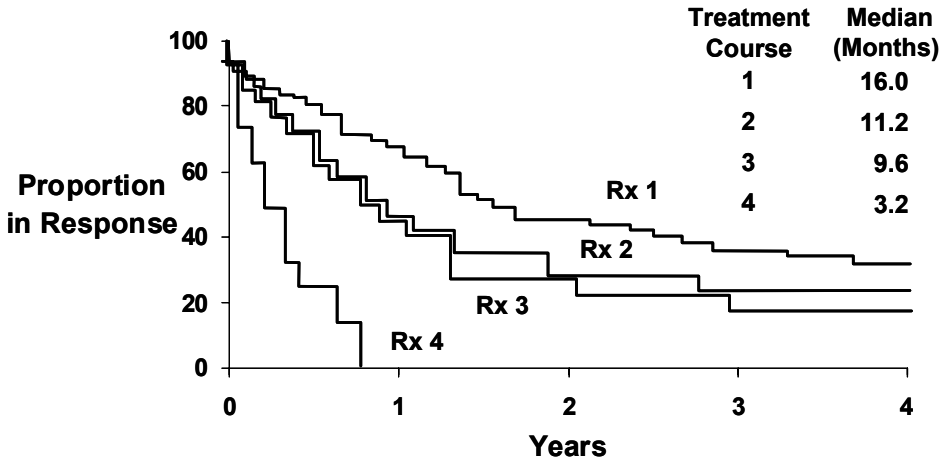
Tositumomab (Anti-B1 Antibody) is an $IgG_{2a,}$ murine monoclonal antibody that binds with high affinity and specificity to the CD20 antigen on the surface of normal and malignant human B cells.[1] The utility of targeting CD20 is demonstrated by clinical data that led to FDA approval of rituximab (Rituxan®) and Y-90 ibritumomab tiuxetan (Zevalin®).

1.4 LOW-GRADE NON-HODGKIN'S LYMPHOMA WITH OR WITHOUT TRANSFORMATION

There are approximately 55,000 new cases and 25,000 deaths annually in the United States as a result of non-Hodgkin's lymphoma. Approximately 30–40% of patients with NHL have low-grade disease.[2,3,4] The median survival of patients with low-grade NHL is approximately 8–10 years from initial diagnosis.

Patients with Stage I or II low-grade NHL have long survivals and may be cured by involved- or extended-field irradiation. Unfortunately, approximately 90% of the patients with this disease present with advanced Stage III or IV disease. These patients are generally incurable with present-day therapy, despite the initially indolent natural history and high initial response rates of low-grade NHL. Single-agent or combination chemotherapy is the standard approach for treating patients with advanced-stage disease. While the response rates with chemotherapy are initially high, all patients ultimately relapse, and the response rates and durations of response typically decline with each subsequent course of chemotherapy.[3] Figure 1 illustrates the duration of response for patients with low-grade NHL after successive treatments. In general, the pattern is for fewer responses and shorter durations of response. Patients with unfavorable characteristics may survive only a few years from diagnosis.[5] Death occurs from organ failure due to infiltrative disease, complications of aggressive therapy, or from transformation to a higher-grade histology, which results in a more rapidly progressing, typically treatment-refractory, and ultimately fatal form of the disease.[6]

Figure 1. Duration of Response with Sequential Therapies



Source: Gallagher CJ, et al. *J. Clin Oncol* 1986;4:1470

1.5 CLINICAL STUDIES WITH IODINE I 131 TOSITUMOMAB

Between 1990 and 13 September 2002, 1651 patients received iodine I 131 tositumomab therapy in clinical studies. (A regulatory history is found in Appendix 3.) Clinical trial experience includes 192 patients who received myeloablative doses of

iodine I 131 tositumomab in conjunction with bone marrow or peripheral blood stem cell transplants. One hundred seventy-one patients received iodine I 131 tositumomab as part of Investigator-sponsored IND studies, and an additional 220 patients were treated on Company-sponsored IND studies not utilized for registration (i.e., first-line treatment, retreatment, >25% bone marrow involvement, mantle cell NHL and iodine I 131 tositumomab plus various chemotherapies). Table 3 in Section 4 outlines the clinical registration of all patients on studies and delineates the patients in the Integrated Safety (n=620) and Integrated Efficacy (n=250) Populations. Inclusion in these populations was based on receiving study drug and data cutoff dates. See Appendix 4 for a summary of all clinical studies.

Following consultation with lymphoma experts and discussion with the Agency, Corixa applied the following definition to the Integrated Efficacy Population (N=250) database:

- A durable responder for a relapsed, refractory, low-grade NHL population is a responding patient with a time to progression of 12 months or more (by independent panel assessment).

Based on the 250 patients in the Integrated Efficacy Population, a total of 78 patients (31%) had a MIRROR Panel–assessed response and a MIRROR Panel–assessed time to progression of at least 12 months. Two patients were disqualified (see Section 4.2.2). Thus, 76 patients constitute the Durable Responder population.

Efficacy Data

Information from 5 clinical studies (RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012) will be presented in support of the requested indication (a description of these studies may be found in Section 4). The primary efficacy data supporting the indication are from 3 studies: the pivotal study in chemotherapy-refractory patients, RIT-II-004; a randomized study of iodine I 131 tositumomab versus unlabeled tositumomab in relapsed or refractory patients, RIT-II-002; and a single-arm study in patients who did not respond or had progressed after rituximab, CP-97-012. Studies RIT-I-000 and RIT-II-001 provide data supportive of the proposed indication. Thus, efficacy data are presented for an integrated population of 250 patients, as well as the individual studies.

Safety Data

The Integrated Safety Population includes patients from the 5 studies noted above, as well as patients from study CP-98-020, an expanded access program (EAP), and 4 patients treated on single-patient protocols. Thus, safety data are presented for 620 patients with relapsed and refractory low-grade or transformed low-grade NHL for whom a non-myeloablative total-body dose of either 65 or 75 cGy of iodine I 131 tositumomab was prescribed, and for whom at least 13 weeks of follow-up data were available as of the data cutoff date (all patients withdrawing from study for any reason within 13 weeks were included in the analysis). Patients were generally heavily pretreated, had experienced multiple relapses (median of 3 prior treatment regimens; range: 1–13 regimens), and had other poor prognostic characteristics such as age greater than 60 years, advanced-stage disease, elevated LDH, and transformed low-grade NHL. A sixth study, RIT-II-003, provides supplemental data regarding the incidence of myelodysplasia or associated acute myelogenous leukemia (AML) in previously untreated patients.

1.5.1 Summary of Efficacy

1.5.1.1 Primary Studies in Support of the Indication for Treatment of Relapsed, Refractory Low-Grade and Transformed Low-Grade Non-Hodgkin's Lymphoma (RIT-II-004 and RIT-II-002)

1.5.1.1.1 RIT-II-004

The primary endpoint of the pivotal trial (RIT-II-004) was a paired comparison of the number of patients having a longer duration of response after iodine I 131 tositumomab therapy to the number of patients having a longer duration of response after their last qualifying chemotherapy (LQC) regimen. Secondary efficacy endpoints included overall response rate (ORR), complete response rate (CR), and time to progression (TTP).

The study enrolled 61 patients and 60 patients received study drug. Patients had refractory, low-grade or transformed low-grade NHL and had been treated with at least 2 different qualifying chemotherapy regimens (protocol-defined regimens listed in Appendix 8). Patients also had to have failed to achieve an objective response or relapsed within 6 months after completion of their last qualifying chemotherapy regimen (LQC). These patients had multiple poor prognostic characteristics: a median age of 60, a median of 4 prior chemotherapies, bulky disease, bone marrow involvement, elevated serum LDH, advanced stage, and most importantly, 38% had transformation from an initial low-grade histology to a higher-grade histology.

An independent, blinded panel, the Masked Independent Randomized Radiology and Oncology Review (MIRROR) Panel, was convened to assess clinical data for the efficacy endpoints. All reported efficacy results are based on the MIRROR Panel review including the MIRROR Panel review of each patient's response to their LQC.

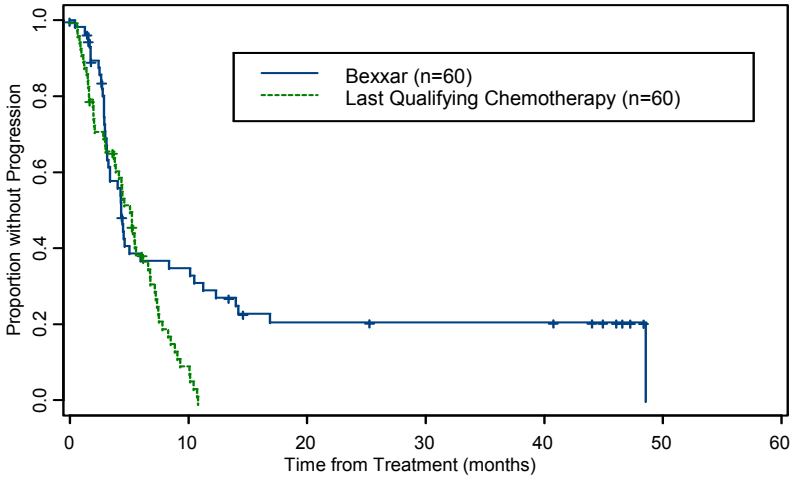
A statistically significant improvement in the primary endpoint was achieved: there were significantly more patients with a longer duration of response (>30 days than comparator) following iodine I 131 tositumomab therapy (n=26) than patients with a longer duration of response after their LQC (n=5; $p<0.001$). Twenty-eight patients had equivalent responses or had no responses to both therapies and one patient was censored.

Improvements in secondary efficacy endpoints following iodine I 131 tositumomab compared to those following LQC were also achieved: overall response (47% vs. 12%; $p<0.001$), duration of response (11.7 vs. 4.1 months; $p<0.001$), and complete response (20% vs. 2%; $p=0.002$).

Fifteen of 60 (25%) patients (including the disqualified patient discussed in Section 4.2.2) were classified as long-term responders (patients with a MIRROR Panel–assessed TTP of a year or more). Seven of the 60 (12%) patients are still in complete response with TTP ranging from 41+ to 49+ months.

Figure 2 illustrates the proportion of patients in response after iodine I 131 tositumomab treatment compared to after treatment with their LQC.

Figure 2. MIRROR Panel–Assessed Time to Progression: Study RIT-II-004



The higher response rate and more durable responses in patients following a single treatment with iodine I 131 tositumomab therapy when compared to their last chemotherapy represents a reversal of the trend generally observed during the sequential treatment of low-grade NHL, where consecutive therapies provide progressively fewer and shorter responses (see Figure 1).[3]

1.5.1.1.2 RIT-II-002

Study RIT-II-002 was a randomized, two-arm, open-label, multicenter study that enrolled patients with chemotherapy-relapsed or -refractory low-grade or transformed low-grade NHL. Patients were randomized to receive either iodine I 131 tositumomab therapy or unlabeled tositumomab alone in a parallel-dose schedule in order to determine the added benefit of the radioimmunoconjugate to the antibody. The primary endpoint was a comparison of the CR rates. Secondary endpoints included ORR, duration of responses and time to progression. The MIRROR Panel assessed all responses.

A total of 78 patients (18% with transformation) participated in the study. Patients had been previously treated with 1–5 chemotherapy regimens (see Table 6). One or more therapies must have included an anthracycline, anthracenedione, or alkylating agent.

A significant difference was observed for the primary efficacy endpoint, complete response rate. The CR rate was 33% (14 of 42 patients) for the patients treated with iodine I 131 tositumomab compared to 8% (3 of 36) for patients treated with unlabeled tositumomab (p=0.012). In addition, the ORR was greater after treatment with iodine I 131 tositumomab: 23 of 42 (55%) patients compared to 7 of 36 (19%) patients (p=0.002). The time to progression was significantly longer for patients treated with iodine I 131 tositumomab than for patients treated with tositumomab alone (relative risk = 0.54; 95% C.I.: 0.31–0.96; p=0.031).

Per protocol, 19 patients initially treated with the unlabeled antibody crossed over to receive iodine I 131 tositumomab following disease progression. A CR was achieved in 42% (8 of 19 patients) with an ORR of 68% (13 of 19 patients) in the crossover patient population.

A total of 20 patients (33%) from the iodine I 131 tositumomab–treated populations, including patients in the crossover arm, were classified as having a long-term response,

including 11 patients continuing in complete response with time to progression ranging from 23+ to 59+ months.

1.5.1.2 Primary Study in Support of Indication for Treatment of Rituximab-Refractory Patients with Non-Hodgkin's Lymphoma (CP-97-012)

The objectives of this study were to assess the response rate, duration of response, and safety of iodine I 131 tositumomab therapy in patients whose disease had not responded or progressed after rituximab therapy. This study was designed to enroll 40 evaluable patients.

Forty-three patients were enrolled in the study, and 40 patients received study drug. All patients were required to have prior treatment with at least 4 doses of rituximab without an objective response, or to have progressed during or following treatment. Twenty-four patients did not respond to their last treatment with rituximab, and of the 16 patients who did respond to rituximab, only 5 patients had a duration of response 6 months or more. Overall, 35 of the 40 patients met the accepted definition of "rituximab refractory" (no response or a response of less than 6 months).

A response, as assessed by MIRROR Panel, occurred in 27 of the 40 (68%) patients with a median duration of response of 16.1 months (95% CI: 10.5 months–NR). A complete response occurred in 13 of 40 (33%) patients; the median duration of complete response has not been reached (95% CI: 14.7 months–NR).

An outcomes analysis was performed using MIRROR Panel–assessed data for iodine I 131 tositumomab and Investigator-assessed data for rituximab. Of the 40 patients, 25 patients had a longer (at least 30 days) duration of response following iodine I 131 tositumomab than following rituximab, 5 patients had a longer duration of response following rituximab than following iodine I 131 tositumomab, 9 patients had equivalent durations of response, and 1 patient was censored ($p<0.001$, McNemar's test). A total of 17 patients (43%) were classified as having a durable response (TTP of one year or more) following iodine I 131 tositumomab therapy.

1.5.1.3 Other Studies Supporting Approval (RIT-I-000 and RIT-II-001)

Data supporting safety and efficacy are available from 2 additional Phase 1 or 2 studies (RIT-I-000 and RIT-II-001). From study RIT-I-000, the maximum tolerated dose (MTD) was determined to be 75 cGy using a standard dose-escalation schedule. The dose-limiting toxicity was transient myelosuppression. These early trials also defined the dosing method and established that iodine I 131 tositumomab could be safely administered at multiple sites and that it was efficacious in patients with NHL. Longer follow-up on these early trials has also demonstrated the long-term nature of the benefits of this therapy.

1.5.1.4 Summary

Bexxar therapy has demonstrated significant overall efficacy and produced durable responses in patients with advanced-stage, relapsed and refractory low-grade NHL, with or without transformation.

In the 5 studies supporting the efficacy of iodine I 131 tositumomab (shown in Table 1), response rates range from 47% to 68%, complete response rates range from 20% to 38%, and durations of responses as long as 7.8+ years have been documented.

Furthermore, all 5 studies show a high percentage of patients with a TTP of 12 months or more, ranging from 21% to 43%.

Table 1. Summary of Efficacy Results

Study Number	Median Prior ChemoTx Regimens (range)	Response		Complete Response		Durable Response[a]	
		Number of Patients (%)	Median TTP (months) (range)	Number of Patients (%)	Median TTP (months) (range)	Number of Patients (%)	Median TTP (months) (range)
Primary Studies							
RIT-II-004 (N=60)	4 (2–13)	28/60 (47%)	13.2 (3.2 – 48.7)	12/60 (20%)	48.7 (10.5 – 48.7)	15/60 (25%)	48.7 (12.4 – 48.7)
RIT-II-002 (N=61[b])	2 (1–4)	36/61 (59%)	NR (3.2 – 58.9+)	22/61 (36%)	NR (6.3 – 58.9+)	20/61 (33%)	NR (12.1 – 58.9+)
CP-97-012 (N=40)	4 (1–11)	27/40 (68%)	16.8 (3.0+ – 36.7+)	13/40 (33%)	31.5 (5.5– 36.7+)	17/40 (43%)	31.5 (12.0 – 36.7+)
Supportive Studies							
RIT-I-000[c] (N=42)	3 (1–11)	27/42 (64%)[d]	15.2[d] (3.7 – 95.8+)	16/42 (38%)[d]	29.1[d] (3.7 – 95.8+)	16/42 (38%)	40.0 (13.1 – 95.8+)
RIT-II-001 (N=47)	4 (1–8)	23/47 (49%)[d]	14.4[d] (3.0+ – 62.1+)	12/47 (26%)[d]	60.1[d] (11.6 – 62.1+)	10/47 (21%)	60.1 (12.6 – 62.1+)

[a] Durable response was defined as patients with a MIRROR Panel response and MIRROR Panel–assessed TTP ≥ 1 year. The MIRROR Panel TTP values were reported.

[b] Patients receiving iodine I 131 tositumomab (Arm A and Arm B Crossover). Excludes patients who only received unlabeled tositumomab (Arm B).

[c] Excludes 17 patients with intermediate- and high-grade lymphoma.

[d] MIRROR Panel assessed when available (i.e., all patients with transformed low-grade NHL and those patients with low-grade NHL who had available radiographs and medical notes and Investigator-assessed TTP of at least 12 months).

TTP = Time to progression; NR = Not reached.

Figure 3 and Figure 4 illustrate that the time to progression and event-free survival are remarkably consistent in the 5 studies. Although the proportion of patients with time to progression of at least 1 year varies in each study (partially related to the extent of prior NHL therapy), progression after 2 years is infrequent and durable responses have been achieved in all studies. Thus, a single administration of Bexxar therapy, based on patient-specific dosing, can lead to long-term durable responses and event-free survival in a relapsed or refractory low-grade NHL population.

Figure 3. Time to Progression Across Studies[a]

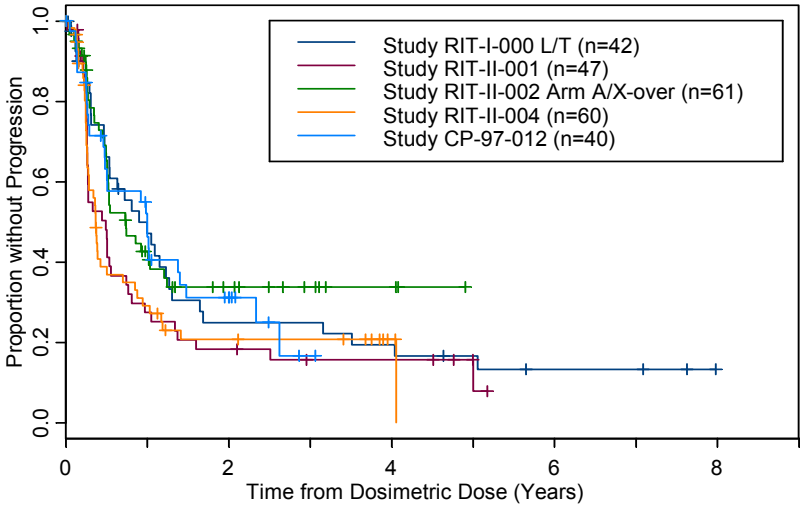
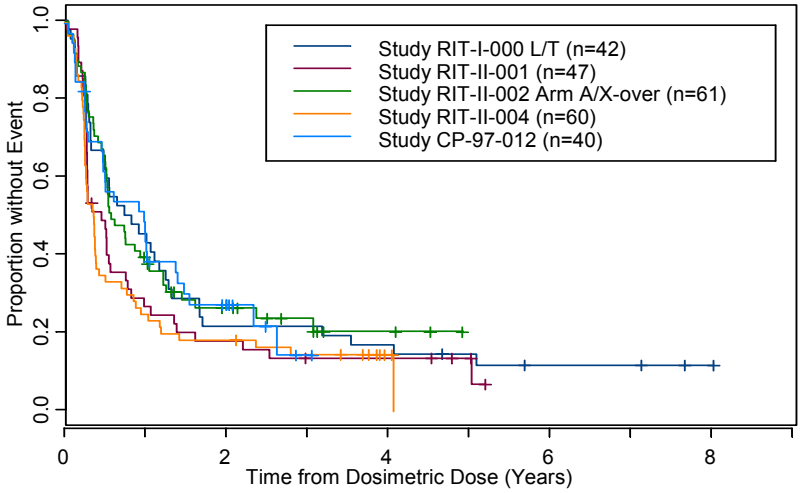


Figure 4. Event-Free Survival Across Studies[a]



[a] Time to progression is defined as the time from start of therapy to the first documented progression. Event-free survival is defined as the time from start of therapy to the first documented progression, subsequent therapy for NHL, or death. The MIRROR Panel censored some patients at their last available response assessment. If the censored patients received subsequent therapy for NHL or died, the event-free survival curve will capture this.

1.5.2 Summary of Safety

Information regarding the safety of iodine I 131 tositumomab is available from the 5 studies described above that support the efficacy of the product, an Expanded Access Program (EAP; CP-98-020), as well as 4 single-patient, compassionate-use administrations (see Section 4 for more information on these studies). Thus, the Integrated Safety Population includes data from 620 patients for whom a total body dose of either 65 or 75 cGy of iodine I 131 tositumomab was prescribed.

The dosimetric and therapeutic infusions were generally well tolerated. Six hundred twenty patients received the dosimetric dose, and 609 patients received the therapeutic

dose. Infusion-rate adjustments were required for only 31 (5%) of the patients during the dosimetric dose and for 24 (4%) of the patients during the therapeutic dose.

The dose-limiting toxicity was acute, reversible bone marrow suppression. Of the 620 patients treated, 42% experienced Grade III/IV neutropenia, 36% experienced Grade III/IV thrombocytopenia, and 11% experienced Grade III/IV anemia. The median durations of Grade III/IV neutropenia and thrombocytopenia were 30 days and 29 days, respectively.

The severity and significance of marrow suppression can be inferred by the amount of hematologic support given and the number of serious infections or bleeding complications reported. One hundred sixty-one of 620 (26%) patients received one or more hematologic supportive care measures at the discretion of the treating physicians following the administration of the therapeutic dose. Sixty-nine patients (11%) received G-CSF, 42 patients (7%) received erythropoietin, 76 patients (12%) received platelet transfusions, and 93 patients (15%) received packed red blood cell transfusions. Serious infections (6%) and Grade III/IV bleeding complications (1.6%) were infrequent.

A total of 142 of 620 patients (23%) experienced one or more serious adverse experiences (SAEs). The most common serious events were fever (3%) and myelodysplastic syndrome/acute myelogenous leukemia (MDS/AML) (3%), followed by sepsis, pneumonia, dyspnea, and thrombocytopenia (all 2%). All other serious events occurred at a frequency of 1% or less.

Iodine I 131 tositumomab therapy may be associated with certain delayed events, including the development of hypothyroidism, human anti-murine antibody (HAMA), and MDS/AML.

- Iodine is actively sequestered in the thyroid gland. Thus, an incidence of hypothyroidism is an expected consequence of systemic exposure to radioactive iodine—hence its longstanding use for ablation of thyroid function in patients with hyperthyroidism. The 2-year and 4-year cumulative incidences for decrease in thyroid function following iodine I 131 tositumomab therapy were 7.3% and 12.1%, respectively. An oral iodide preparation was administered to block the uptake of iodine 131 and to reduce the frequency of radiation-induced hypothyroidism. This precaution was specified in the clinical trials protocols and would be specified in the proposed package insert. Through monitoring of TSH levels, patients can be diagnosed and treated before the onset of symptoms.
- Bexxar therapy uses a radiolabeled murine antibody because of the advantageous kinetics of murine antibody vs. humanized or chimeric antibodies in the radioimmunotherapy setting. Development of human anti-murine antibodies is a possible consequence of administration of all murine antibody therapies. Patients were monitored for the presence of HAMA at baseline, and for the development of HAMA after the dosimetric dose and at various time points during the study. The 1-, 2-, and 4-year cumulative incidences of developing HAMA were 9.4%, 10.1%, and 10.1%, respectively. No patients developed HAMA after 15 months.
- There were a total of 19 Investigator-reported cases of MDS or AML: 1 case in the EAP and 18 cases in the 233 patients enrolled in the other 5 studies who were prescribed 65 or 75 cGy total body radiation. A masked, independent review was performed by an expert hematomorphologist, Dr. John Bennett. Based on Dr. Bennett's masked review, 5 patients (1 in the EAP and 4 in the other studies) had preexisting MDS by morphological and clinical criteria before

administration of iodine I 131 tositumomab therapy, and 1 patient was found to have a morphologically normal marrow and peripheral blood. Given the limited long-term follow-up (1.5 years) in the EAP, data are only summarized for the other studies. Based on the masked independent review, 13 of 229 (5.7%, 95% CI: 3.1%–9.5%) patients were diagnosed with MDS/AML following iodine I 131 tositumomab therapy with an annualized incidence of 2.2%/year (95% CI: 1.3%/year–3.8%/year). A review of the clinical and therapeutic history of these patients revealed characteristics typically associated with an increased risk for the development of secondary myeloproliferative disorders following chemotherapy and/or standard radiotherapy, such as previous treatment with multiple regimens that included repetitive courses of alkylating agents.

Five percent of the patients experienced other non-hematologic malignancies after drug administration; half of the malignancies were skin cancers (basal cell, squamous cell, or unspecified).

The safety profile of iodine I 131 tositumomab therapy is well defined. Individualized patient treatment, based on the total body clearance of iodine I 131 tositumomab (dosimetry), produces predictable toxicities. Routine monitoring of laboratory parameters can assist in the management of the most frequently expected toxicities of myelosuppression and hypothyroidism. The incidence of MDS/AML is comparable with that seen with the systemic therapies used to treat patients with advanced-stage, relapsed/refractory lymphoma.

2. BACKGROUND INFORMATION

2.1 LOW-GRADE AND TRANSFORMED LOW-GRADE NON-HODGKIN'S LYMPHOMA

2.1.1 Incidence

Collectively, the non-Hodgkin's lymphomas (NHLs) are the 5th leading cause of cancer deaths in the United States. In 2000, there were approximately 55,000 new diagnoses of NHL and 25,000 deaths.[7] The incidence of NHL increases with age, and there has been an increase in age-adjusted incidence of approximately 1–2% annually for at least 4 decades.[8] The overall incidence of NHL has increased by 50% in the last 15 years,[9] a statistic expected to increase further in coming years with the increased longevity of the population.

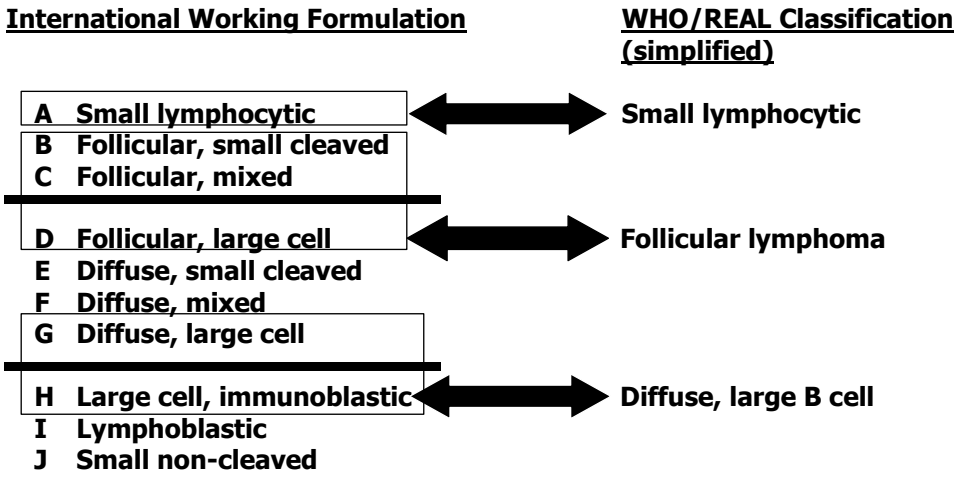
2.1.2 Classification of the Non-Hodgkin's Lymphomas

Our understanding of the biology and natural history of NHL has evolved over the past 40 years, especially regarding the relationship of histology, immunophenotype, and molecular genetics to clinical outcomes. At the time of the initiation of clinical trials with iodine I 131 tositumomab, the International Working Formulation (IWF) classification was commonly used. The IWF histological classification of newly diagnosed patients with NHL separated their neoplasms into low, intermediate, and high grade.[4] Oncologists applied this nomenclature to the natural history of disease and used it as a guide for the selection of therapy.[10]

The iodine I 131 tositumomab trials were conducted at a time when the IWF was the predominant histological classification for non-Hodgkin's lymphomas. The IWF divided the non-Hodgkin's lymphomas into 3 categories: low (IWF A, B, C), intermediate (IWF D, E, F, G) and high (IWF H, I, J) grade based on clinical behavior. The IWF has been

supplanted by more modern classification schemes. The most widely accepted current histological classification is the World Health Organization/Revised European American Lymphoma (WHO/REAL) formulation. Figure 5 suggests a translation of the IWF classification to the WHO/REAL system. Of special note, follicular lymphoma is now a single entity with three grades which correspond to the IWF categories B, C, and D. Similarly, diffuse large cell lymphoma incorporates the IWF categories G and H. Several new entities (e.g., mantle cell lymphoma and marginal zone lymphoma) that did not exist in the IWF are recognized in the WHO/REAL formulation. In general, the iodine I 131 tositumomab experience was developed in patients with diagnoses of IWF A, B, or C and patients whose lymphomas had undergone histological transformation to IWF categories D, E, F, G, or H.

Figure 5. Non-Hodgkin's Lymphoma Histological Classification



2.1.3 Natural History and Treatment of Disease

2.1.3.1 Natural History

While the natural history of disease in patients with intermediate- and high-grade NHL is one of an accelerated and aggressive course, subsets of patients are curable with systemic chemotherapy.[11] In contrast, patients with the low-grade variants generally have a prolonged disease course but are incurable, except for a small percentage who present with very early-stage, localized disease and are potentially curable with local radiation therapy.[12,3]

The low-grade NHLs represent more than one-third of the new diagnoses of NHL. Ninety percent of the patients with low-grade NHL have disseminated disease (Stage III or IV) at presentation.[10] A variety of treatments,[3,10] including the option to "watch and wait,"[13] are used as initial management of advanced-stage disease. Despite the initial chemosensitive nature of low-grade NHL, patients are generally incurable and, on average, show signs and symptoms of disease progression within 2 to 3 years.[10]

2.1.3.2 Treatment of Disease

Treatments for first and subsequent recurrences of disease can vary considerably, but generally include multi-drug combination regimens.[10,14-17] However, response frequency is lower and duration of response tends to be shorter following each successive

regimen.[3] In the last 5 years, the CD20-directed monoclonal antibody rituximab has been used alone[18] or in combination with chemotherapy[19] for the treatment of patients with advanced, low-grade NHL.

The most prominent adverse experiences reported for multi-drug combination chemotherapy regimens are hematologic. The need for treatment delays and dosage adjustments with repeated cycles due to hematologic toxicity is often noted. The incidence of reported treatment-related deaths associated with salvage regimens is 0–15%,[16] many secondary to infectious complications associated with repetitive and/or prolonged marrow suppression. There is also an array of non-hematologic toxicities that are often dose limiting, either due to single agents or to overlapping toxicities from several agents.

2.1.3.3 Transformation

With prolonged survival and clonal expansion, the low-grade NHLs may transform to higher-grade histologies.[6,13,20-24] Following histologic transformation, the lymphomas typically display higher proliferative rates and more aggressive courses. Transformation of the low-grade NHLs evolves in a stepwise fashion[25] through a series of mutations within the expanding low-grade lymphoma clones.[26] This phenomenon is intrinsic to low-grade NHL, since transformation also occurs in patients who have not received mutagenic, cytotoxic therapies.[13] In autopsy series, the majority of the patients dying from the consequences of low-grade NHL had evidence of histologic transformation.[24] With transformation, survival is typically shortened to less than 1 year.[6] Subjects in the iodine I 131 tositumomab clinical development trials have been predominantly patients with low-grade subtypes (IWF A, B, or C). Depending upon the study, up to 38% of the patients had evidence of transformation to a higher grade of NHL (IWF D, E, F, G, or H).

Each of the low-grade subtypes, including their histologic transformations, is associated with a very high level of CD20 expression. An extensive review of the medical literature was conducted to confirm this observation. Harris and colleagues describe over 90% of the cases as positive for CD20,[27] and Jaffe describes them as “almost always positive.”[28] Contos et al. reported that 22 of 22 follicular, small-cleaved cell lymphomas and 18 of 20 small lymphocytic lymphomas expressed CD20.[29] In a smaller study, Horning and colleagues specifically addressed the issue of immunophenotype in transformed low-grade lymphoma.[30] These investigators found that 8 of 10 transformed lymphomas expressed the CD20 antigen. Even after the selective pressure of rituximab therapy, occurrence of CD20-negative lymphomas is quite infrequent.[31,32]

2.2 RATIONALE FOR THE DEVELOPMENT OF IODINE I 131 TOSITUMOMAB THERAPY

The incurable nature of low-grade NHL and the unrelenting pattern of multiple remissions and relapses in these patients continue to stimulate a search for more effective therapies. The goals of this research are the provision of long-term remissions.

2.2.1 Unconjugated Antibodies in the Treatment of NHL

2.2.1.1 Various Lymphocyte Antigens Have Been Studied

A wide variety of lymphocyte antigens have been targeted. Unmodified murine monoclonal antibodies (MAbs) have included customized, patient-specific anti-idiotype

MAbs,[33-35] anti-CD20 MAb,[36] and antibodies against CD19 and CD22 with or without toxins.[37-40]

One of the anti-CD20 MAbs, rituximab, is in widespread clinical use. However, up to 50% of patients do not respond to initial rituximab therapy. The reasons for this failure are unknown. A variety of mechanisms are known to limit the efficacy of unlabeled antibodies. These may include inability of antibody to gain access to tumor, non-homogeneous distribution of antigen on tumor cells and the limited ability of natural effector mechanisms to eliminate antibody-coated NHL cells by the mechanisms of complement-mediated cytotoxicity and/or antibody-dependent cellular cytotoxicity.

2.2.1.2 Tositumomab

Tositumomab is an IgG_{2a} murine monoclonal antibody initially developed in 1978 at the Dana-Farber Cancer Institute, Boston.[1] It binds to the CD20 antigen, a 35-kD transmembrane phosphoprotein that is expressed by greater than 90% of all B-cell lymphomas, chronic lymphocytic leukemia and by all normal B cells with the exception of very early progenitor (pre-B) cells and terminally differentiated plasma cells.[1,40] CD20 is not expressed on cells of other hematopoietic cell lineages[41] or other normal tissues.[1,40,42]

Structural studies indicate that CD20 is not shed from the cell surface and does not internalize upon antibody binding.[43] The recognition epitope for tositumomab is found within the extracellular domain of the CD20 antigen. CD20 is involved in cell cycle initiation and cellular differentiation and has been associated with calcium ion regulation.[44,45]

Characterization of tositumomab occurred during the second International Workshop on Human Leukocyte Differentiation Antigens (Boston, September 1984).[46] In 1982, tositumomab (clone B1, murine anti-CD20 monoclonal antibody) produced by Coulter Corporation became available as a commercial diagnostic reagent for the specific designation of CD20-positive lymphocytes. This MAb is a class 2 *in vitro* diagnostic reagent used in flow cytometry and immunohistochemistry for phenotyping human B lymphocytes. The World Health Organization recognizes tositumomab as the reference anti-CD20 antibody; all other anti-CD20 antibodies are compared to tositumomab.[46]

In *in vitro* studies using human B lymphocytes, the binding of tositumomab to CD20-positive cells has been shown to invoke multiple immune effector functions, including (1) antibody-dependent cellular cytotoxicity (ADCC),[47] (2) complement-dependent cytotoxicity (CDC),[46] and (3) apoptosis.[48]

2.2.2 Radiolabeled Anti-CD20 MAbs for the Therapy of Low-Grade B-Cell Lymphomas

Lymphomas in general, and low-grade NHL specifically, are very sensitive to ionizing radiation and can, in a low percentage of cases, have prolonged survival by appropriately administered radiation therapy, i.e., local radiation for Stage I/II disease or total body irradiation (TBI) as a component of high-dose therapy with stem cell rescue for more advanced disease. Any method that can increase the relative dose of radiation to NHL cells versus bone marrow stem cells should provide a significant increase in therapeutic index. In fact, a steep dose response relationship exists for low-grade lymphomas between the total dose of external beam radiotherapy and the probability of local control, with very low recurrence rates at total doses of 4400 cGy or greater.[49]

Thus, the reason that radiolabeled anti-CD20 monoclonal antibodies should be effective is that the tumor cells are highly radiosensitive and the radioimmunoconjugate (iodine I 131 tositumomab) can deliver tumor-specific radiation in patients with widely disseminated disease.

CD20-specific antibodies, including tositumomab, selectively target B cells. Tositumomab binds only to CD20-positive cells and no other hematopoietic or non-hematopoietic tissues.[1] Fortunately, CD20 is not expressed on early B-cell progenitors or plasma cells.[1,40] Thus, whereas anti-CD20 temporarily eliminates normal B cells from circulation, the normal B-cell population recovers, and plasma cells that produce antibodies as the result of prior immune responses are not affected.

Equally important, certain intrinsic characteristics make CD20 an ideal target for radioimmunotherapy: (1) expression on >90% of B-cell NHLs;[1,40] (2) presence in high density at the cell surface; (3) lack of shedding into the circulation as the result of tethering of the transmembrane CD20 protein;[1] and (4) failure to internalize following binding with tositumomab. (Internalization would lead to accelerated degradation and potential dehalogenation of iodine 131 radioconjugates.)[50] This lack of antigen modulation produces a stable target for radiolabeled antibody.

Furthermore, radioimmunoconjugates do not rely solely on the immune system's normal antibody effector mechanisms to kill tumor cells. This is important since patients with cancer often have suppressed or defective immune systems.

2.2.2.1 Advantages of Iodine 131 as a Radiotherapeutic Agent

A number of clinical trials have been performed using a radioimmunoconjugate to treat B-cell lymphomas. The choice of the radionuclide has varied; however, most trials have used either iodine 131 or yttrium 90 as the radionuclide. Table 2 compares the two radionuclides.

Table 2. Comparison of Radionuclides

Properties	Iodine 131	Yttrium 90
Emission	Beta emitter (0.6 MeV) Gamma (0.36 MeV)	Beta emitter (2.2 MeV)
Beta path length	0.8 mm	5.3 mm
Half-life	8 days	2.7 days
Biological clearance	Rapid (urine)	Slow
Uptake in normal tissue	Thyroid	Bone, liver
Ability to image	Yes	No
Administration	Outpatient in most states	Outpatient

Iodine 131 was chosen as the radionuclide for conjugating to tositumomab antibody for a number of reasons:

- Iodine 131 has a long clinical record. It has demonstrated clinical efficacy in the treatment of hyperthyroidism and thyroid cancer, and has been used to treat many thousands of such patients worldwide over more than 50 years.
- Most health-care institutions are experienced in handling the isotope.

- Iodine 131 emits gamma radiation that can be used for both tumor cell elimination and for dosimetry to determine patient-specific therapeutic dosage for each patient.
- Unlike yttrium 90, iodine 131 neither seeks nor localizes in bone. This property provides a rationale for the reduced rate and severity of myelosuppressive events with iodine 131.[51-53]
- The beta particles emitted by radioactive decay have an effect over several cell diameters resulting in a "cross-fire" effect from antibody-bound cells, thereby killing neighboring lymphoma cells. This effect minimizes the loss of therapeutic activity related to the non-homogeneous distribution of antibody in tumor tissues.
- The short path length of the beta particles emitted by iodine 131 would be expected to limit radiation exposure to adjacent normal organs.
- Iodine 131–labeled metabolites of antibody and free iodine 131 derived from iodine I 131 tositumomab are released into the blood stream and are rapidly excreted in the urine as free iodine, iodotyrosine, and small peptides, thereby limiting the radiation dose to normal tissues.[50]

3. TOSITUMOMAB AND IODINE I 131 TOSITUMOMAB

3.1 COMPOSITION OF IODINE I 131 TOSITUMOMAB THERAPY

BEXXAR® therapy is the proposed trade name for the therapeutic package containing the combination of the unlabeled IgG_{2a} anti-CD20 murine monoclonal antibody, tositumomab, and the same MAb radiolabeled with iodine 131 (iodine I 131 tositumomab).

3.2 DOSING REGIMEN

3.2.1 Description of Dosing Regimen

In the treatment of cancer the therapeutic dose of a drug can be fixed or it can be tailored to an individual patient's characteristics. Because the efficacious dose range of many oncology drugs is narrow due to toxicity, tailored dosing is usually preferred when feasible. Dosing with radioimmunoconjugates can be based on individual patient pharmacokinetics (dosimetry), a fixed mCi dose, or a dose based on mCi/m^2 of body surface area or mCi/kg of body weight.[54] In the case of iodine I 131 tositumomab, dosing based on individual patient pharmacokinetics (dosimetry) is made possible by the measurement of gamma emission from iodine 131.

The goal of this dosing method is to administer the correct amount of radioactivity (mCi) to consistently achieve a pre-defined total body radiation dose (cGy). Treating every patient with a consistent total body dose should increase the predictability of the efficacy and toxicity as compared to regimens based upon administering a fixed amount of radioactivity based solely on body weight or surface area. In contrast to complex organ dosimetry, the total body dosimetry method used to calculate the therapeutic dose of iodine I 131 tositumomab is relatively simple.[55]

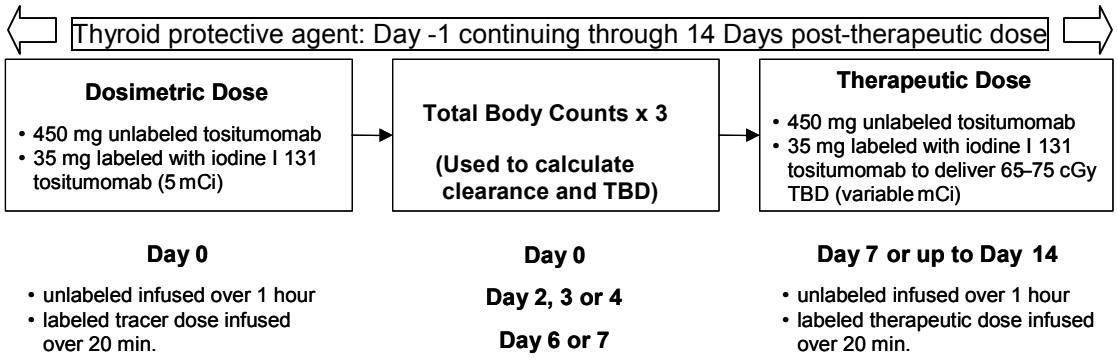
Figure 6 is a schematic presentation of the dosing methodology for iodine I 131 tositumomab therapy. All patients are treated with thyroid protective agent from one day prior to the dosimetric dose through 14 days following the therapeutic dose.

The initial IV infusion of unlabeled antibody is administered over one hour. This infusion is followed by a tracer amount of labeled antibody conjugated to iodine 131 administered over 20 minutes (dosimetric dose). The administration of an unlabeled dose of antibody prior to the radiolabeled conjugate has been shown to improve biodistribution of the radionuclide, resulting in increased uptake in the tumor tissue.[56,57]

Whole body anterior gamma camera scans for the purpose of measuring total body radiation (total body gamma counts) are obtained within 1 hour after completion of the administration of dosimetric dose (before urination); 2, 3, or 4 days after dosimetric dose (after urination); and 6 or 7 days after the dosimetric dose (after urination) using a gamma camera with an appropriate medium- or high-energy collimator. The gamma camera counts from these scans are used to determine the rate of radiation clearance and radioactivity (mCi) to be administered to deliver the desired therapeutic total body radiation dose (cGy).

The therapeutic dose is delivered between Day 7 and Day 14. The unlabeled antibody is again administered over one hour followed by the labeled therapeutic dose.

Figure 6. Iodine I 131 Tositumomab Therapy



3.2.2 Rationale for Dosing Regimen

The use of iodine I 131 tositumomab and the dosing regimen were based on preclinical and clinical data. Some of the key experiments are summarized below.

3.2.2.1 Preclinical Studies

Preclinical studies demonstrated that

- Localization of iodine I 131 tositumomab was B-cell specific.[58,59]
- Iodine 131 was excreted primarily in the urine.[59]
- As with other anti-CD20 antibodies, B cells were profoundly, but temporarily, decreased after treatment with iodine I 131 tositumomab.
- There were no significant drug-related effects on the number of T cells.
- Tumor uptake of iodine I 131 tositumomab was increased after predosing with unlabeled tositumomab.[60]

3.2.2.2 Clinical Studies

The maximum tolerated, non-myeloablative total-body dose (TBD) to be given to previously treated patients with NHL was established in the Phase 1 study RIT-I-000, using a dose-escalation schedule evaluating doses beginning at 25 cGy and increasing by 10-cGy increments until dose-limiting toxicity (DLT) was reached. Two of 3 patients had DLT at 85 cGy TBD. Thus, the maximum tolerated total body dose was determined to be 75 cGy. This dose (75 cGy) was attenuated for obese patients and patients with lower pre-therapy platelet counts as detailed below.

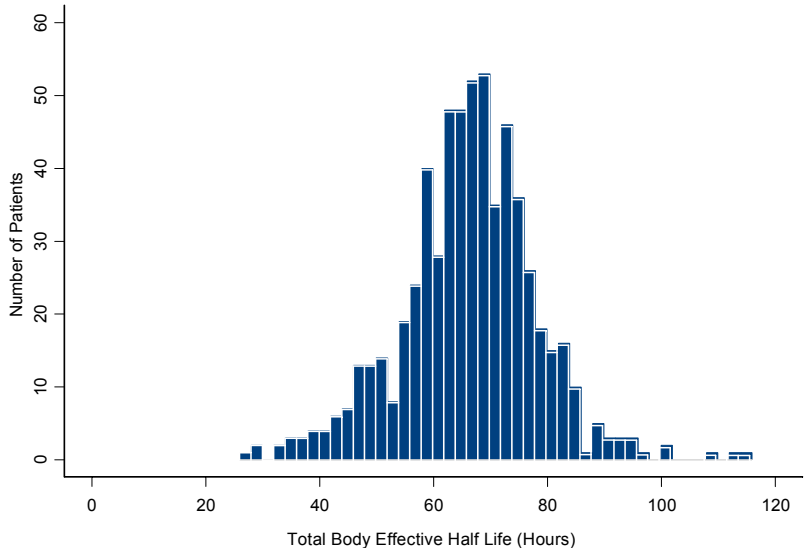
The dose for obese patients was adjusted to 137% of their calculated lean body mass. The adjustment was introduced to account for the fact that obese patients can be modeled as an outer shell of fat, with little radioactivity accumulation in the region surrounding the lean body mass.[61] Clinical data were consistent with this model in that 2 of 3 obese patients who received an unattenuated dose of 75 cGy developed Grade IV thrombocytopenia and Grade IV neutropenia. Of 14 obese patients who received an attenuated dose of 75 cGy to the lean body mass, only 2 (14%) developed Grade IV thrombocytopenia and 3 (21%) developed Grade IV neutropenia. By comparison, for the whole population, rates of Grade IV toxicity for platelets and neutrophils were 16% and 18%, respectively.

The prescribed TBD of 75 cGy was adjusted to 65 cGy for patients with a platelet count between 100,000/mm^3 and 150,000/mm^3 (mild thrombocytopenia). This adjustment was based on data suggesting these patients sustained a higher incidence of Grade III/IV hematological toxicity when treated with 75 cGy. The Grade III/IV neutropenia and thrombocytopenia for 20 patients with mild thrombocytopenia that received a 75 cGy TBD were 70% and 65%, respectively. The Grade III/IV neutropenia and thrombocytopenia for 38 patients with mild thrombocytopenia that received a 65 cGy TBD were 51% and 58%, respectively.

The effect of administering unlabeled tositumomab prior to the administration of labeled antibody was evaluated in the first 25 patients in study RIT-I-000. Patients received either 0, 95, or 475 mg of unlabeled antibody as a pre-dose with a 10-mg dose of labeled antibody. Total body residence times (TBRTs; i.e., a measure of clearance of iodine I 131 tositumomab) of radioactivity were longer in those patients who received the larger pre-dose so that a lower administered activity (mCi) of iodine I 131 tositumomab was needed to deliver the prescribed total body dose of radiation. In addition, there was a trend toward improved tumor targeting with iodine I 131 tositumomab in patients with splenomegaly or high tumor burden who received the higher pre-dose. Based on these results, all subsequent patients received a total protein dose of 485 mg (450 mg unlabeled tositumomab and 35 mg iodine I 131 tositumomab).

The clearance of radioimmunoconjugates has been observed to be highly variable from patient to patient. This phenomenon was observed when patients were treated with iodine I 131 tositumomab (see Figure 7 below). The variability in clearance results in variability in TBRT and the associated total body effective half life.

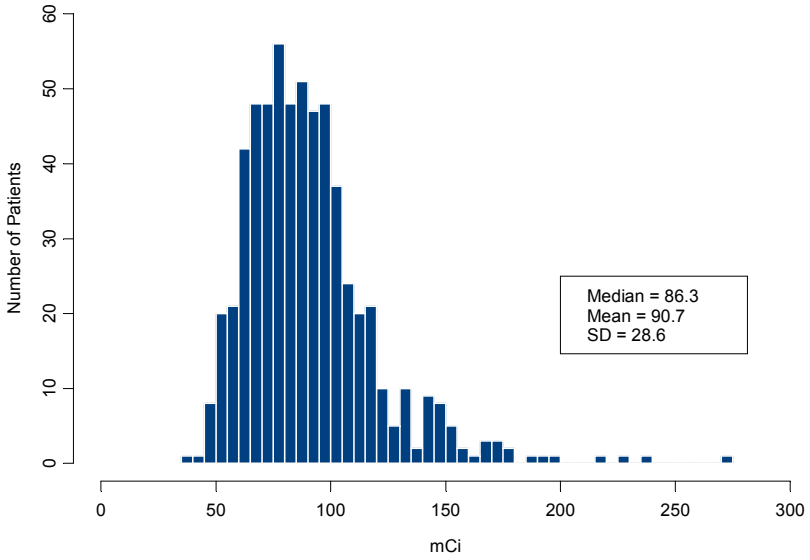
Figure 7. Total Body Effective Half Life Varies from Patient to Patient



TBRTs correlate with known parameters, such as lean body mass, tumor cell mass, spleen mass, and bone marrow involvement; but knowledge of only those parameters is not sufficient to optimize an individual dose. Therefore, a dosimetry method was devised to allow calculation of a patient specific administered activity that would produce a desired total body dose of radiotherapy. Total body clearance is significantly correlated to blood clearance, and using dosimetry based on total body counts is a simple and useful surrogate for the more complicated blood-based or image-based red marrow dosimetry.

Figure 8 demonstrates the wide range in the mCi dose of radioactivity required to target a total body dose of 75 cGy in 608 patients.

Figure 8. mCi Required to Deliver 75 cGy TBD (N=608)



4. OVERVIEW OF THE IODINE I 131 TOSITUMOMAB THERAPY CLINICAL PROGRAM

Between 1990 and 13 September 2002, 1651 patients received iodine I 131 tositumomab therapy in clinical studies. (A regulatory history is found in Appendix 3.) Clinical trial experience includes 192 patients who received myeloablative doses of iodine I 131 tositumomab in conjunction with bone marrow or peripheral blood stem cell transplants. One hundred seventy-one patients received iodine I 131 tositumomab as part of Investigator-sponsored IND studies, and an additional 220 patients were treated on company-sponsored IND studies not utilized for registration (i.e., first-line treatment, retreatment, >25% bone marrow involvement, mantle cell NHL and iodine I 131 tositumomab plus various chemotherapies). Table 3 below outlines the clinical registration of all patients on studies and delineates the patients for the Integrated Safety (n=620) and Integrated Efficacy (n=250) Populations based on receiving study drug and data cutoff dates. See Appendix 4 for a summary of all clinical studies.

Table 3. Clinical Enrollment as of September 2002 for All Patients on Studies

Study	Registered	Registered but Did Not Receive Study Drug	Registered / Study Drug Administered (Safety/Efficacy Data Collected)	Integrated Safety Population	Integrated Efficacy Population
RIT-I-000 (Phase I/II)	59	0	59	22[a]	42[b]
RIT-II-001 (Phase II)	47	0	47	47	47
RIT-II-002 Arm A	42	0	42	42	42
RIT-II-002 Arm B	36	0	36	0	0
RIT-II-002 Crossover	19	0	19	19	19
RIT-II-004 (Refractory)	61	1	60	59[c]	60
CP-97-012 (Rituxan Failure)	43	3	40	40	40
CP-98-020 (EAP)	791	32	759	387[d]	0[e]
Six Single-Patient Studies	6	0	6	4[f]	0
Myeloablative Studies	192	NA	192	0	0
Non-Myeloablative Studies Investigator-Sponsored IND	196	25[g]	171	0	0
Non-Myeloablative Studies Corixa-Sponsored IND	224	4	220	0	0
Total	**1716**	**65**	**1651**	**620**	**250**

[a] Excludes 37 patients who did not receive 65 or 75 cGy and/or had intermediate-/high-grade lymphoma.
[b] Excludes 17 patients with intermediate- or high-grade lymphoma.
[c] Excludes 1 patient with mantle cell NHL.
[d] Patients with >13 weeks of follow-up as of data cutoff date and submitted to FDA in March 2002.
[e] Patients on EAP protocol were included for safety and not included for efficacy (independent verification of responses was not performed).
[f] Two single-study patients did not receive 65 or 75 cGy.
[g] Includes patients who have not yet received iodine I 131 tositumomab as part of a multiple-agent therapy.
NA = complete data not available assumed all patients received study drug.

The proposed indication for iodine I 131 tositumomab therapy is based on efficacy and safety derived from 3 primary clinical studies (RIT-II-004, RIT-II-002, and CP-97-012), 2 additional supportive clinical studies (RIT-I-000, RIT-II-001), an Expanded Access Study (CP-98-020), and 4 single-patient, compassionate-use administrations.

4.1 EFFICACY OF IODINE I 131 TOSITUMOMAB THERAPY

Analyses were conducted on an intent-to-treat basis for all patients who received any portion of the study drug, including only the dosimetric dose, in studies RIT-II-002, RIT-II-004, and CP-97-012. In all studies, efficacy was based on the response definitions shown in Appendix 2. For studies RIT-II-004, RIT-II-002 and CP-97-012, an independent review of the response assessments was performed on all patients by the MIRROR Panel. The MIRROR Panel also reviewed the responses of patients with transformed low-grade NHL in studies RIT-I-000 and RIT-II-001. An additional review of the Investigator's assessment of response on durable responders occurred in October 2001 including all long-term responding patients from studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012.

The MIRROR Panel was composed of teams each including a radiologist and oncologist. All were board certified in their respective disciplines. The panel reviewed both patient radiographs and patient medical notes, while remaining masked to the Investigators' assessments of response. Efficacy endpoints included response rate, complete response rate, duration of response, and time to progression based on the MIRROR Panel independent review assessment. In study RIT-II-004, the panel reviewed masked radiographs and medical notes associated with the patient's LQC, as well as those associated with iodine I 131 tositumomab therapy. In study RIT-II-002, the panel reviewed masked radiographs and medical notes associated with patients in both arms, treatment with the labeled antibody and with the unlabeled antibody, and the crossover arm.

In July 2002, the FDA requested a confirmatory independent re-review of 37 patients from studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012 (referred to as MIRROR2 Panel). Each of the 37 patients had a time to progression of at least 12 months on their original MIRROR Panel review. The majority (26 of 37 patients) were patients enrolled in the earlier studies RIT-I-000 or RIT-II-001, which were the 2 studies with MIRROR Panel review performed on only a subset of patients. More conservative response definitions were employed for this second review. All lesions had to be no longer present on radiographs for a patient to be a CR; other studies had considered lesions <1 cm to be below detectable limits and not represent NHL. Progressive disease in the confirmatory MIRROR2 Panel was defined as greater than or equal to a 25% increase from the nadir value of the sum of the product of greatest perpendicular diameters (SPPD) of all measurable lesions, a significant change in evaluable lesions, or the appearance of any new lesion.

The MIRROR2 Panel radiologist conducted the evaluation of the radiographs without knowledge of the clinical history and the MIRROR2 Panel oncologists conducted evaluations of redacted medical notes without knowledge of the radiographic interpretations. Each panel member reviewed clinical material in a chronological, step-wise fashion. Response assignments were made for each assessment timepoint and frozen before materials from the next assessment timepoint were reviewed. For each assessment timepoint, the individual radiologist response assignment and oncologist response assignment were combined to create a joint review assignment using a logic table. Where the reviews were in agreement, the joint review assignment became the final assignment of response outcome for the patient. Where the reviews were not in

agreement, a formal joint review was necessitated. In the formal joint review, the oncologist made a final joint review response assignment employing the radiologist's assessments, the radiographs, and/or consultation with the radiologist.

The MIRROR2 review confirmed that 36 of the 37 patients reviewed were long-term durable responders (i.e., had response with a time to progression in excess of one year).

Efficacy data are provided below for each of the studies. Data from the confirmatory MIRROR2 were used if available, data from the original MIRROR Panel were used for other patients, and data from the Investigator were used for the subset of patients from studies RIT-I-000 and RIT-II-001 without MIRROR Panel assessments.

4.1.1 Individual Studies

4.1.1.1 Pivotal Study RIT-II-004

Multicenter, Pivotal Study of Iodine I 131 Tositumomab (Murine) Radioimmunotherapy for Chemotherapy Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that Have Transformed to Higher Grade Histologies

The pivotal study RIT-II-004 was an open-label, multicenter trial in patients with refractory low-grade or transformed low-grade non-Hodgkin's lymphoma. At the time of study inception and conduct starting in 1996, FDA agreed that the study design would be acceptable for licensure of the product for treatment of this chemotherapy-refractory population of patients.

The natural history of low-grade NHL is characterized by a series of responses to therapy almost always followed by relapses. With each successive treatment, lower response rates and shorter durations of response are expected.[3,15,62] Thus, by using each patient as their own control, demonstration that the response to iodine I 131 tositumomab exceeded the response to the last qualifying chemotherapy would provide evidence of improvement in a surrogate endpoint indicative of clinical benefit. The utility of this approach is well documented in the statistical and regulatory literature. It is particularly useful in settings where no standard therapy exists for comparison and where there is substantial between-patient variability. At the time the study was conducted, there was no approved or standard therapy for this indication. The technique improves the precision of the treatment comparison and provides greater statistical power.[63]

The primary endpoint of the study was a comparison, as assessed independently by the MIRROR Panel, between the number of patients having a longer duration of response (i.e., >30 days longer) after iodine I 131 tositumomab therapy and the number of patients having a longer duration of response after their LQC regimen. Efficacy outcomes after the LQC and iodine I 131 tositumomab therapy were assessed by the Investigators and the MIRROR Panel. Secondary efficacy endpoints were response rate, complete response rate, and time to progression.

The proposed sample size was 60 patients, based on an estimated absolute difference of 25% in the proportion of patients experiencing a longer (≥30 days) duration of response with iodine I 131 tositumomab therapy.

All patients were chemotherapy-refractory. Patients had to have received at least 2 prior qualifying chemotherapy regimens and had either not responded (i.e., achieved a best response of stable or progressive disease) or had responded (i.e., achieved a best response of partial response or complete response) and then progressed within 6 months of completion of their LQC.

The qualifying chemotherapy regimens were prospectively defined, appropriate therapeutic regimens for NHL that included single-agent regimens such as chlorambucil, multi-agent regimens such as CHOP or CVP, and aggressive salvage regimens such as DHAP or ESHAP. In addition, the regimens had to be appropriate for the patient's histologic diagnosis (patients with transformed low-grade NHL must have received a chemotherapy regimen appropriate for transformed disease), and of sufficient duration (at least 2 cycles for therapy administered in cycles or at least 6 weeks for therapy administered daily). Radiographs and medical notes documenting lack of response or early relapse were also required.

Patient demographics are summarized in Table 4. One patient who entered the study was later found to have mantle cell lymphoma. This patient was included in the analysis because all efficacy results were reported on the basis of intent-to-treat.

Table 4. Patient Demographics: Study RIT-II-004 (N=60)

Male/female	38/22
Median age (years) (range)	60 (38–82)
Median time since diagnosis (months) (range)	53 (9–334)
Median number of prior chemotherapy regimens (range)	4 (2–13)
Grade	
Low grade	36/60 (60%)
Transformed low grade	23/60 (38%)
Mantle cell	1/60 (2%)
Bone marrow involvement	33/59 (56%)
Bulky disease (≥5 cm)	42/60 (70%)
Elevated LDH	26/59 (44%)

Note: Differences in the denominator are due to missing data.

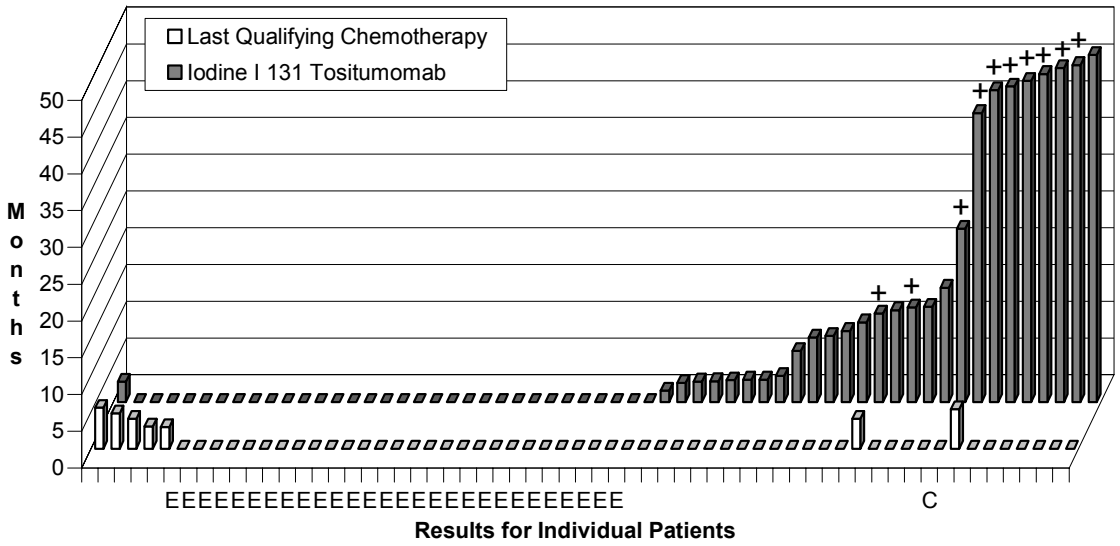
Sixty patients received the dosimetric dose, and 58 patients received both the dosimetric dose and the therapeutic dose. The median follow-up from the dosimetric dose was 30.2 months (range: 0.5–60.5 months) and 46.9 months (range: 43.0–60.5 months) for patients alive at the data cutoff date.

The primary efficacy endpoint of the study was the comparison between the number of patients having a longer duration of response (>30 days) after iodine I 131 tositumomab therapy and the number of patients having a longer duration of response after their LQC regimen. Iodine I 131 tositumomab had significantly more patients with longer durations of response (26 vs. 5; $p<0.001$, McNemar's test).

Figure 9 illustrates the comparison of the duration of response for each of the patients following treatment with LQC (white bars) and following treatment with iodine I 131 tositumomab (black bars). There were 7 patients who responded to their LQC and 28 patients who responded to iodine I 131 tositumomab. Of the 60 patients, 26 had a longer response to iodine I 131 tositumomab, 5 had a longer response to the LQC, and 1 patient's response to LQC was censored (because in retrospect the MIRROR Panel could not validate that the patient had not progressed following partial response to her LQC), making the comparison inappropriate. Twenty-eight patients responded to

neither therapy and are represented by bars of no height in the central portion of the graph. The comparison for duration of response was significantly greater for iodine I 131 tositumomab than for the LQC (p<0.001, Prentice-Wilcoxon).

Figure 9. Primary Efficacy Endpoint: MIRROR Panel–Assessed Paired Comparison of Duration of Response[a]: Pivotal Study (RIT-II-004)



[a] Duration of response for both LQC and iodine I 131 tositumomab as assessed by the MIRROR Panel. E = Equivalent duration of response or no response to either therapy; C = Censored duration on LQC. "+" represents a patient continuing in response at last assessment.

The assessments of the secondary efficacy endpoint data are summarized in Table 5.

Table 5. MIRROR Panel–Assessed Efficacy Data: Study RIT-II-004 (N=60)

	Last Qualifying Chemotherapy (N=60)	Iodine I 131 Tositumomab (N=60)	P-value[a]	P-value[b]
Response	7/60 (12%)	28/60 (47%)	<0.001	NA
Median (95% CI) duration of response for responders (months)	4.1 (3.0–5.4)	11.7 (6.9–47.2)	<0.001	<0.001
Complete response	1/60 (2%)	12/60 (20%)	0.002	NA
Median (95% CI) duration of response for complete responders (months)	4.8 (NA)	47.2 (NA)	0.003	0.001

[a] P-values for response rates based on McNemar's test vs. 0.50; p-values for durations based on generalized McNemar's test.

[b] Paired Prentice-Wilcoxon test for censored data for comparisons of duration.

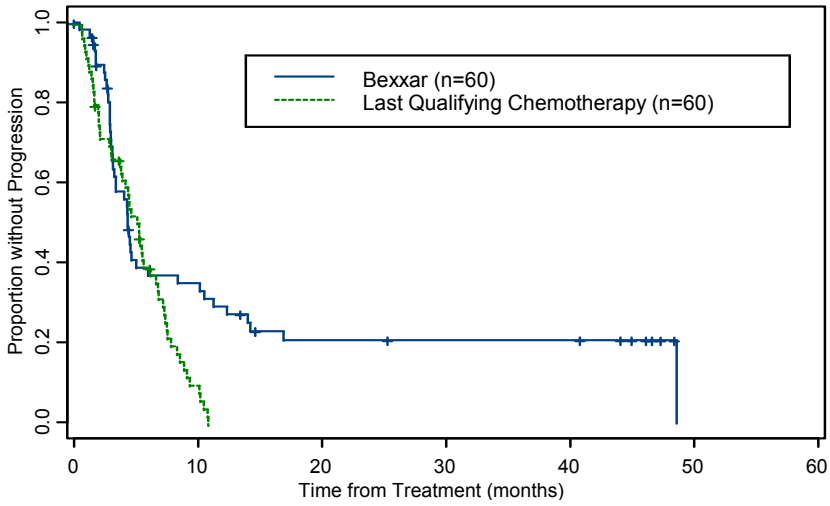
NA = Not applicable.

Responses were significantly improved after iodine I 131 tositumomab therapy in comparison to the LQC: the overall response rate improved from 12% to 47%

(p<0.001); median duration of response increased from 4.1 months to 11.7 months (p<0.001); and the rate of complete response improved from 2% to 20% (p=0.002).

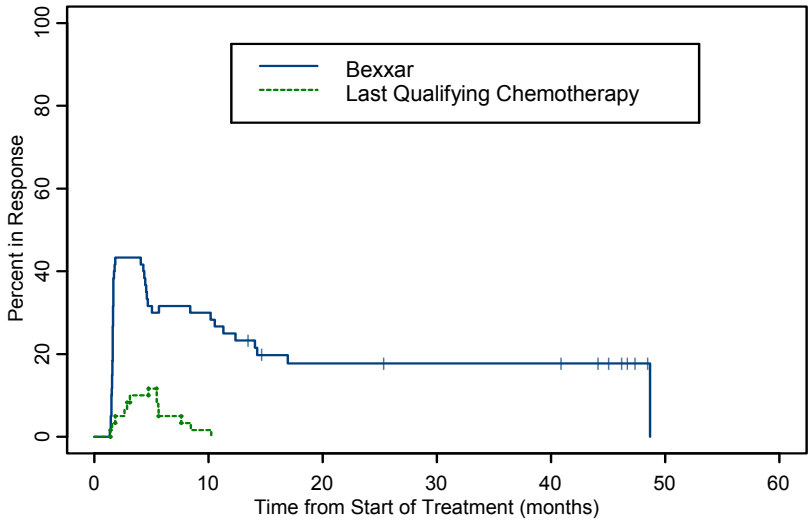
The times to progression for patients after iodine I 131 tositumomab therapy and after LQC are shown in Figure 10 (p=0.204, Prentice-Wilcoxon).

Figure 10. MIRROR Panel–Assessed Time to Progression: Study RIT-II-004



The proportion of patients in response over time after treatment with either iodine I 131 tositumomab or LQC is displayed in Figure 11 (p<0.001, Prentice-Wilcoxon). The areas-under-the-curves represent the average amount of time that the patients in each population spent in response.

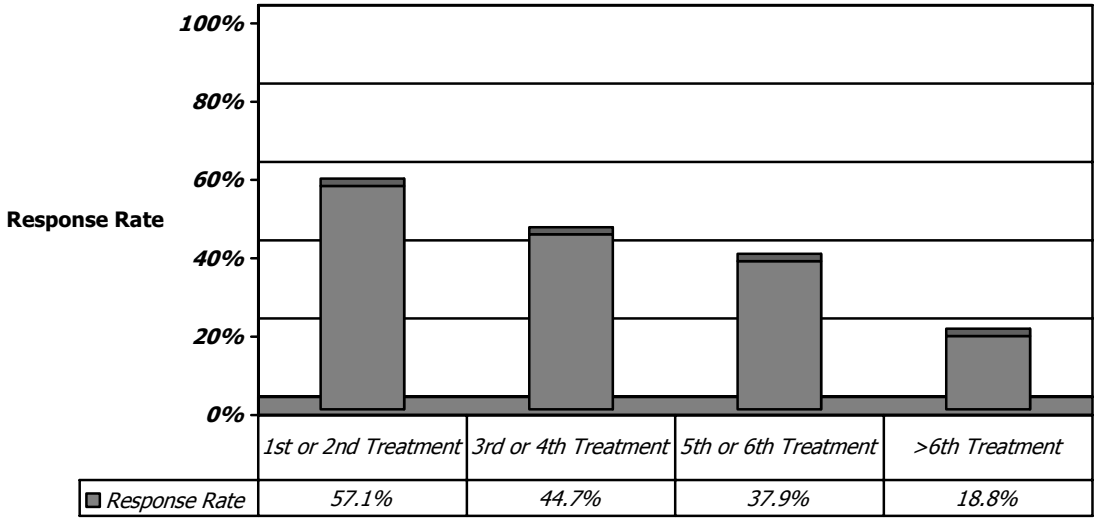
Figure 11. MIRROR Panel–Assessed Proportion of Patients in Response: Study RIT-II-004



Using the definition of TTP ≥ 1 year, 15 of 60 (25%) patients were classified as long-term durable responders. All patients were assessed by the MIRROR Panel. The

longest time to progression for a patient from this study is 48.7 months. Ten patients are in continuing response at last observation and are censored. Two or the 10 patients were assessed by the MIRROR Panel to be in response at their last assessment but were withdrawn from the study by the Investigator, and one additional patient continuing in Investigator-assessed CR at 57.5+ months was being followed by PET scans that the MIRROR Panel believed were not sufficient to fully assess response and was censored by the MIRROR Panel at 25.4+ months. The observation of prolonged complete remissions in the remaining 7 patients who had progressed after multiple chemotherapy regimens and who did not respond, or progressed within 6 months of their latest chemotherapy regimen is unexpected. Figure 12 shows the Investigator-assessed response rates to prior chemotherapy for patients enrolled in RIT-II-004. This clinical experience roughly parallels the observations of Gallagher shown in Figure 1. The results of RIT-II-004 represent a reversal of usual outcome reported for successive therapies in patients with low-grade NHL.

Figure 12. Response to Prior Chemotherapy by Treatment Course for Patients Enrolled in Study RIT-II-004 (N=60)



A review of the literature did not reveal reports of clinical trials in refractory patient populations comparable to patients enrolled in study RIT-II-004 (i.e., low-grade or transformed low-grade patients with NHL who had received a median of 4 prior qualifying chemotherapy regimens and of whom only 12% had a response to their LQC). Thus, the patients enrolled in this study represent a refractory patient population with poor prognosis.

4.1.1.2 Randomized Controlled Study RIT-II-002

A Randomized Study of Iodine I 131 Tositumomab versus Tositumomab in Chemotherapy-Relapsed/Refractory Low-Grade or Transformed Low-Grade Non-Hodgkin's Lymphoma (NHL)

Study RIT-II-002 was a randomized, open-label, multicenter study that included patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. The study was designed to determine the added benefit of the radioconjugate (iodine I 131 tositumomab) to the unlabeled antibody (tositumomab). The trial also examined safety and efficacy. Patients received either the standard Bexxar regimen of tositumomab plus

iodine I 131 tositumomab including both a dosimetric and a therapeutic dose or the same regimen with an equal total dose of antibody as unconjugated antibody. Patients randomized to tositumomab were allowed to cross over and receive iodine I 131 tositumomab following disease progression.

The primary endpoint of the study was complete response rate. Secondary endpoints included overall response rate, duration of overall and complete response, time to progression and safety. All responses, duration of response, and time to progression were assessed by the MIRROR Panel.

Patients were required to have a histologically confirmed diagnosis of low-grade or transformed low-grade non-Hodgkin's B-cell lymphoma and to have had 1–3 prior chemotherapy regimens that included an anthracycline, an anthracenedione, or an alkylating agent.

A total of 78 patients with relapsed or refractory low-grade or transformed low-grade NHL were enrolled in this multicenter study. The median duration of follow-up was 30.9 months (range: 1.8–58.9 months). Patient demographics and baseline characteristics for the two arms of the study are presented in Table 6. The arms were well balanced.

Table 6. Patient Demographics: Study RIT-II-002 (N=78)

	Iodine I 131 Tositumomab (N=42)	Tositumomab (N=36)
Gender		
Male	23 (55%)	18 (50%)
Female	19 (45%)	18 (50%)
Age (years) median (range)	56 (28–75)	55 (32–85)
Median time (months) since diagnosis (range)	31 (5–185)	28 (7–236)
Prognostic Indicators		
Grade		
Low grade	36 (86%)	28 (78%)
Transformed low grade	6 (14%)	8 (22%)
Elevated LDH	17/41 (41%)	14 (39%)
Bulky disease (≥5 cm)	24/38 (63%)	19/33 (58%)
Bone marrow involvement	24 (57%)	17/34 (50%)
Median number of prior chemotherapy regimens (range)	2 (1–4)	2 (1–5)
Investigator-assessed response to most recent prior chemotherapy[a]		
CR/CCR/PR	30/41 (73%)	27/35 (77%)
SD/PD	11/41 (27%)	8/35 (23%)
Median duration (months) of response from most recent prior chemotherapy regimen (range)	6 (1–12)	6 (1–18)

[a] Investigator-assessed unconfirmed response rate.

Note: Differences in the denominator are due to missing data.

A significant difference between the two arms was observed for the primary efficacy endpoint (see Table 7). The complete response rate (CR or CCR) for patients treated with iodine I 131 tositumomab was 33% (14 of 42) compared to 8% (3 of 36) for patients treated with unlabeled tositumomab (p=0.012). The overall response rate (PR, CR, CCR) after iodine I 131 tositumomab, 23 of 42 (55%), was significantly greater than after tositumomab, 7 of 36 (19%; p=0.002). The median duration of response after iodine I 131 tositumomab was not reached, compared to 28.1 months after tositumomab.

Table 7. MIRROR Panel–Assessed Efficacy Endpoints: Iodine I 131 Tositumomab vs. Tositumomab: Study RIT-II-002

Efficacy Endpoint	Iodine I 131 Tositumomab (N=42)	Tositumomab (N=36)	P-value[b]
Primary endpoint:			
Complete response[a]	14/42 (33%)	3/36 (8%)	0.012
Secondary endpoints:			
Overall response	23/42 (55%)	7/36 (19%)	0.002
Median time (days) to response (95% CI)	49 (48–52)	53 (50–93)	0.167
Median duration (months) of response (95% CI)	NR (7.4–NR)	28.1 (7.6–NR)	0.877
Median duration (months) of complete response (95% CI)	NR (NR–NR)	NR (28.1–NR)	0.380
Median time to progression (months) (95% CI)	6.3 (4.9–NR)	5.5 (2.9–6.0)	0.031

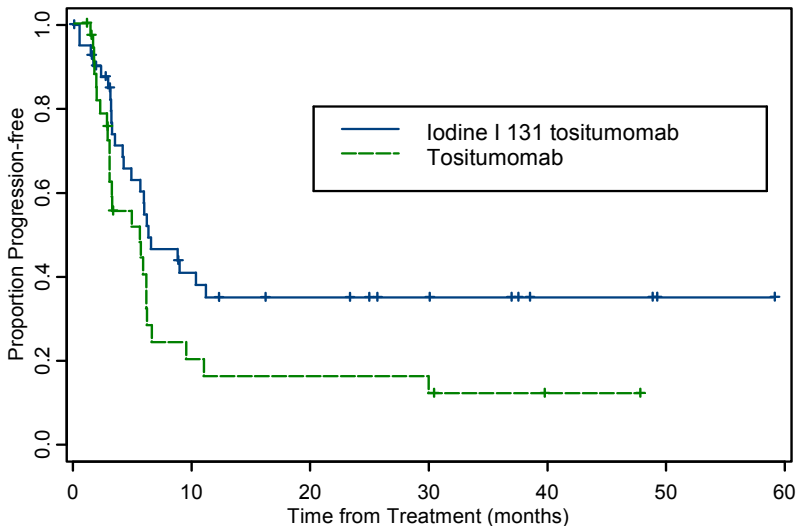
[a] For response definitions see Appendix 2.

[b] Fisher's exact test for response rates; logrank test for duration measures.

NR = Not reached; CI = 95% confidence interval.

The time to progression was significantly longer for patients treated with iodine I 131 tositumomab than for patients treated with tositumomab (relative risk = 0.54, 95% CI: 0.31–0.96, p=0.031; see Figure 13).

Figure 13. MIRROR Panel–Assessed Time to Progression: Study RIT-II-002



Following disease progression, 19 patients who were initially treated with the unlabeled tositumomab crossed over to receive treatment with iodine I 131 tositumomab. The efficacy data for these 19 patients are summarized in Table 8.

Table 8. MIRROR Panel–Assessed Tertiary Efficacy Endpoints: Patients Treated with Tositumomab then Crossed Over and Treated with Iodine I 131 Tositumomab: Study RIT-II-002

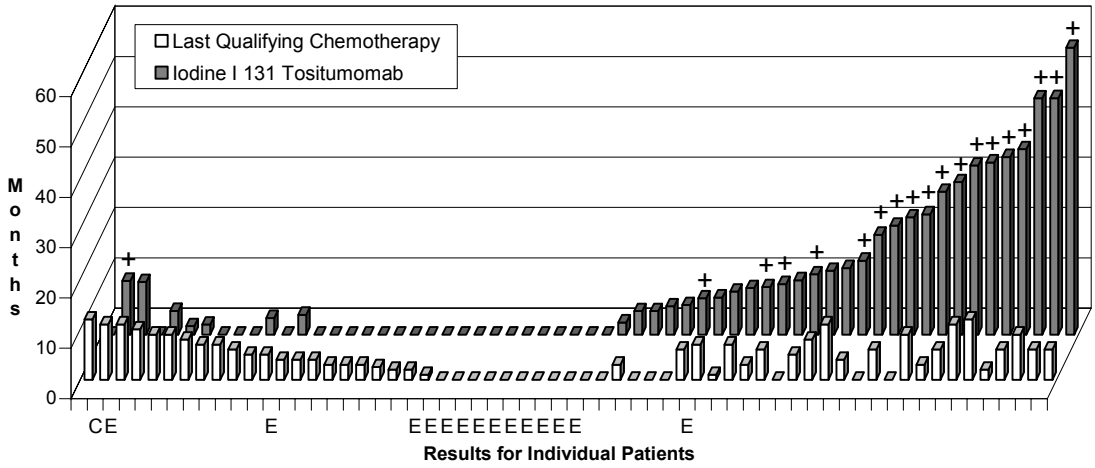
Efficacy Endpoint	Tositumomab (N=19)	Crossover to Iodine I 131 Tositumomab (N=19)	P-value[a]
Complete response[a]	0/19 (0%)	8/19 (42%)	0.008
Median duration (months) of complete response (95% CI)	0 (NA)	NR (12.6–NR)	0.006
Response	3/19 (16%)	13/19 (68%)	0.002
Median time (days) to response (95% CI)	53 (50–93)	53 (50–56)	0.007
Median duration (months) of response (95% CI)	7.6 (4.8–7.8)	12.6 (10.5–NR)	0.001
Median time to progression (months) (95% CI)	5.5 (2.8–6.0)	12.4 (6.4–NR)	0.010

[a] McNemar's test for response rate; Prentice-Wilcoxon for duration.

NA = Not applicable; NR = not reached; 95% CI = 95% confidence interval.

Figure 14 illustrates a comparison of the duration of response for each of the patients treated with iodine I 131 tositumomab [n=61; treated in the initial randomization (n=42) and following crossover (n=19)] following treatment with their prior chemotherapy (white bars) and following treatment with iodine I 131 tositumomab (black bars). Of the 61 patients, 28 had a longer response to iodine I 131 tositumomab, 19 had a longer response to prior chemotherapy, 3 had equivalent durations of response, and 1 had a censored duration of response on iodine I 131 tositumomab after the patient withdrew from study while in response. Ten patients responded to neither therapy and are represented by bars of no height in the central portion of the graph. The comparison for duration of response approached significance for patients treated with iodine I 131 tositumomab (p=0.06, Prentice-Wilcoxon).

Figure 14. Paired Comparison of Duration of Response[a]: Study RIT-II-002



[a] MIRROR Panel–assessed duration of response after iodine I 131 tositumomab therapy was compared to the Investigator-assessed unconfirmed duration of response to prior therapy.

E = Equivalent duration of response or no response to either therapy; C = Censored duration of response on iodine I 131 tositumomab.

"+" represents a patient continuing in response at last assessment.

A substantial number of long-term durable responders were observed in this study. A total of 20 of 61 (33%) patients who received iodine I 131 tositumomab treatment either in the initial randomized arm or as crossover therapy were classified as long-term durable responders. The MIRROR Panel–assessed information (CT scans and medical notes) from all patients. The longest time to progression is 58.9+ months.

4.1.1.3 Rituxan-Failure Study CP-97-012

Study CP-97-012: Phase II Study of Iodine I 131 Tositumomab for Non-Hodgkin's Lymphoma Patients Who Have Previously Received Rituximab

The data from this study are provided in support of conventional approval.

This was a single-arm, open-label, multicenter study of iodine I 131 tositumomab in the treatment of patients with NHL who were previously treated with rituximab therapy.

The objectives were to assess the safety, response rate and duration of response to iodine I 131 tositumomab therapy in patients who had previously relapsed or did not respond to rituximab.

This study was designed to enroll 40 evaluable patients. Forty-three patients were enrolled in the study and 40 patients received study drug. All patients were required to have prior treatment with at least 4 doses of rituximab without an objective response or to have progressed following treatment.

Three patients withdrew prior to receiving the dosimetric dose: patient 012-035-005 progressed after enrollment and sought alternate therapy, patient 012-036-011 had a potential response to rituximab without subsequent relapse and was discontinued, and patient 012-037-013 withdrew to seek alternate therapy.

Patient demographics and baseline characteristics are summarized in Table 9.

Table 9. Patient Demographics: Study CP-97-012 (N=40)

Gender	
Male	27 (68%)
Female	13 (33%)
Median age (years) (range)	57 (35–78)
Median time from diagnosis to protocol entry (months) (range)	50 (11–170)
Median number of prior chemotherapy regimens (range)	4 (1–11)
Response to most recent rituximab therapy	
CR/CCR/PR	16 (40%)
SD/PD	24 (60%)
Median duration (months) of response to most recent rituximab therapy	4.7
Number of patients with duration or response to most recent rituximab therapy of ≥6 months	5 (13%)
Previously received radiotherapy	13 (33%)
Grade at protocol entry	
Low grade	25 (63%)
Transformed low grade	12 (30%)
Intermediate grade	3 (8%)
Bone marrow involvement	12 (30%)
Bulky disease (≥5 cm)	19 (48%)
Elevated LDH	12/39 (31%)

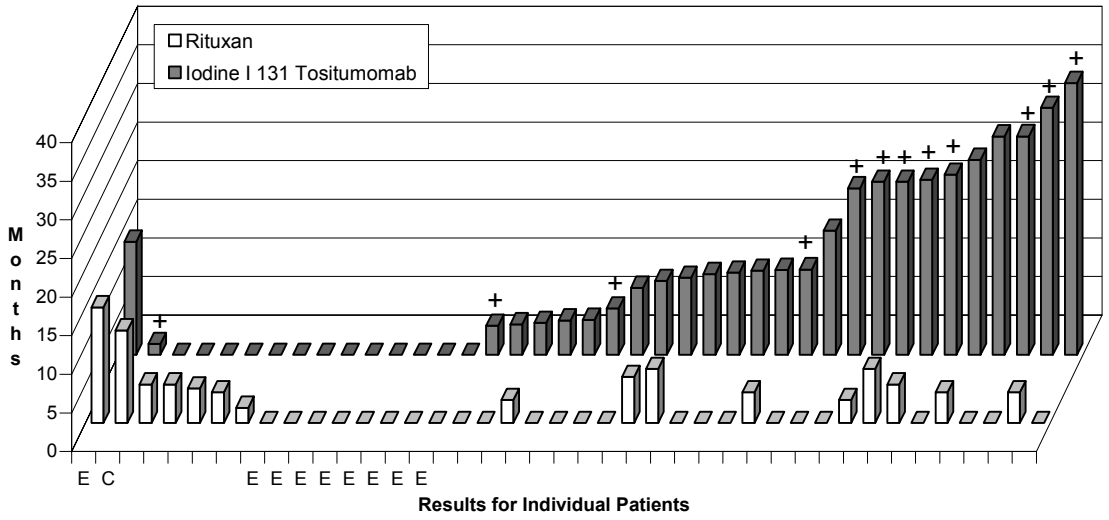
Note: Differences in the denominator are due to missing data.

The median follow-up from the first dosimetric dose for the 40 patients is 25.6 months (range: 1.2–40.0 months).

A response, as assessed by the MIRROR Panel, occurred in 27 of 40 (68%) patients, with a median duration of response of 16.1 months (95% C.I.: 10.5 months–NR). A complete response occurred in 13 of 40 (33%) patients; the median duration of complete response has not been reached (95% C.I.: 14.7 months–NR).

Figure 15 illustrates the comparison of the duration of response for each of the 40 patients following treatment with rituximab (white bars) and following treatment with iodine I 131 tositumomab (black bars). Based on the Investigator's assessment of response to rituximab, 16 patients responded to their prior rituximab. Based on the review of the MIRROR Panel, 27 patients responded to their iodine I 131 tositumomab therapy. Of the 40 patients, 25 patients had a longer (at least 30 days) duration of response to their iodine I 131 tositumomab therapy than to their prior rituximab, 5 patients had a longer duration of response to prior rituximab than subsequent iodine I 131 tositumomab, 1 patient had equivalent durations, and 1 patient was excluded from the analysis as the shorter of the two paired observations was censored as an ongoing responder on their last MIRROR Panel assessment. Eight patients responded to neither therapy (bars with no heights). The comparison for duration of response was significantly greater for iodine I 131 tositumomab ($p<0.001$, Prentice Wilcoxon).

Figure 15. Paired Comparison of Duration of Response[a]: Study CP-97-012



[a] Duration of confirmed response was assessed by MIRROR Panel only after iodine I 131 tositumomab therapy. Investigator-assessed duration of unconfirmed response after Rituxan was used for the comparison.

E = Equivalent duration of response or no response; C = Censored duration of response.

"+" represents a patient continuing in response at last assessment.

The observation that the duration of response after treatment with iodine I 131 tositumomab is longer than the duration of response after the previous treatment is a consistent observation. These results (Figure 15) are supported by the data from study RIT-II-004 (Figure 9) and study RIT-II-002 (Figure 14). Taken together these results support the approval of iodine I 131 tositumomab for the proposed indication for the treatment of patients who have failed rituximab.

4.1.1.4 Other Studies Supporting Approval of Iodine I 131 Tositumomab

There are 2 other studies that support the proposed indication for the treatment of patients with multiply relapsed or refractory low-grade or transformed low-grade, B-cell non-Hodgkin's lymphoma.

4.1.1.4.3 Study RIT-I-000

A Phase I/II Study of Radiolabeled Anti-B1 Monoclonal Antibody for the Treatment of B-Cell Lymphomas

Study RIT-I-000 was a Phase 1/2 dose-escalation, single-arm, open-label, single-center study of iodine I 131 tositumomab. The full spectrum of patients with NHL (i.e., low grade, transformed low grade, intermediate grade, and high grade) was enrolled in this study. Patients with low-grade or transformed low-grade NHL were required to have not responded to or relapsed following receipt of at least one prior chemotherapy regimen (bone marrow transplantation was not an exclusion). Patients with intermediate- or high-grade NHL without prior diagnosis of low grade NHL must have either not responded to or progressed during an initial standard chemotherapy regimen, had a recurrence or failed to respond to bone marrow transplant, or had risk factors making them poor candidates for bone marrow transplantation. Fifty-nine patients were enrolled in this study from 24 April 1990 to 17 January 1996. The objectives of this study were to

assess tumor targeting, the utility of pretreatment with unlabeled tositumomab, safety, maximum tolerated total body dose (TBD) (cGy), and efficacy of iodine I 131 tositumomab.

Separate dose escalations were performed for the unlabeled pre-dose (the dose levels were 0, 95, and 475 mg) and the radiolabeled therapeutic dose (the starting dose was 25 cGy TBD and doses were increased in 10-cGy increments to a maximum of 85 cGy). Gamma emissions were measured daily for 7 days following the dosimetric dose. The gamma count data were used to determine each patient's clearance of the drug (yielding a total body residence time [TBRT]), which was utilized to determine the patient-specific activity (mCi) required to deliver a desired TBD (cGy) of radiation. All 59 patients received at least one dosimetric dose, and 90% (53/59) of patients received at least one therapeutic dose ranging from 25 to 85 cGy TBD of iodine I 131 tositumomab.

Patient demographics and baseline characteristics are provided in Table 10.

Table 10. Patient Demographics: Study RIT-I-000 (N=59)

Male/female	37/22
Median age (years) (range)	50 (23–75)
Time from diagnosis to study entry (months) (range)	45 (5–214)
Median number of prior chemotherapy regimens (range)	3 (1–11)
Grade	
Low grade	28/59 (47%)
Transformed low grade	14/59 (24%)
Intermediate grade	15/59 (25%)
High grade	2/59 (3%)
Bone marrow involvement	17/56 (30%)
Bulky disease (≥5cm)	14/22 (64%)
Elevated LDH	30/59 (51%)
Response to last prior chemotherapy[a]	
Response (PR + CCR + CR)	30/58 (52%)
Complete response (CCR + CR)	19/58 (33%)

[a] Unconfirmed response rates.

Note: Differences in the denominator are due to missing data.

The MTD was determined to be 75 cGy using the dose-escalation schedule. The dose limiting toxicity was myelosuppression.

MIRROR Panel–assessed data were available and used in all analyses for 25 of the 59 patients. These included all patients with transformed low-grade NHL and all patients with low-grade NHL who were durable responders. Investigator-assessed data were used for the other 34 patients.

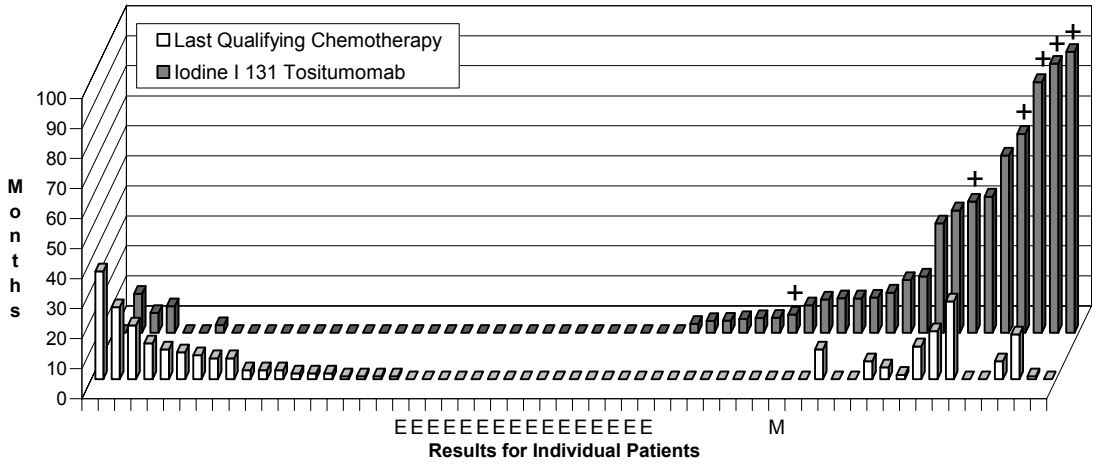
Twenty-eight of 59 (47%) patients responded, and 16 of 59 (27%) had a complete response. The median follow-up from the dosimetric dose was 39 months (range: 2–107 months) and 86 months (range: 67–107 months) for patients alive at the data

cutoff date. Outcomes for patients with low-grade or transformed low-grade lymphoma were superior to those in patients with more aggressive histologies.

Sixteen patients (27%) were determined to be long-term durable responders (i.e., responses with TTP ≥ 1 year). Nine patients (15% of the enrolled patients) had durable responses beyond 3 years, including 5 patients in ongoing complete response between 56+ and 96+ months (5–8 years) post therapy. Of note, 3 of these 5 patients in ongoing response had progressed after prior bone marrow transplantation.

Figure 16 illustrates the comparison of the duration of response for each of the patients following prior therapy (white bars, unconfirmed response) and following subsequent treatment with iodine I 131 tositumomab (black bars, confirmed response). One patient with missing duration data was excluded. Of the remaining 58 patients, 23 patients had a longer (at least 30 days) duration of response following iodine I 131 tositumomab; 19 patients had a longer duration of response following their prior therapy, and 16 patients had no response to either therapy. Although the number of patients with longer duration of response following iodine I 131 tositumomab was not statistically greater than the number of patients with longer duration of response following their prior therapy (p=0.17; Prentice-Wilcoxon), 5 patients treated with iodine I 131 tositumomab remain in CR with durations of response of 3.6 to 7.8 years.

Figure 16. Paired Comparison of Duration of Response[a]: Study RIT-I-000



a Investigator-assessed duration of unconfirmed response after prior therapy and Investigator- or MIRROR Panel–assessed (when available) duration of confirmed response after iodine I 131 tositumomab were used for the comparison.

E = Equivalent duration of response or no response to either therapy; M = Missing duration data.

"+" represents a patient continuing in response at last assessment.

4.1.1.4.4 Study RIT-II-001

A Phase II Study of the Validation of Dosimetry for Iodine I 131 Tositumomab for the Treatment of Patients with Relapsed and Refractory Low-Grade and Transformed Low-Grade NHL

This study transferred the patient-specific dosimetry method to multiple sites to demonstrate the reproducibility of those methods developed in the single-center Phase 1/2 study (RIT-I-000) described above.

The primary objective of this multicenter study (7 sites) was to demonstrate that each independent site could accurately and reproducibly conduct the whole body dosimetry. Additional objectives of this study were to evaluate the efficacy and safety of iodine I 131 tositumomab therapy in a multicenter study prior to initiation of a pivotal trial. Dosimetry methods and calculations from each participating site were reviewed and validated by a central dosimetry center at the University of Michigan.

Patients could be enrolled on this study if they had progressive disease of either low-grade or transformed low-grade lymphoma within one year of completion of the last chemotherapy regimen administered. At least one of the previous chemotherapy regimens must have contained an anthracycline or anthracenedione. Progression after single-agent steroids was not sufficient for study entry.

Patient demographics and baseline characteristics are provided in Table 11.

Table 11. Patient Demographics: Study RIT-II-001 (N=47)

Male/female	25/22
Median age (years) (range)	49 (23–74)
Time from diagnosis to study entry (months) (range)	41 (8–264)
Median number of prior chemotherapy regimens (range)	4 (1–8)
Grade	
Low grade	33/47 (70%)
Transformed low grade	14/47 (30%)
Bone marrow involvement	24/47 (51%)
Bulky disease (≥5cm)	10/20 (50%)
Elevated LDH	18/47 (38%)
Response to last chemotherapy[a]	
Response (PR + CCR + CR)	24/47 (51%)
Complete response (CCR + CR)	8/47 (17%)

[a] Unconfirmed response rates.

Note: Differences in the denominator are due to missing data.

Forty-seven patients with relapsed/refractory low-grade or transformed low-grade NHL were enrolled. All 47 patients received the dosimetric dose, and 98% (46/47) of the patients received the therapeutic dose.

The median follow-up from the dosimetric dose was 34.0 months (range: 0.2–66.4 months) and 60 months (range: 56–66 months) for patients alive at the data cutoff date.

Forty-three of the 46 (93%) and 46 of the 46 (100%) original site calculations of the administered activity (mCi) were within 5% and 10%, respectively, of the University of Michigan dosimetry center's calculations.

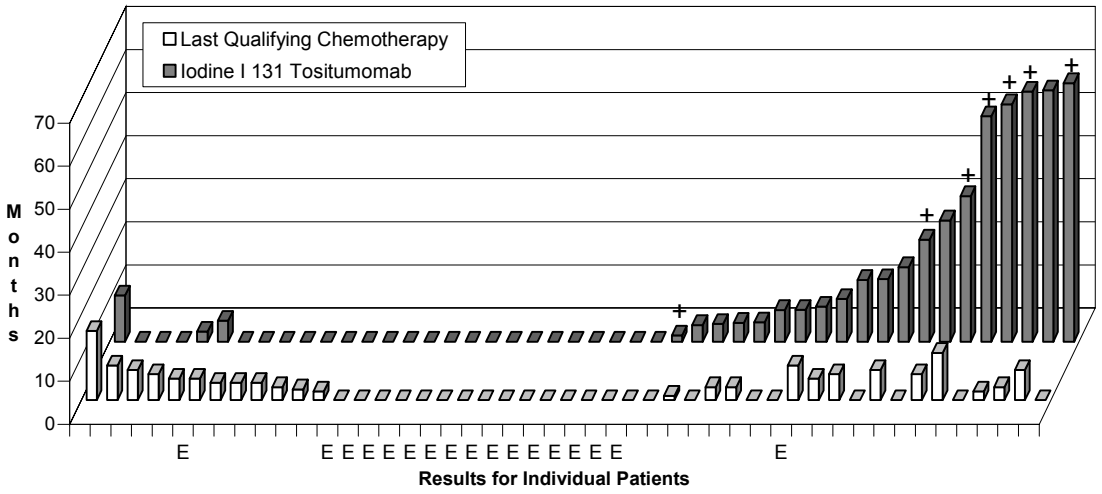
MIRROR Panel assessments were obtained and included in all analyses for 20 patients with transformed low-grade NHL and all patients with low-grade NHL who had Investigator-assessed time to progression of at least one year and available

radiographs/medical notes. Investigator-assessed data were used for the other 27 patients.

The overall response rate was 49% (23/47), and the complete response rate was 26% (12/47). Ten patients (21%) were observed to be long-term durable responders (TTP ≥ 1 year). Four patients continue in complete response between 54.1+ and 62.1+ months (4.5+ – 5.2+ years) post therapy.

Figure 17 illustrates the comparison of the duration of response for each of the patients (n=47) following their prior therapy (white bars) and following treatment with iodine I 131 tositumomab (black bars). Of the 47 patients, 19 patients had a longer (at least 30 days) duration of response following iodine I 131 tositumomab; 11 patients had a longer duration of response following their prior therapy; and 2 patients had equivalent durations of response. Fifteen patients responded to neither therapy (bars of no height) (p=0.030, Prentice-Wilcoxon).

Figure 17. Paired Comparison of Duration of Response[a]: Study RIT-II-001



[a] Investigator-assessed duration of unconfirmed response after prior therapy and Investigator- or MIRROR Panel-assessed (when available) duration of response after subsequent iodine I 131 tositumomab were used for the comparison.

E = Equivalent duration of response or no response to either therapy.

"+" represents a patient continuing in response at last assessment.

4.2 INTEGRATED EFFICACY POPULATION AND TWO SUB-POPULATIONS: LONG-TERM DURABLE RESPONDERS AND PATIENTS WITH TRANSFORMED NHL

Results are presented below for an Integrated Efficacy Population and for 2 subpopulations drawn from the Integrated Efficacy Population: patients with a durable response and patients with transformed low-grade NHL.

4.2.1 Integrated Efficacy Population

The Integrated Efficacy Population includes 250 of the 303 patients who received study drug in the following studies: RIT-II-004 (n=60); RIT-II-002 (n=61); CP-97-012 (n=40), RIT-I-000 (n=42); RIT-II-001 (n=47). Thirty-six patients enrolled in study RIT-II-002 who

received unlabeled tositumomab on the control arm of the study and 17 patients with intermediate- or high-grade NHL enrolled in study RIT-I-000 per protocol were excluded in this analysis. Four patients who were enrolled in the two pivotal studies and did not have low-grade NHL are included: 1 patient in study RIT-II-004 was determined to have mantle cell NHL subsequent to enrollment and 3 patients with follicular large cell (i.e., intermediate-grade NHL by International Working formulation) were eligible and enrolled in study CP-97-012.

The demographics for the 250 patients in the Integrated Efficacy Population are summarized in Table 12.

Table 12. Patient Demographics: Integrated Efficacy Population (N=250)

Male/female	149/101
Median age (years) (range)	56 (23–82)
Median time from diagnosis to study entry (months) (range)	44 (5–334)
Median number of prior chemotherapies (range)	3 (1–13)
Grade	
Low	175/250 (70%)
Transformed low	71/250 (28%)
Mantle cell/intermediate[a]	4/250[a] (2%)
Stage III/IV disease at entry	226/250 (90%)
Bone marrow involvement	113/245 (46%)
Bulky disease (≥5cm)	120/198 (61%)
Elevated LDH	100/244 (41%)
Modified IPI score [b]	
0–1	51/243 (21%)
2	97/243 (40%)
3	70/243 (29%)
4–5	25/243 (10%)

[a] One patient in RIT-II-004 had mantle cell NHL and 3 patients in CP-97-012 had intermediate grade.

[b] Modified IPI is defined by the following risk factors (age > 60, Stage III/IV, elevated LDH, KPS ≤ 70, extranodal disease). Standard IPI is defined by the following risk factors (age > 60, Stage III/IV, elevated LDH, KPS ≤ 60 [i.e., ECOG ≥ 2], 2 or more extranodal sites). Patients were considered low risk (0–1 factor), low-intermediate risk (2 factors), high-intermediate risk (3 factors), and high risk (4–5 factors).

Note: Changes in the denominator are due to missing data.

The median follow-up from the first dosimetric dose for this patient population was 29.8 months (range: 0.2–107.3 months).

Response was evaluated for all 250 patients. As noted previously, MIRROR Panel reviews were conducted for all patients in studies RIT-II-002, RIT-II-004, and CP-97-012. Additional MIRROR Panel reviews for studies RIT-I-000 and RIT-II-001 were also performed for all patients with transformed low-grade NHL and all patients with

low-grade NHL and Investigator-assessed time to progression of at least 12 months (2 patients without available radiographs/medical notes and 1 patient without discernable baseline disease were excluded). Thus, in the Integrated Efficacy Population, only 44 patients, from studies RIT-I-000 and RIT-II-001, with low-grade NHL and Investigator-assessed time to progression of less than 12 months were not assessed by the MIRROR Panel. Efficacy data are summarized in Table 13.

Table 13. Efficacy Data[a]: Integrated Efficacy Population (N=250)

Response	141/250 (56%)
Median (95% CI) duration of response for responders (months)	13.0 (10.8–18.8)
Complete response	75/250 (30%)
Median (95% CI) duration of response for complete responders (months)	58.4 (40.8–NR)
Median (95% CI) time to progression or death (months)	6.4 (5.9–9.7)
Median (95% CI) time to progression or death for responders (months)	15.2 (12.4–20.2)
Time to progression one year or more[b]	78/250 (31%)

[a] MIRROR Panel assessed for 208 of the 250 patients.
[b] MIRROR Panel assessed for all 78 patients.
NR = Not reached.

Time to progression and event-free survival for the Integrated Efficacy Population are presented in Figure 18 and Figure 19, respectively.

Figure 18. Time to Progression for Integrated Efficacy Population (N=250)

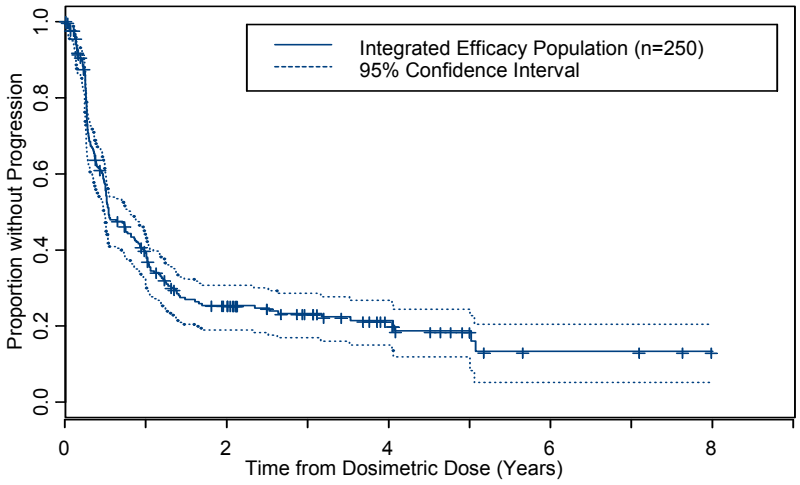
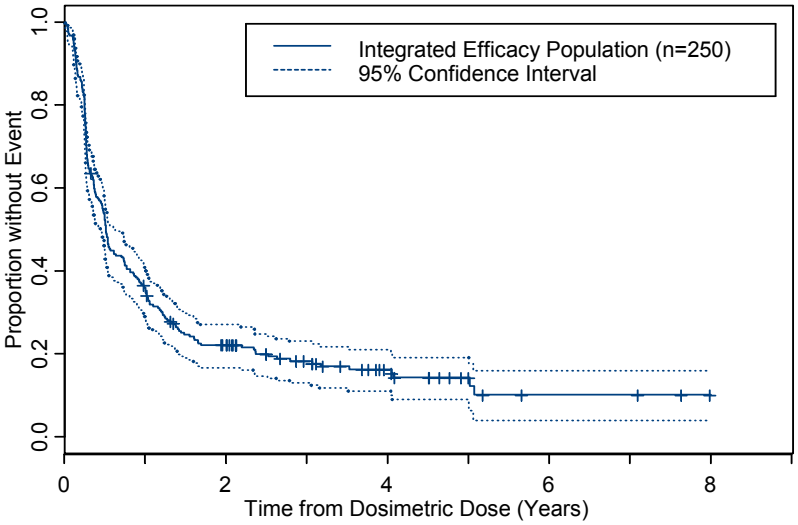
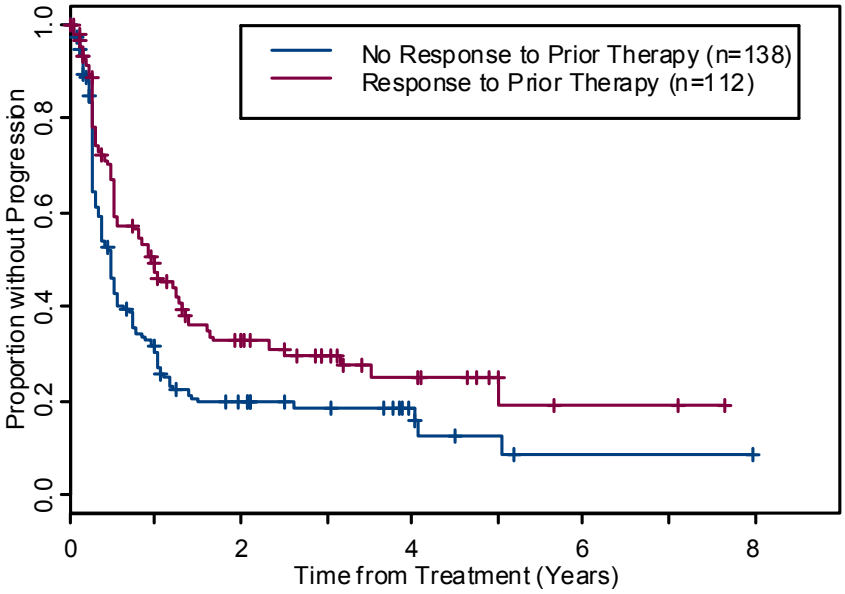


Figure 19. Event-Free Survival for Integrated Efficacy Population (N=250)



One hundred twelve of the 250 patients had responded to their last chemotherapy regimen or rituximab and 138 of the 250 patients had no response to their prior chemotherapy regimen or rituximab. Figure 20 shows the time to progression following iodine I 131 tositumomab therapy for both subgroups. Although the time to progression curve for patients who had no response to their last therapy is expectedly lower than that for patients who had responded, the shapes of the curves are similar and demonstrate that durable responses occurred both in patients who had not responded to prior therapy and those who had responded.

Figure 20. Integrated Efficacy Population: Long-Term Responses Observed in Refractory Patients



4.2.2 Long-Term Durable Responders

Following consultation with lymphoma experts and discussion with the Agency, Corixa applied the following definition of long-term durable response to the Integrated Efficacy Population database:

- A durable responder for a relapsed, refractory, low-grade NHL population, is a responding patient with a time to progression of 12 months or more (by MIRROR Panel assessment).

Based on the 250 patients in the Integrated Efficacy Population, a total of 78 patients had a MIRROR Panel–assessed response and a MIRROR Panel–assessed time to progression of at least 12 months. Following discussions with FDA, Corixa removed 2 of the 78 patients because of the existence of confounding factors. Patient 000-002-056 was removed because the confounding effect of metastatic breast cancer made assessment of lymphoma response too problematic. Patient 004-014-001 was removed because the patient had been determined by the MIRROR Panel to have not progressed following a partial response to their prior fludarabine treatment at study entry, which confounded the response to subsequent iodine I 131 tositumomab therapy. Table 14 presents the number of patients with durable responses by study.

Table 14. Number of Patients with Durable Responses by Study

Study	Number of Durable Responders Identified	Numbers of Durable Responders Retained
RIT-I-000	16	15
RIT-II-001	10	10
RIT-II-004	15	14
RIT-II-002	20	20
CP-97-012	17	17
Total Number	**78**	**76**

Of the 76 patients with MIRROR Panel–assessed durable responses, approximately 30 other patients had issues that were raised by the FDA. Corixa believes each of these patients should be included in the durable responder population. These patients are categorized and summarized below. Further details are presented for a subset of the patients in Appendix 9.

- Eight patients with durable responses in the initial study (RIT-I-000) received 2 or 3 sequential dosimetric doses of antibody (10 mg, 105 mg or 485 mg unlabeled and labeled tositumomab doses) prior to the therapeutic dose as part of the protein dose-ranging study to determine the amount of tositumomab in the iodine I 131 tositumomab (Bexxar) regimen. The total dose of unlabeled and iodine 131–labeled tositumomab given in the standard Bexxar regimen is 970 mg (485 mg dosimetric, 485 mg therapeutic). The maximum total dose given to the 8 patients was 1089 mg (a 12% overage) and thus is most likely insufficient to produce a major shift in therapeutic outcome. Five of these 8 patients also received total body radiation doses less than 65 or 75 cGy (1 patient at 35 cGy, 2 patients at 45 cGy and 2 patients at 55 cGy) as part of the dose-ranging study to determine the MTD. Inclusion of these patients was based on having MIRROR Panel–assessed durable responses. It would be expected that at lower total body doses, the outcomes would be biased against iodine I 131 tositumomab therapy.
- Eight patients with durable responses in study RIT-II-002 had been randomized to receive unlabeled tositumomab and subsequently relapsed. As per protocol, patients who had disease progression after treatment with unlabeled tositumomab could cross over to receive iodine I 131 tositumomab therapy. Of the 19 patients who crossed over to receive iodine I 131 tositumomab therapy, 8 had a durable response. The concern could be that if a patient had had a response to the unlabeled tositumomab, additional tositumomab therapy could have produced a better or more extended response. However, none of the 8 patients with durable responses after iodine I 131 tositumomab therapy had experienced any response to unlabeled tositumomab. Therefore, it is likely that the durable responses observed in these patients represent the effect of the iodine I 131 tositumomab therapy.
- In 10 patients with durable responses (000-002-058, 002-011-915, 002-032-001, 004-013-008, 004-014-008, 004-016-001, 004-016-003, 012-035-006, 012-036-007, and 012-037-001), the FDA had questions or concerns about the timing of disease progression. Details for these patients are provided in Appendix 9. For 4 of these 10 patients, the change in the date of progression would not affect the patients' inclusion in the durable response patient population as the patient would still have a time to progression of at least 12 months under the FDA scenario.

All cases had been reviewed by one or more MIRROR Panels. These panels operated under strict guidelines set forth in specific charters. Corixa believes that the MIRROR Panel results accurately reflect the clinical outcomes for these patients. In addition, the Investigator also assessed 9 of the 10 patients to have time to progression of at least 12 months.

- FDA raised concerns about 4 additional patients. Details for these patients are provided in Appendix 9.

  Two patients (001-005-008 and 002-011-009) had a small volume of disease at study entry. However, both patients had relapse confirmed by biopsy prior to study entry and both met study entry criteria.

  One patient's (012-037-002) eligibility based on histology was questioned. The patient had discordant histologic diagnoses on contemporaneous biopsies of bone marrow and left cheek (preauricular) mass, with one being called follicular, small cleaved lymphoma and the other being called diffuse large cell lymphoma. The patient was considered to have transformed low-grade lymphoma by the referee pathologist, Dr. Elaine Jaffe, NCI.

  One patient (002-011-016) had a complex medical course potentially making response evaluations difficult. However, Corixa believed the complexity of the medical course did not interfere with the response assessments by the MIRROR panel.

Thus, a total of 76 patients constitute the population of durable responders characterized in this section.

The demographics for the 76 patients in the Durable Responder Population are summarized in Table 15.

Table 15. Patient Demographics: Durable Responders (N=76)

Male/female	46/30
Median age (years) (range)	52 (23–82)
Median time from diagnosis to study entry (months) (range)	42 (9–264)
Median number of prior chemotherapies (range)	3 (1–8)
Grade	
Low	61/76 (80%)
Transformed low	15/76 (20%)
Stage III/IV disease at entry	67/76 (88%)
Bone marrow involvement	30/74 (41%)
Bulky disease (≥5 cm)	37/75 (49%)
Bulky disease (>500 g)	13/75 (17%)
Elevated LDH	18/75 (24%)
Modified IPI score [a]	
0–1	25/75 (33%)
2	31/75 (41%)
3	16/75 (21%)
4–5	3/75 (4%)

[a] Modified IPI defined as number of risk factors (age > 60, Stage III/IV, elevated LDH, KPS ≤ 70, extranodal disease). Standard IPI is defined by the following risk factors (age > 60, Stage III/IV, elevated LDH, KPS ≤ 60 [i.e., ECOG ≥ 2], 2 or more extranodal sites). Patients were considered low risk (0–1 factor), low-intermediate risk (2 factors), high-intermediate risk (3 factors), and high risk (4–5 factors).

Note: Differences in the denominator are due to missing data.

The median follow-up from the first dosimetric dose for this patient population was 44.6 months (range: 15.5–107.3 months). All 76 patients received their prescribed therapeutic dose.

Response was evaluated for all 76 patients. The MIRROR Panel–assessed efficacy data are summarized in Table 16.

Table 16. MIRROR Panel–Assessed Efficacy Data: Durable Responders (N=76)

Response	76/76 (100%)
Median (95% CI) duration of response for responders (months)	58.4 (36.5–NR)
Complete response	58/76 (76%)
Median (95% CI) duration of response for complete responders (months)	59.1 (47.2–NR)
Median (95% CI) time to progression or death (months)	60.1 (37.9–NR)

NR = Not reached.

Time to progression as assessed by the MIRROR Panel and event-free survival for the 76 patients is shown in Figure 21 and Figure 22, respectively.

Figure 21. Durable Responders: Time to Progression

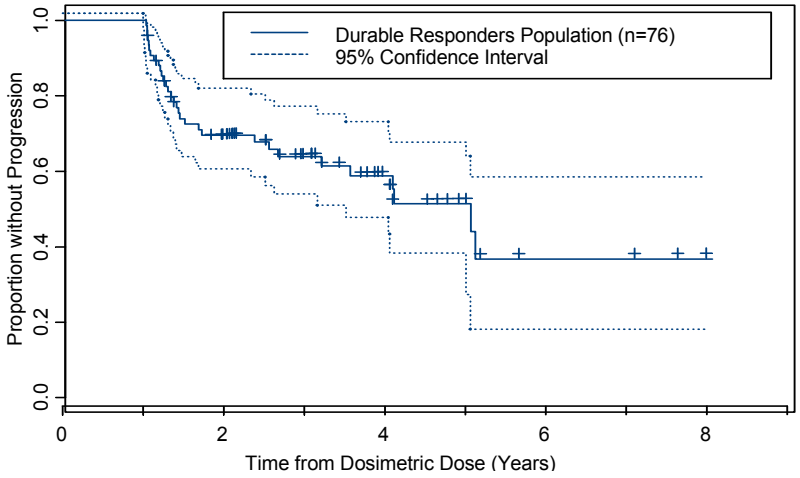
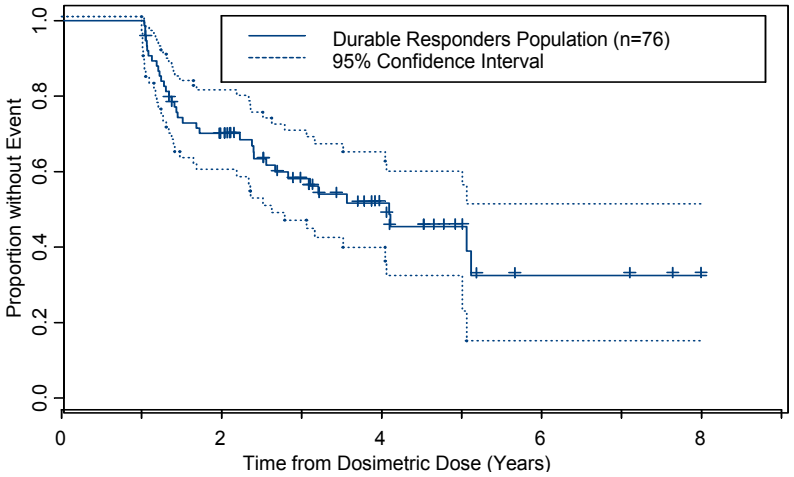
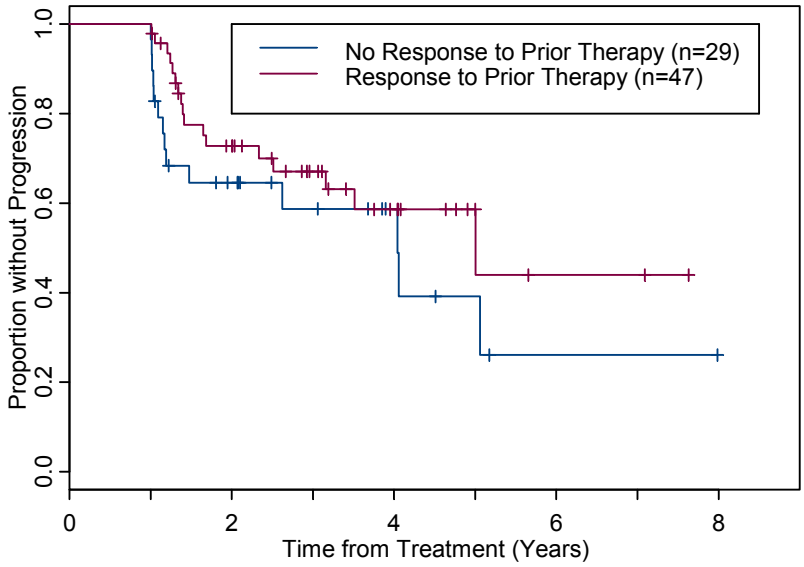


Figure 22. Durable Responders: Event-Free Survival



Forty-seven of the 76 patients had responded to their last therapy and 29 of the 76 patients had no response to their last therapy. Figure 23 shows the time to progression following iodine I 131 tostiumomab therapy for both subgroups and again demonstrates that durable responses occurred in patients who had not responded to their prior therapy as well as in those who had responded.

Figure 23. Long-Term Responses in Refractory Patients



Prognostic factors were examined in the durable responder group and all other patients in the Integrated Efficacy Population. A number of well-recognized prognostic factors were less prevalent in the durable responder group, such as: absence of a response to last chemotherapy, histology other than follicular, elevated LDH, both measures of bulky disease, and IPI score ≥ 3 (see Table 17).

Table 17. Prognostic Factors in Durable Responders

Characteristic	Durable Responders (N=78)[a] (TTP ≥ 12 mos.)	Other Patients (N=172) (TTP < 12 mos.)	P-value
Age (>60 years)	23%	37%	**0.030**
Prior chemotherapy (≥4)	33%	49%	**0.020**
No response to last chemotherapy	30%	55%	**<0.001**
Prior radiotherapy	26%	34%	0.239
Stage IV at study entry	63%	71%	0.240
Transformed low-grade histology	22%	31%	0.130[b]
Non-follicular histology	18%	34%	**0.011**
Bone marrow involvement	41%	49%	0.325
Elevated LDH	23%	49%	**<0.001**
Bulky disease (>500 g)	17%	40%	**<0.001**
Bulky disease (≥5 cm diameter)	49%	68%	**0.011**
Modified IPI score (≥3)	25%	46%	**0.003**[c]

[a] Includes two patients with TTP >12 months but disqualified for confounding factors.
[b] Chi-square test of transformed vs. low-grade.
[c] Chi-square test of modified IPI 0–2 vs. 3–5.

These results suggest that prognostic factors defined in the chemotherapy experience in non-Hodgkin's lymphoma also apply to radioimmunotherapy. To provide assurance that the beneficial results observed with iodine I 131 tositumomab treatment did not simply result from patient selection, prognostic information for each patient in the durable responder group was examined. Seventy-five of the 76 patients had one or more poor prognostic factors with a median of 3 poor prognostic factors for the group (see Figure 24).

Figure 24. Number of Poor Prognostic Factors in Durable Responders

Patient	Re-sponse	TTP (mos.)	Age >60 yrs	≥3 Prior Chemo Tx	No Response to Last Therapy	Prior Radio Tx	Stage IV	Trans-formed	Non-follicular	Bone Marrow Involve-ment	Elevated LDH	Bulky (tumor > 500 g)	MP Max Tumor Diameter ≥5 cm	Modified IPI ≥3
000-002-006	CCR	15.7												
000-002-010	PR	15.2												
000-002-013	CCR	13.1												
000-002-015	PR	48.5												
000-002-016	PR	13.8												
000-002-020	CCR	95.8+												
000-002-022	PR	19.7												
000-002-025	CCR	91.6+												
000-002-026	CR	20.2												
000-002-030	CCR	85.1+												
000-002-034	CCR	37.9												
000-002-051	CCR	55.7+												
000-002-057	CCR	42.2												
000-002-058	CCR	60.7												
000-002-059	CCR	67.8+												
001-003-007	CCR	16.1												
001-004-001	CCR	30.2												
001-004-008	CCR	60.1												
001-005-008	CCR	35.5+												
001-006-002	CCR	25.2+												
001-007-001	PR	12.6												
001-007-002	CCR	60+												
001-007-004	CCR	54.1+												
001-008-001	CCR	62.1+												
001-008-006	CCR	57.2+												
002-011-001	CCR	58.9+												
002-011-009	CR	12.2+												
002-011-016	CCR	48.6+												
002-011-022	CR	49+												
002-011-907	CR	35.1+												
002-011-908	CR	32+												
002-011-915	CCR	14.5												
002-025-003	CCR	37.3+												
002-025-901	CR	12.1												
002-025-904	CR	14.9												
002-030-012	CR	29.9+												
002-030-925	PR	15.7+												
002-030-926	PR	12.4												
002-031-001	CR	24.8+												
002-032-001	CR	23.2+												
002-034-003	CR	38.3+												
002-034-004	CR	25.5+												
002-034-005	CCR	36.8+												
002-034-017	CR	16.1+												
002-034-906	CR	21.7+												
004-013-008	CCR	47.4+												
004-013-009	CR	45.1+												
004-013-015	CR	40.9+												
004-014-008	PR	12.4												
004-014-009	PR	17.0												
004-016-001	CR	46.7+												
004-016-003	CR	48.5+												
004-016-008	CCR	13.5+												
004-016-013	PR	14.3												
004-020-005	CCR	48.7												
004-020-007	PR	14.7+												
004-020-008	PR	14.1												
004-021-002	CR	44.2+												
004-029-003	CR	46.2+												
012-035-002	PR	12.2												
012-035-004	CR	36.7+												
012-035-006	PR	12.2												
012-035-007	PR	28.0												
012-035-009	PR	12.0												
012-035-011	PR	12.6+												
012-035-012	CR	24.4+												
012-035-013	PR	17.7												
012-036-007	CCR	16.8												
012-036-008	CR	34.3+												
012-036-010	CR	24.9+												
012-036-012	CR	24+												
012-037-001	CCR	31.5												
012-037-002	CR	16.5												
012-037-008	CR	29.9+												
012-037-014	CR	23.4+												
012-037-015	CR	24.1+												

Index: Yes Missing No

4.2.3 Transformed Low-Grade NHL Patient Population

Treatment of patients with low-grade non-Hodgkin's lymphoma whose tumors have undergone transformation to more aggressive histologies remains a challenge for clinicians. Transformation represents an important prognostic event in the natural history and treatment course of patients with lymphoma. Recent reviews by hematopathologists[64] and hematologists-oncologists[11] have re-emphasized that the natural history of the low-grade NHLs encompasses histological progression in both pattern and cell type, with a negative impact on response to therapy and prognosis. Taken in this context, histological transformation represents a significant poor prognostic variable.

The Integrated Efficacy Population includes data on 71 patients who had a diagnosis of transformed low-grade NHL at some point prior to study entry and who received study drug in one of the 5 studies (RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, and CP-97-012).

The MIRROR Panel reviewed the responses of all 71 patients with transformed low-grade NHL. In addition, a retrospective central pathology review was conducted for the patients with transformed low-grade NHL. Of the 71 patients, 53 patients had adequate slides or diagnostic materials for reviewing both the original low-grade NHL diagnosis (obtained between 1978–1997) and the diagnosis for the transformed histology (obtained between 1988–1999). The results of the central pathology review of the 53 patients with pathology slides for both the initial low-grade and transformed low-grade NHL diagnoses confirmed that 47 of the 53 patients had histological transformation from low-grade (IWF Types A, B, C) to intermediate- or high-grade (IWF Types D, E, F, G, or H) NHL, 5 did not have confirmation of histological transformation, and 1 was classified as intermediate grade at diagnosis. The remaining 18 patients without histological specimens for both the low-grade and transformed low-grade diagnoses could not be confirmed for the following reasons: 15 patients were classified as having transformed low-grade NHL but did not have both specimens available for review, 1 patient was reclassified as low-grade, 1 patient's central review was non-diagnostic, and 1 patient's central review was not conducted. Some of these interpretations were re-reviewed as requested by FDA by a second independent reviewer, Dr. Elaine Jaffe, NCI.

The demographics are summarized for the 71 transformed low-grade NHL patients and for the 47 patients with confirmed histological transformation in Table 18. The majority of the patients had elevated LDH and had an IPI score of 3 or higher.

Table 18. Patient Demographics: Transformed Low-Grade NHL Patient Population

	All Patients (N=71)	Patients with Histologic Review and Confirmation (N=47)
Male/female	41/30	26/21
Median age (years) (range)	59 (37–80)	58 (37–80)
Median time (months) from NHL diagnosis to study entry (range)	74 (8–334)	53 (8–334)
Median time (months) from transformed diagnosis to study entry (range)	21 (0–123)	18 (0–119)
Median number of prior chemotherapies (range)	4 (1–11)	4 (1–9)
Histology (IWF)	*Investigator Assessed*	*Central Review Assessed*[a]
Follicular large cell	13/71 (18%)	12/47 (26%)
Diffuse small cleaved cell	4/71 (6%)	1/47 (2%)
Diffuse mixed cell	12/71 (17%)	4/47 (9%)
Diffuse large cell	28/71 (39%)	26/47 (55%)
Large cell immunoblastic	2/71 (3%)	4/47 (9%)
Other	12/71 (17%)	
Stage III/IV disease at protocol entry	63/71 (89%)	43/47 (91%)
Bone marrow involvement	20/71 (28%)	12/47 (26%)
Bulky disease (≥5 cm)	45/70 (64%)	30/46 (65%)
Elevated LDH	38/67 (57%)	25/45 (56%)

[a] Twenty-three patients had complex histologies and were classified into IWF categories based on their most aggressive histologic component.

Note: Differences in the denominator are due to missing data.

The median follow-up from the first dosimetric dose was 19.4 months (range: 0.5–101.4 months) for the 71 patients and was 22.0 months (range: 0.5–101.4 months) for the 47 patients with pathology-confirmed transformed low-grade NHL.

A total of 69 of 71 (97%) patients received their prescribed therapeutic dose. MIRROR Panel–assessed responses were obtained for all 71 patients. Patients withdrawing from study prior to response assessment were considered to have progressive disease. The MIRROR Panel review of efficacy data for the 71 transformed low-grade NHL patients and the 47 histologically confirmed transformed low-grade NHL patients is summarized in Table 19.

Table 19. MIRROR Panel Review of Efficacy Data: Transformed Low-Grade NHL Patient Population

	All Patients (N=71)	Patients with Histologic Confirmation[b] (N=47)
Overall Response[a]	28/71 (39%)	19/47 (40%)
Median (95% CI) duration of response for responders (months)	14.7 (10.8–40.8)	14.4 (8.8–40.8)
Complete Response	18/71 (25%)	11/47 (23%)
Median (95% CI) duration of response for complete responders (months)	36.5 (14.4–59.1)	36.5 (14.4–59.1)
Median (95% CI) time to progression (months)	4.3 (3.2–10.2)	4.3 (3.3–10.2)
Median (95% CI) time to progression for responders (months)	16.5 (12.4–42.2)	16.1 (10.2–42.2)

[a] For response definitions see Appendix 2.

[b] Forty-seven of the 71 patients were confirmed as transformed based on review of available slides for both the original diagnosis of low-grade and the diagnosis of transformation.

Figure 25 shows the time to progression data for the 71 patients with Investigator-assessed diagnoses of transformed NHL and for the 47 patients who had confirmation as transformed by central pathologic review.

Figure 25. Time to Progression for the Transformed Population (N=71) Compared to the Subpopulation Who Were Confirmed by Central Pathology

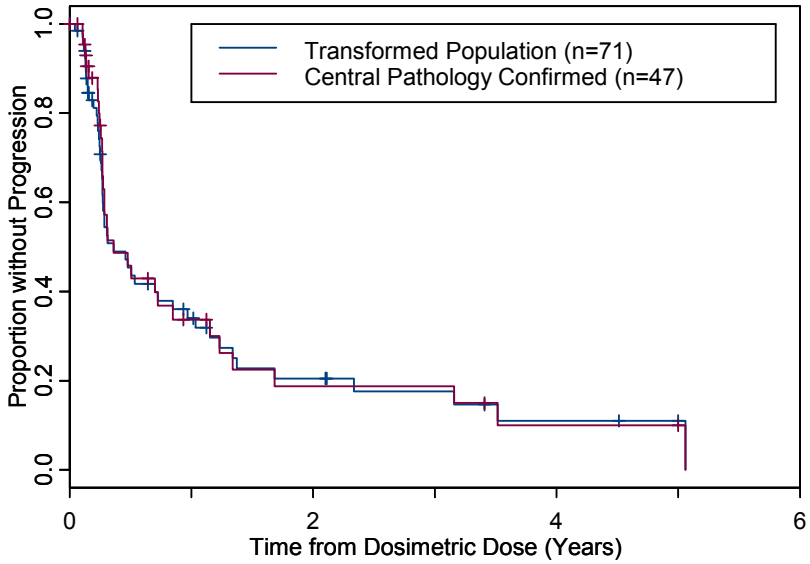
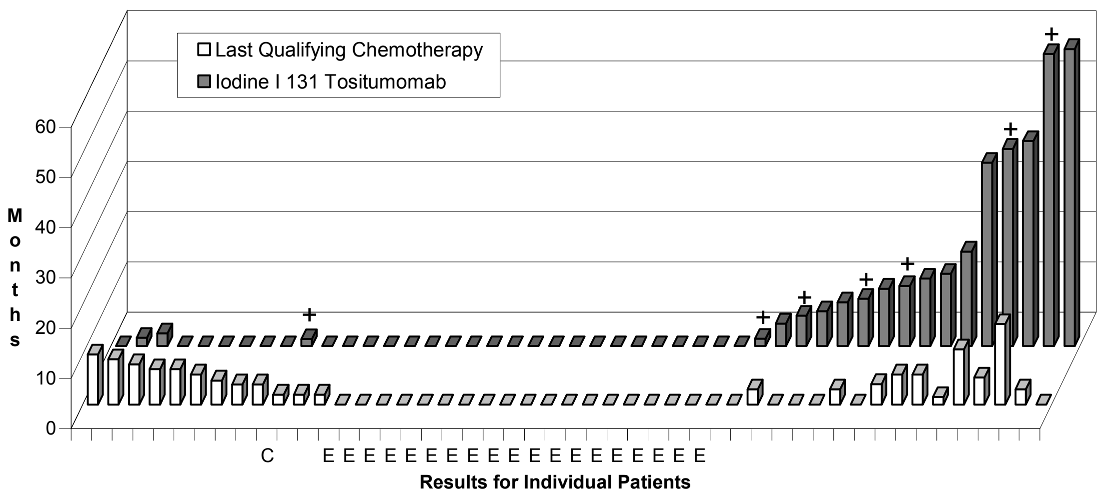


Figure 26 illustrates a comparison of the duration of response for each of the 47 patients with histologically confirmed, transformed low-grade NHL following treatment with their prior therapy (white bars) and subsequent treatment with iodine I 131 tositumomab (black bars). Of the 47 patients 16 had a longer response to iodine I 131 tositumomab and 11 had a longer response to their prior therapy. Nineteen responded to neither

therapy and are represented by bars of no height in the central portion of the graph. One patient had a censored duration of response on iodine I 131 tositumomab.

Figure 26. Paired Comparison of Duration of Response[a]: Transformed Low-Grade NHL Patient Population (N=47)



[a] MIRROR Panel–assessed duration of response after iodine I 131 tositumomab therapy was compared to the Investigator-assessed duration of response for the prior therapy. (MIRROR Panel–assessed duration of response was used for LQC in Study RIT-II-004.)

E = Equivalent duration of response or no response to either therapy.

"+" represents a patient continuing in response at last assessment.

4.3 SAFETY OF IODINE I 131 TOSITUMOMAB

This section provides an integrated summary of the safety of iodine I 131 tositumomab therapy for a population of 620 patients.

Table 20 shows the number of patients receiving study drug, as well as the number of patients from each study included in the integrated safety population as determined by discussions with the FDA. The population includes all relapsed/refractory low-grade or transformed low-grade NHL patients for whom a total body dose of 65 or 75 cGy was prescribed in studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004, CP-97-012, CP-98-020 (EAP) and the 4 single-patient compassionate-use studies (CP-97-014c, CP-97-016c, CP-98-023c, and CP-98-024c).

Table 20. Number of Patients in Safety Population

Study	Number of Patients Receiving Study Drug[a]	Number of Patients in Safety Population	Explanation of the Differences in the Number of Patients
RIT-I-000	59	22	Excludes 37 patients who received total body doses other than 65 or 75 cGy or who had intermediate- or high-grade NHL
RIT-II-001	47	47	
RIT-II-002 (Arm A)	42	42	Excludes safety data following unlabeled tositumomab only (Arm B) for 36 patients[b]
RIT-II-002 (Arm B)	36	0	
RIT-II-002 (Crossover)	19	19	
RIT-II-004	60	59	Excludes 1 patient with mantle cell NHL
CP-97-012	40	40	
Expanded Access (EAP)	759	387	Excludes 372 patients with less than 13 weeks of follow-up as of the data cutoff
Single Patient Studies	6	4	Excludes 2 patients administered <65 cGy[c]
TOTAL		**620**	

[a] Number of patients receiving iodine I 131 tositumomab as of 13 September 2002.

[b] Includes 42 patients who received iodine I 131 tositumomab (Arm A) and 19 patients who received iodine I 131 tositumomab (Arm B Crossover) after progressing on Arm B but does not include data for the 36 patients (Arm B) after receiving unlabeled tositumomab alone (Arm B).

[c] Two single study patients had a prior transplant and did not receive 65 or 75 cGy.

4.3.1 Demographics

Demographics for the 620 patients are summarized in Table 21.

Table 21. Patient Demographics: Integrated Safety Population (N=620)

Male/Female	343/277
Median age (years) (range)	57 (23–88)
Median time (months) from diagnosis to protocol entry (range)	45 (2–334)
Number of patients with ≥ 4 prior therapies	225 (36%)
Median number of prior therapies (range)	3 (1–13)
Previously received rituximab	218 (35%)
Grade at protocol entry	
Low grade (previously treated)	473 (76%)
Transformed low grade	143 (23%)
Intermediate grade	4 (1%)
Stage III/IV disease at protocol entry	556/619 (90%)
Bone marrow involvement	285/617 (46%)
Bulky disease (≥5 cm)	277/564 (49%)
Elevated LDH	299/586 (51%)

A total of 609 of 620 patients received either all or part of the therapeutic dose. The reasons that 11 patients did not receive any portion of the dose included progressive disease (6), death (2), HAMA response (1), reactivation of latent hepatitis B virus (1) and disorientation following the dosimetric dose (1).

The median follow-up from the first dosimetric dose for the 620 patients was 18.4 months and ranged from 0.1–99.0 months. Median follow-up ranged from 45.5 months in study RIT-I-000 to 17.7 months in the EAP. Overall, 522 patients had over 6 months of follow-up, 441 patients had over 1 year of follow-up, and 226 patients had over 2 years of follow-up.

4.3.2 Clinical Adverse Experiences

4.3.2.1 Adverse Experiences During the Infusions

The infusions of the dosimetric dose and the therapeutic dose of tositumomab and iodine I 131 tositumomab were well tolerated. Patients were routinely premedicated with acetaminophen and an antihistamine (typically, diphenhydramine) prior to the infusions.

Infusion-rate adjustments of the dosimetric dose were required for only 31 (5%) of 616 patients for whom data were available. Infusion-rate adjustments of the therapeutic dose were required for only 24 (4%) of 608 patients with available data. There were 2 patients with a Grade IV adverse experience (hydronephrosis and an anaphylactoid reaction); both were after the therapeutic dose. Neither patient was hospitalized. The patient with hydronephrosis had a suspected urinary tract infection probably related to a urethral obstruction. Thus, the event was considered unrelated or only remotely related to drug administration. The patient with the anaphylactoid reaction received the intended 65 cGy total body therapeutic dose after the rate of administration was decreased by 50%. This event was considered probably related to drug administration.

Table 22 summarizes the adverse experiences that occurred during the day of infusion for both the dosimetric and the therapeutic dose.

Table 22. Summary of Adverse Experiences on the Day of the Dosimetric Infusion and the Day of the Therapeutic Administration

	Dosimetric Infusion (N=616)	Therapeutic Infusion (N=609)
Total number with an AE	160 (26%)	128 (21%)
Number with Grade III AEs	6 (1%)	9 (1%)
Number with Grade IV AEs	0 (0%)	2 (<1%)
Most frequent AEs	Fever, pruritus	Chills, nausea

4.3.2.2 All Adverse Experiences

Five hundred fifty of 620 (89%) patients had at least one adverse experience (AE). Asthenia (32% of patients), nausea (25%), and fever (22%) were the three most common non-hematologic terms reported, followed by pain (14%), chills (13%), cough increased (12%), rash (12%), infection (11%), headache (10%) and vomiting (10%).

Three hundred forty-seven of 620 (56%) patients had at least one documented hematologic AE. For laboratory values of the hematologic adverse experiences, only Grade III and IV events were coded, and all were classified as possibly related to study drug. Analyses were based on all recorded laboratory values, missing data values were not imputed, and data were not carried forward. The most common hematologic adverse experiences were ANC < 1000 cells/mm^3 (42%), WBC < 2000 cells/mm^3 (38%), platelets < 50,000/mm^3 (36%), and hemoglobin < 8.0 g/dL (11%).

All AEs, regardless of relationship to study drug, that occurred in 5% or more of the patients in the Integrated Safety Population are summarized in Table 23 and Table 24, respectively. The tables also include the number and percent of those adverse experiences that were Grade III or IV.

Table 23. Non-Hematologic Adverse Experiences by Patient Occurring in ≥5% of the Integrated Safety Population (N=620)

	Regardless of Relationship	
Preferred Term	**All Grades**	**Grade III/IV**
Asthenia	199 (32%)	15 (2%)
Nausea	154 (25%)	10 (2%)
Fever	136 (22%)	11 (2%)
Pain	87 (14%)	12 (2%)
Chills	78 (13%)	5 (1%)
Cough increased	72 (12%)	3 (<1%)
Rash	72 (12%)	1 (<1%)
Infection[a]	67 (11%)	5 (1%)
Headache	64 (10%)	1 (<1%)
Vomiting	64 (10%)	6 (1%)
Abdominal pain	57 (9%)	11 (2%)
Anorexia	56 (9%)	3 (<1%)
Myalgia	56 (9%)	2 (<1%)
Diarrhea	55 (9%)	1 (<1%)
Arthralgia	54 (9%)	7 (1%)
Dyspnea	52 (8%)	18 (3%)
Pruritus	48 (8%)	0 (0%)
Rhinitis	44 (7%)	0 (0%)
Pharyngitis	39 (6%)	0 (0%)
Sweating	39 (6%)	1 (<1%)
Back pain	35 (6%)	6 (1%)
Peripheral edema	34 (5%)	0 (0%)
Chest pain	33 (5%)	2 (<1%)
Hypotension	31 (5%)	4 (1%)

[a] The COSTART term for infection includes a subset of all infections (e.g., upper respiratory infections). Other terms are mapped to other preferred terms (e.g., pneumonia and sepsis). A complete analysis of all infections is presented in Section 4.3.7.

Hematologic AEs that occurred in 5% or more of the patients in the Integrated Safety Population are summarized in Table 24.

Table 24. Hematologic Adverse Experiences Occurring in ≥5% of the Integrated Safety Population (N=620)

Preferred Term	Grade III/IV	Grade IV
Neutropenia[a]	256 (42%)	109 (18%)
Thrombocytopenia[a]	223 (36%)	98 (16%)
Anemia[a]	69 (11%)	13 (2%)

[a] Adverse experiences derived from laboratory data. All laboratory hematologic adverse experiences were classified as possibly/probably related to study drug.
NCI CTC toxicity grades:
ANC (1000 cells/mm^3): Grade III/IV = <1.0, Grade IV = <0.5.
Platelets (1000/mm^3): Grade III/IV = <50, Grade IV = <25.
Hemoglobin (g/dL): Grade III/IV = <8.0, Grade IV = <6.5.

Sixty-five percent (404 of 620) of the Integrated Safety Population experienced at least one Grade III/IV adverse experience regardless of relationship to study drug. The vast majority of Grade III/IV adverse experiences were laboratory-derived hematologic AEs. The only non-hematologic Grade III/IV AEs reported in >2% of the Integrated Safety Population were dyspnea (3%) and asthenia (2%).

Overall, 142 of 620 (23%) patients experienced one or more serious adverse experiences (SAEs). The investigators considered 64 of 620 (10%) patients to have experienced one or more SAEs possibly or probably related to study drug. SAEs occurring in 1% or more of patients are listed in Table 25 for all SAEs and for all SAEs reported to be possibly or probably related to study drug.

A total of 114 of 620 (18%) patients experienced an AE resulting in hospitalization or prolongation of hospitalization within 90 days of administration of study drug. Forty-two patients (6.8%) were hospitalized on one or more occasions with infection-related events, including unexplained fever, neutropenic fever, or documented infection with or without neutropenia.

Table 25. Serious Adverse Experiences by Patient that Occurred in ≥1% of the Integrated Safety Population (N=620)

Preferred Term	Regardless of Relationship	Possibly/Probably Related
Patients who reported at least one SAE	142 (23%)	64 (10%)
Non-Hematologic AEs		
Fever	19 (3%)	12 (2%)
Sepsis	15 (2%)	7 (1%)
Pneumonia	12 (2%)	4 (1%)
Dyspnea	11 (2%)	1 (<1%)
Pain	9 (1%)	1 (<1%)
Asthenia	8 (1%)	3 (<1%)
Pleural Effusion	8 (1%)	0 (0%)
Vomiting	8 (1%)	3 (<1%)
Abdominal Pain	7 (1%)	0 (0%)
Dehydration	7 (1%)	1 (<1%)
Hematologic AEs		
Myeloproliferative disorder[a]	18 (3%)	15 (2%)
Thrombocytopenia	10 (2%)	10 (2%)
Anemia	9 (1%)	8 (1%)
Neutropenia	9 (1%)	8 (1%)

[a] One additional patient developed acute myeloblastic leukemia. See Section 4.3.9.

4.3.3 Hematologic Toxicity

Initial analyses were based on all recorded laboratory values, missing data values were not imputed, and data were not carried forward (Table 26). Additional analyses based on imputation of missing values are presented subsequently in Section 4.3.8.

The most common hematologic Grade III/IV adverse experiences were neutropenia, 42% (Grade III < 1000 cells/mm^3); thrombocytopenia, 36% (Grade III < 50,000/mm^3); and anemia, 11% (Grade III < 8.0 g/dL). Analyses based on all recorded laboratory values (Table 26) revealed the median platelet nadir was 62,000/mm^3, ANC nadir 1,100 cells/mm^3, and hemoglobin nadir 10.8 g/dL. Based on all patients, 16% experienced Grade IV thrombocytopenia (platelet count < 25,000/mm^3), 18% Grade IV neutropenia, and 2% Grade IV anemia.

Table 26. Hematology for Integrated Safety Population (N=620)

Laboratory Parameter[a]	Endpoint	Integrated Safety Population (N=620)
Platelets	Number of patients	612[b]
	Median time to nadir (days)	34
	Median nadir (/mm^3)	62,000
	Number (%) Grade III/IV	223 **(36%)**
	Median[c] duration of Grade III/IV (days)	**29**
	Number (%) Grade III/IV without recovery[d] to Grade II	32 **(5%)**
	Number (%) Grade III/IV without recovery[d] to baseline grade	79 (13%)
	Number (%) Grade IV	98 (16%)
	Median[c] duration of Grade IV (days)	29
ANC	Number of patients	611[b]
	Median time to nadir (days)	43
	Median nadir (cells/mm^3)	1,100
	Number (%) Grade III/IV	256 **(42%)**
	Median[c] duration of Grade III/IV (days)	**30**
	Number (%) Grade III/IV without recovery[d] to Grade II	19 **(3%)**
	Number (%) Grade III/IV without recovery[d] to baseline grade	46 (8%)
	Number (%) Grade IV	109 (18%)
	Median[c] duration of Grade IV (days)	21
Hemoglobin	Number of patients	613[b]
	Median time to nadir (days)	47
	Median nadir (g/dL)	10.8
	Number (%) Grade III/IV	69 **(11%)**
	Median[c] duration of Grade III/IV (days)	**19**
	Number (%) Grade III/IV without recovery[d] to Grade II	8 **(1%)**
	Number (%) Grade III/IV without recovery[d] to baseline grade	24 (4%)
	Number (%) Grade IV	13 (2%)
	Median[c] duration of Grade IV (days)	15

[a] Grade III/IV toxicity derived from hematologic parameters.
NCI CTC toxicity grades:
ANC (1000 cells/mm^3): Grade II = 1.0 to <1.5, Grade III = 0.5 to <1.0, Grade IV = <0.5.
Platelets (1000/mm^3): Grade II = 50 to <75, Grade III = 25 to <50, Grade IV = <25.
Hemoglobin (g/dL): Grade II = 8.0 to <10.0, Grade III = 6.5 to <8.0, Grade IV = <6.5.

[b] Seven patients did not have ANC, platelet count, or hemoglobin follow-up; 1 patient did not have ANC or platelet count follow-up; and 1 patient had WBC recovery but no differentials documenting ANC recovery. Of these 9 patients without hematologic follow-up, 4 patients did not receive the therapeutic dose.

[c] Kaplan-Meier estimate

[d] Recovery can occur at any time point after the Grade III/IV toxicity.

4.3.3.1 Documented Recovery after Hematologic Toxicity

Of the 223 patients with Grade III/IV thrombocytopenia (Table 26), 32 patients did not have documented recovery to Grade II; of the 256 patients with Grade III/IV neutropenia, 19 patients did not have documented recovery to Grade II; and of the 69 patients with Grade III/IV anemia, 8 patients did not have documented recovery to Grade II. In total, 42 of 620 (7%) patients did not have documented recovery of all parameters from Grade III/IV to Grade II at any time point after hematologic Grade III/IV toxicity. Thirty of the 42 patients had ≤ 90 days of hematologic follow-up after the therapeutic dose and 12 of the 42 had over 90 days of hematologic follow-up after the therapeutic dose. The subsequent clinical courses of these 42 patients are delineated below.

- 26 received subsequent therapy for NHL prior to documented recovery.
- 15 died prior to documented recovery. The cause of death was attributed to progressive NHL for 12 of the 15 patients. One patient (001-008-002) died from gastrointestinal hemorrhage 4 days following the dosimetric dose and prior to the therapeutic dose; one patient (020-034-095) died from renal failure 44 days following the therapeutic dose, and one patient (020-065-233) died from septic shock 25 days following the therapeutic dose.
- 1 patient has an ongoing complete response at Year 2 without recovery.

4.3.3.2 Delayed Hematologic Toxicity

Delayed hematological toxicity, defined as Grade III or IV thrombocytopenia, neutropenia, or anemia more than 90 days after the therapeutic dose (i.e., RIT Day > 90 days), occurred in 63 of 620 (10%) patients. Included in the 63 patients were 51 patients who recovered from initial myelosuppression but later developed thrombocytopenia, neutropenia, or anemia. The occurrence of late hematological toxicity was partially explained (as described below) in 32 of the 63 patients.

- 2 patients developed myelosuppression after a second administration of iodine I 131 tositumomab as allowed in study RIT-I-000.
- 7 patients developed myelosuppression in association with pre-existing MDS (3 patients) or MDS that developed after iodine I 131 tositumomab (4 patients).
- 6 patients received “full dose” treatment before the development of dose attenuations for lower platelet counts and obesity.
- 6 patients developed myelosuppression after subsequent therapy for NHL.
- 11 patients had Grade III/IV toxicity between RIT Day 91 and RIT Day 120 and recovered to Grade II at their Month 4 or Month 6 evaluation.

Figure 27, Figure 28, and Figure 29 show the platelet counts, ANC and hemoglobin for all the patients over time, respectively. These plots illustrate the following points: (1) Each plot demonstrates the general U-shaped trend for hematologic values, from baseline through nadir to recovery, for the population as a whole. The vertical clusters of data show the protocol-specified weekly follow up especially during Weeks 2–13 and again at Week 26. (2) The data points in the lower right portion of the plots represent Grade III or IV values occurring more than 90 days after the therapeutic dose with the percent of patients experiencing Grade III/IV toxicity after 90 days represented in the lower right box in each plot.

Figure 27. Platelet Count over Time: Integrated Safety Population (N=620)

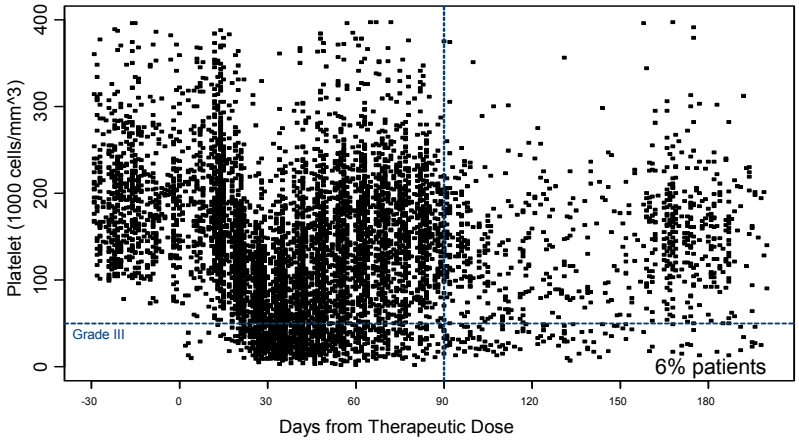


Figure 28. ANC over Time: Integrated Safety Population (N=620)

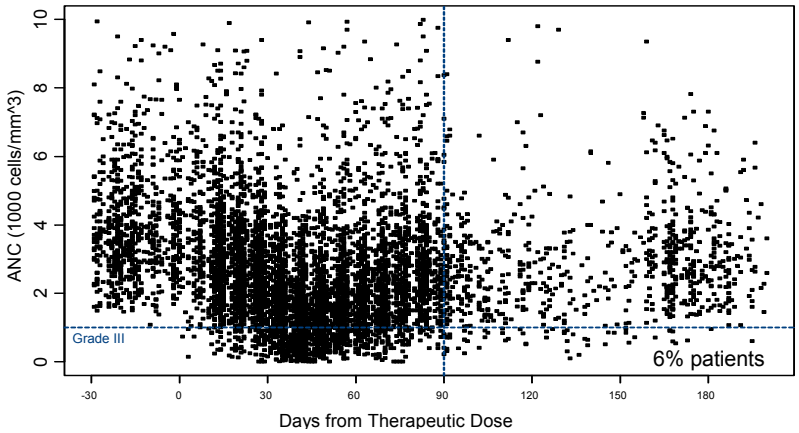
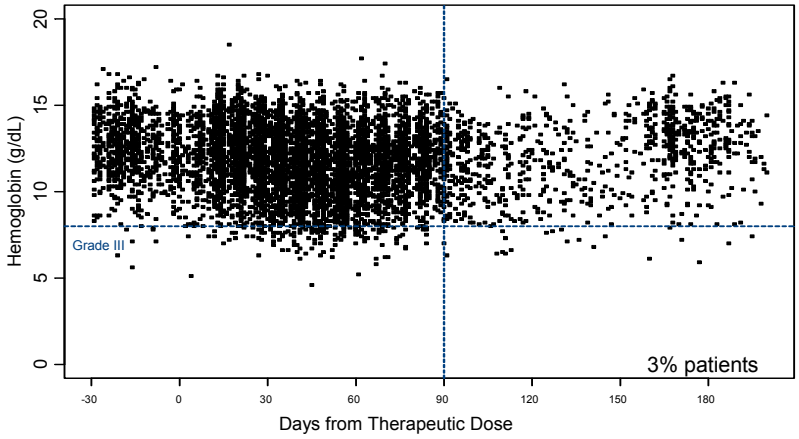


Figure 29. Hemoglobin over Time: Integrated Safety Population (N=620)



4.3.4 Exploratory Analysis of Factors Influencing Grade III/IV Hematologic Toxicity

The factors that were included in the analyses of incidence and duration of Grade III/IV platelet, ANC, and hemoglobin toxicity are listed in Table 27.

Table 27. Description of Factors for Univariate Analyses

Category	Subgroups
Gender	Male, female
Age	≤60 years, >60 years
Prior number of chemotherapy regimens	1–3 regimens, 4 or more regimens
Prior number of therapies	1–3 therapies, 4 or more therapies
Bone marrow involvement	None (0%), 1–10%, >10%
Baseline count	
Platelet	<150,000/mm^3, ≥150,000/mm^3
ANC	<3,000 cells/mm^3, ≥3,000 cells/mm^3
Hemoglobin	<12.0 g/dL, ≥12.0 g/dL
Grade at protocol entry	Low, Transformed low-grade, Intermediate
Tumor burden	≤500 g, >500 g
Lymph node ≥5 cm	Yes, No
Time from diagnosis to study entry	<48 months, ≥48 months
Time from last chemotherapy to study entry	0-6 months, >6–12 months, >12 months
Investigator-assessed response to last chemotherapy	No response (SD/PD), Response (CR, CCR, PR)
Prior radiotherapy	Yes, No
Baseline LDH	Low/normal, Elevated
Prior fludarabine	Yes, No
Modified International Prognostic Index (IPI)	Low risk=0/1, Low/intermediate risk=2, Intermediate/high risk=3, High risk=4/5

The significant factors identified as predictors of either increased risk of hematologic toxicity or duration of hematologic toxicity in the univariate analyses are categorized in Table 28. Each “x” represents a factor associated with a significant p-value ($p<0.05$) from the univariate analyses.

Table 28. Univariate Analyses of Factors Associated with Increased Risk/Duration of Hematologic Toxicity

	Occurrence of Grade III/IV		
	Neutropenia	**Thrombocytopenia**	**Anemia**
Age ≤ 60		X	
≥ 4 prior therapies	X	X	X
Reduced baseline count (see Table 27)	X	X	X
Prior fludarabine	X	X	X
% Bone marrow involvement	X	X	
Transformed/Intermediate			X

Multivariate analyses excluded variables (e.g., prior fludarabine) that were not captured in all studies. In the multivariate analyses, the baseline values and number of prior therapies were significant predictors of Grade III/IV platelet, ANC, and hemoglobin toxicity. In addition, baseline degree of bone marrow involvement was a significant predictor for both Grade III/IV thrombocytopenia and neutropenia.

4.3.5 Supportive Care

Supportive care for hematologic toxicity was administered at the discretion of the Investigators per their institutions' guidelines and represents a surrogate for the severity of hematologic toxicity.

Of 620 patients, 161 (26%) received one or more hematologic supportive care measures during recovery from hematologic toxicity following the therapeutic dose. Sixty-nine patients (11%) received G-CSF; 42 patients (7%) received erythropoietin; 76 patients (12%) received platelet transfusions; and 93 patients (15%) received packed red blood cell transfusions.

Data on the length of supportive care were not collected for the EAP. Data regarding the length of supportive care are available for 233 patients in the other studies. Thirty-one (13%) patients received G-CSF for a median of 15 days. Sixteen (7%) patients received erythropoietin for a median of 52 days. Thirty-seven (16%) patients received platelet transfusions on a median of 2 occasions. Finally, 38 (16%) patients received packed red blood cell transfusions on a median of 2 occasions.

4.3.6 Bleeding Episodes

Fifty-three of 620 (8.5%) patients experienced a bleeding event. A list of all the bleeding events, the number of Grade III or IV bleeding events, and the number of deaths within 90 days of study drug are shown in Table 29.

Table 29. Patients with Bleeding Episodes: Integrated Safety Population (N=620)

Type of Bleed (COSTART Preferred Term)	Number of Patients	Number of Patients with a Grade III or IV Event	Deaths within 90 Days of Study Drug
Ecchymosis	13 (2%)	1	0
Epistaxis	13 (2%)	0	NA
GI hemorrhage[c]	5 (1%)	5	2
Gum hemorrhage[d]	3 (<1%)	0	NA
Hemoptysis	3 (<1%)	1[a]	1[a]
Hemorrhage[e]	3 (<1%)	2	1
Lung hemorrhage[f]	1 (<1%)	1[b]	0
Melena	8 (1%)	1[a]	1[a]
Petechiae	4 (1%)	0	NA
Rectal hemorrhage[g]	3 (<1%)	0	NA
Subdural hematoma	1 (<1%)	1[b]	0
Vaginal hemorrhage[h]	2 (<1%)	0	NA

[a] Patient 020-014-350 experienced a Grade III melena on study day 54, a Grade III hemoptysis on study day 55, and death attributed to progressive disease on study day 57.

[b] Patient 004-020-007 experienced a Grade III subdural hematoma on study day 920, a Grade IV lung hemorrhage on study day 1023, and death attributed to progressive disease on study day 1028.

[c] Verbatim terms: GI bleed, GI bleeding, upper GI bleed, possible GI bleed.

[d] Verbatim terms: gum bleeding, hemorrhage – gums, slight bleeding from gums.

[e] Verbatim terms: CNS bleed after fall, suspect bleed/vascular event, extravasation.

[f] Verbatim term: pulmonary hemorrhage.

[g] Verbatim term: rectal bleeding.

[h] Verbatim terms: increased vaginal bleeding, vaginal bleeding.

Ten patients (1.6%) experienced 12 bleeding events that were Grade III or IV. The patients, type of bleed, grade, study day of bleed, lowest platelet count within a week of the event, study day of death, and cause of death, if applicable, are listed in Table 30.

Table 30. Patients with Grade III or IV Bleeding Events

Patient ID	Type of Bleed (COSTART Preferred Term)	Grade	Study Day	Platelet Count[a] ($1000/mm^3$)	Study Day of Death	Cause of Death
001-009-003	Ecchymosis	3	59	49	643	Progression of NHL
002-025-901[b]	Hemorrhage	4	467	16	470	Progression of NHL
002-034-008	Gastrointestinal hemorrhage	4	54	22[e]	281	Progression of NHL
004-020-007[c]	Subdural hematoma	3	920	30		
	Lung hemorrhage	4	1023	2	1028	Progression of NHL
012-036-005[d]	Gastrointestinal hemorrhage	3	49	19	66	Progression of NHL
020-013-384	Gastrointestinal hemorrhage	3	38	15[e]		
		3	50	33[e]		
		4	56	49[e]	NA	
020-014-350[d]	Melena	3	54	13		
	Hemoptysis	3	55	13	57	Progression of NHL
020-028-156	Gastrointestinal hemorrhage	3	43	10	339	Progression of NHL
020-034-376[d]	Hemorrhage	4	35	159	35	Found dead at home. History of antiphospholipid antibody syndrome. No autopsy performed.
020-052-229[d]	Gastrointestinal hemorrhage	4	58	139	63	Progression of NHL

[a] Lowest platelet count within a week of the event.
[b] Patient 002-025-901 developed MDS on Day 418.
[c] Patient 004-020-007 developed MDS on Day 626.
[d] Death within 90 days of bleeding event.
[e] Receiving platelet transfusions.

Eight of the 10 patients had Grade III or IV thrombocytopenia at the time of the bleeding event. Six of the ten patients with Grade III or IV bleeding events died within 90 days after the bleeding event. Four of the 6 patients died within 90 days of study drug administration. The other 2 patients died 15 and 34 months after study drug administration, following a diagnosis of MDS. In all but one case, the Investigator attributed death to progressive disease. Patient 020-034-376 was found dead at home on Day 35. There was no confirmation of bleeding; there was no autopsy. She had a history of antiphospholipid antibody syndrome.

4.3.7 Infections

Infections for all 620 patients were summarized from the preferred COSTART terms. Based on these data, 236 of 620 patients (38%) experienced one or more possible infections. The majority of these were viral (rhinitis, pharyngitis, flu symptoms, or herpes) or other minor infections (infections, increased coughing, etc.). There were 24 of 620 (4%) patients who had pneumonia and 15 of 620 (2%) with sepsis.

Thirty-seven of 620 (6%) patients had 42 serious infections (see Appendix 5 for detailed information). The most common serious infections were bacteremia/septicemia (13) and pneumonia (13), followed by skin infections (4), catheter-related infections (4), bronchitis and cough (2 each), and urinary tract infection, shingles and sore throat (1 each). Six of the 37 patients had Grade III/IV neutropenia at the time of or just prior to the infection. Four of the 6 patients recovered; 2 patients expired within 3 weeks of the infection, both due to progressive disease. An additional 10 patients experienced a serious infection without concomitant neutropenia and died within 90 days of the dosimetric dose. In 7 of the 10 cases, the Investigator attributed the death to progressive disease. The other 3 patients died of respiratory failure due to aspiration pneumonia on study day 35; neutropenic sepsis most likely related to subsequent chemotherapy on study day 59; and septic shock on study day 28. One further patient died >90 days following the dosimetric dose, on study day 168, from sepsis, pneumonia and respiratory failure.

4.3.8 Further Characterization of the Extent of Hematologic Toxicity and Recovery Patterns

During Phase 1 evaluation, myelosuppression was identified as the dose-limiting toxicity of iodine I 131 tositumomab. As a consequence, hematologic toxicity was expected and hematological parameters were to be monitored in all clinical trials of iodine I 131 tositumomab. Protocols typically called for weekly CBC evaluations from Week 3 to at least Week 10 following the dosimetric dose; however, CBC monitoring could be discontinued once stable hematological recovery had been documented to baseline grade (CP-98-020, EAP) or Grade 0 (all other studies).

Patients could be withdrawn from study for reasons including: disease progression, death, withdrawal of consent, or start of additional therapy for NHL. Thus, a number of patients do not have a full characterization of the evolution of their hematological parameters through Week 13, a timepoint at which most would be expected to have recovered from the transient myelosuppression associated with iodine I 131 tositumomab. This may be the result of early recovery or early withdrawal, both instances leading to the suspension of hematological monitoring, per protocol. In addition to patient withdrawal, there were instances where data collection was incomplete.

In an effort to provide the best possible estimate of the extent of hematological toxicities following iodine I 131 tositumomab, Corixa performed additional analyses. These

analyses were performed in order to further characterize the extent of hematologic toxicity and the recovery pattern for the Integrated Safety Population. These analyses included an analysis of hematological toxicity and recovery employing standard methods of censoring (Table 31) as well as a worst-case analysis, assuming where data were not available, that toxicity had occurred, and where recovery was not documented, that recovery had not occurred (Table 32).

4.3.8.1 Analysis of Two Subpopulations with Complete Data

In the standard analysis presented in Section 4.3.8.1 and in Table 31, the data on hematologic recovery was analyzed for the 620 patients that comprise the Integrated Safety Population. Grade III/IV neutropenia, thrombocytopenia, and anemia occurred in 42%, 36%, and 11% of patients, respectively.

To ascertain the effect of missing hematology values in the 620-patient safety population, especially on the duration of the nadir (Weeks 5–9) and time to recovery (prior to Week 13), Corixa performed analyses on two subpopulations of patients with complete data (after consultation with the FDA):

1. 493-patient subpopulation from the 620-patient population with complete hematology data for at least 4 of the 5 weeks between Weeks 5–9 (the time period for the expected occurrence of the hematologic nadir).
2. 418-patient subpopulation from the 493-patient population with complete hematology data for at least 4 of the 5 weeks between Weeks 5–9 and at Week 13 (the time period within which hematologic recovery is typically noted).

For the 493-patient subpopulation, 127 patients were excluded from the 620-patient population for missing data. The reasons for missing data in the 127 patients within this time frame were as follows:

- 19 patients had hematological recovery to baseline grade before Week 9 and no further weekly counts were indicated;
- 63 patients were withdrawn from the study before Week 9 because of progressive disease (n=45), death (n=13), and other reasons (n=5); and
- 45 patients remained on study, but had more than one missing data point during this time period.

For the 418-patient subpopulation, 75 patients were excluded from the 493-patient subpopulation for missing Week 13 data. The reasons for missing data at Week 13 were as follows:

- 27 patients had hematological recovery to baseline grade before Week 13;
- 44 patients were withdrawn from the study before Week 13 because of progressive disease (n=40), death (n=3), and other reasons (n=1); and
- 4 patients remained on study but had missing data for this Week 13 time point.

The hematologic toxicity for the 620-patient population was compared to the toxicity reported for (1) the 493-patient subpopulation with complete Week 5–9 hematology, and (2) the 418-patient subpopulation who had complete Week 5–9 data and Week 13 data (Table 31). Hematologic recovery was analyzed separately for recovery to Grade II and recovery to the patient's baseline grade.

Table 31. Hematology Summary of Integrated Safety Population Compared to the Two Subpopulations

Laboratory Parameter[a]	Endpoint	Integrated Safety Population (N=620)	Subpopulation Week 5–9 Data (N=493)	Subpopulation Week 5–9 and Week 13 Data (N=418)
Platelets	Number of patients	612[b]	493	418
	Median time to nadir (days)	34	34	34
	Median nadir (/mm^3)	62,000	61,000	62,000
	Number (%) Grade III/IV	223 **(36%)**	188 **(38%)**	150 **(36%)**
	Median[c] duration of Grade III/IV (days)	**29**	**29**	**29**
	Number (%) Grade III/IV without recovery[d] to Grade II	32 **(5%)**	18 **(4%)**	10 **(2%)**
	Number (%) Grade III/IV without recovery[d] to baseline grade	79 (13%)	58 (12%)	39 (9%)
	Number (%) Grade IV	98 (16%)	84 (17%)	66 (16%)
	Median[c] duration of Grade IV (days)	29	29	29
ANC	Number of patients	611[b]	493	418
	Median time to nadir (days)	43	43	44
	Median nadir (cells/mm^3)	1,100	1,000	1,100
	Number (%) Grade III/IV	256 **(42%)**	228 **(46%)**	190 **(45%)**
	Median[c] duration of Grade III/IV (days)	**30**	**29**	**30**
	Number (%) Grade III/IV without recovery[d] to Grade II	19 **(3%)**	9 **(2%)**	3 **(1%)**
	Number (%) Grade III/IV without recovery[d] to baseline grade	46 (8%)	31 (6%)	18 (4%)
	Number (%) Grade IV	109 (18%)	98 (20%)	82 (20%)
	Median[c] duration of Grade IV (days)	21	20	21
Hemoglobin	Number of patients	613[b]	493	418
	Median time to nadir (days)	47	48	48
	Median nadir (g/dL)	10.8	10.9	11.0
	Number (%) Grade III/IV	69 **(11%)**	56 **(11%)**	42 **(10%)**
	Median[c] duration of Grade III/IV (days)	**19**	**18**	**18**
	Number (%) Grade III/IV without recovery[d] to Grade II	8 **(1%)**	5 **(1%)**	1 **(<1%)**
	Number (%) Grade III/IV without recovery[d] to baseline grade	24 (4%)	18 (4%)	11 (3%)
	Number (%) Grade IV	13 (2%)	10 (2%)	8 (2%)
	Median[c] duration of Grade IV (days)	15	10	13

[a] Grade III/IV toxicity derived from hematologic parameters.
NCI CTC toxicity grades:
ANC (1000 cells/mm^3): Grade II = 1.0 to <1.5, Grade III = 0.5 to <1.0, Grade IV = <0.5.
Platelets (1000/mm^3): Grade II = 50 to <75, Grade III = 25 to <50, Grade IV = <25.
Hemoglobin (g/dL): Grade II = 8.0 to <10.0, Grade III = 6.5 to <8.0, Grade IV = <6.5.

[b] Seven patients did not have ANC, platelet count, or hemoglobin follow-up; 1 patient did not have ANC or platelet count follow-up; and 1 patient had WBC recovery but no differentials documenting ANC recovery. Of these 9 patients without hematologic follow-up, 4 patients did not receive the therapeutic dose.

[c] Kaplan-Meier estimate.

[d] Recovery can occur at any time point after the Grade III/IV toxicity.

As seen in the bolded values in Table 31, the hematologic profile as defined by the 620 patients is quite similar to the hematologic profile of the 418 patients with hematology data for Weeks 5–9 and at Week 13.

4.3.8.2 Worst-Case Analysis of Hematologic Toxicity

Corixa performed an additional analysis in which patients with incomplete data were arbitrarily assigned a worst-case hematologic outcome (Table 32). To create the worst-case scenario, patients (who for reasons stated above had "incomplete" Week 5–9 data) were assumed to have experienced Grade III/IV toxicity regardless of their hematology values and regardless of their time on-study. These patients were classified as having recovered to Grade II if they had documented Grade 0/I/II hematologic parameters on or after Week 9.

Four patients who did not receive a therapeutic dose and did not have any hematologic follow-up were excluded from the worst-case analyses. Taking a conservative approach, 8 patients who did not receive the radiolabeled portion of the therapeutic dose, but who had hematologic follow-up, were included in the worst-case analyses (2 of the 8 patients had Grade III/IV hematologic toxicity). Thus, a total of 616 patients are included in the worst-case analysis.

4.3.8.2.1 Incidence and Duration of Hematologic Toxicity Based on the Worst-Case Analysis

Table 32 shows the Grade III/IV hematologic toxicity of the Integrated Safety Population under worst-case analysis.

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

Table 32. Grade III/IV Hematologic Toxicity of Integrated Safety Population Under Worst-Case Analysis (N=616)

	ANC Grade III/IV	Platelet Grade III/IV	Hemoglobin Grade III/IV	Any Grade III/IV
Documented Grade III/IV	256 (42%)	223 (36%)	69 (11%)	322 (52%)
Assumed Grade III/IV[a]	94 (15%)	78 (13%)	94 (15%)	80 (13%)
Total	**350 (57%)**	**301 (49%)**	**165 (27%)**	**402 (65%)**

[a] Patients with incomplete Week 5–9 data and no documented Grade III/IV at any time.

Table 33 compares those patients with documented Grade III/IV toxicity to those patients assumed to have had Grade III/IV or had no Grade III/IV toxicity. Patients with assumed Grade III/IV toxicity were generally patients who were withdrawn from study either due to early progressive disease or death, potentially accounting for the higher incidence of

death and termination from study within the first 90 days among those patients assumed to have toxicity (Table 34).

Table 33. Comparison of Safety Endpoints for Documented, Assumed, or No Grade III/IV Hematologic Toxicity

	Documented Grade III/IV (N=322)	Assumed Grade III/IV (N=80)	No Grade III/IV (N=218)	Total (N=620)
Supportive Care	141 (44%)	7 (9%)	13 (6%)	161 (26%)
SAE (any relationship)	85 (26%)	25 (31%)	32 (15%)	142 (23%)
SAE (possibly/probably related)	49 (15%)	6 (8%)	9 (4%)	64 (10%)
Death within 90 Days	27 (8%)	21 (26%)	4 (2%)	52 (8%)
Death within 90 Days – reason other than PD	5 (2%)	2 (3%)	1 (<1%)	8 (1%)
Termination from study within 90 days	85 (26%)	41 (51%)	22 (10%)	144 (23%)

4.3.8.2.2 Recovery after Hematologic Toxicity Based on the Worst-Case Analysis

Based on the assumptions of the worst-case scenario, Table 34 presents the number of patients without documented recovery to Grade II at any time for platelets, ANC, or hemoglobin. Recovery was not documented for 75 patients, including 42 patients with documented Grade III/IV toxicity without documented recovery and 33 patients with no documented Grade III/IV toxicity and less than Week 9 hematologic follow-up.

Table 34. Number and Disposition of Patients Without Documented Recovery of Platelets, ANC, or Hemoglobin

		Patient Disposition after Study Termination				
	Total Number of Patients	Death	Study Termination for PD	Subsequent Therapy	Other	No Therapy[a]
Grade III/IV without documented recovery	42	15	0	26	1[b]	0
No Grade III/IV but incomplete hematologic data[c]	33	13	2	12	1[b]	5
Total: No documented recovery	75	28[d]	2	38	2[b]	5

[a] Patients did not receive the therapeutic dose and had incomplete hematologic data for recovery.

[b] One patient has an ongoing CR with no recovery to Grade II at Year 2; one patient was lost to follow-up and had incomplete hematologic data.

[c] Patients had less than Week 9 hematology.

[d] Causes of death (23 patients with progressive NHL, 1 patient (001-008-002) from gastrointestinal hemorrhage on study day 4 prior to the therapeutic dose, 1 patient (020-065-233) from septic shock on study day 32, 1 patient (012-037-005) from respiratory failure on study day 35, 1 patient (020-034-095) from renal failure on study day 54, and 1 patient (020-034-376) from unknown causes on study day 35.

The 42 patients with Grade III/IV toxicity without documented recovery had additional circumstances that were described in Section 4.3.3.1.

The remaining 33 were patients who had incomplete hematologic data (<9 weeks follow-up) and no Grade III/IV toxicity. The reasons for incomplete data are described below:

- 31 of the 33 patients were terminated from the study prior to Week 9 (see Table 34). This included 5 patients not receiving the therapeutic dose, 12 patients who initiated subsequent therapy between 17 and 77 days after the dosimetric dose, and 13 patients who died between 10 and 70 days after the dosimetric dose.
- 1 patient had WBC recovery, but differentials were not obtained to document ANC recovery.
- 1 patient was lost to follow-up.

In summary, assuming a "worst-case" scenario, there were a total of 75 of 616 patients (12%) for whom there was no documented recovery to ≤ Grade II for platelets, ANC and/or hemoglobin. This includes 42 patients (7%) with Grade III/IV hematologic toxicity and no documented recovery to Grade II and 33 patients (5%) with insufficient data to assess their maximum hematologic toxicity or recovery. The remaining 541 patients (88%) had documented recovery for platelets, ANC and hemoglobin.

4.3.9 Myelodysplastic Syndromes / Acute Myelogenous Leukemia (MDS/AML)

A long-term safety concern associated with radioimmunotherapy, as well as with therapy with several classes of chemotherapy, is myelodysplasia and associated acute myelogenous leukemia. Patients treated with iodine I 131 tositumomab were followed for the development of MDS/AML from study entry to the data cutoff date for each study or until death. Information was collected semiannually.

Data from the EAP are not as useful in estimating the incidence of MDS/AML, due to the shorter follow-up in that patient population (median follow-up equals 1.5 years). However, these data do provide some assurance that there is no marked increase in MDS/AML during the 18 months post treatment with iodine I 131 tositumomab. Only 1 patient of the 387 patients in the EAP study was noted to have developed MDS/AML. In an independent review of pathology material, this patient had evidence of pre-existing MDS at study entry.

The 233 patients from the other studies had a median follow-up of 2.4 years. In this population, 18 patients developed MDS/AML with a crude incidence of MDS/AML of 7.7% (95% CI: 4.6%–11.9%) and an annualized incidence of 3.0%/year (95% CI: 1.9%/yr–4.8%/yr). Table 35 compares the characteristics of patients who had MDS/AML with characteristics of those who did not have MDS/AML.

Table 35. MDS/AML Summary: Integrated Safety Population

	Non-EAP Patients (N=233)		All Patients (N=620)	
	MDS/AML (N=18)	**No MDS/AML (N=215)**	**MDS/AML (N=19)**	**No MDS/AML (N=601)**
Platelet count < 150,000/mm^3	61%	29%	63%	25%
Median number of prior chemotherapy regimens (range)	4 (2–8)	3 (1–13)	4 (2–8)	2 (1–13)
Number (%) of patients receiving at least one chemotherapy regimen containing an alkylating agent	18 (100%)	212/215 (99%)	NA	NA
Prior radiotherapy	44%	28%	42%	24%
Median follow-up (months)	33.0 (8.2–92.8)	28.2 (0.2–99.0)	32.2 (5.6–92.8)	18.3 (0.1–99.0)

NA = Data not available for patients enrolled on EAP.

These results suggest that patients who developed MDS were more likely to have received more prior chemotherapy regimens and prior radiotherapy and to have platelet counts less than 150,000/mm^3.

Table 36 summarizes the incidence of MDS/AML by study.

Table 36. Annualized Incidence of Investigator-Reported Cases of MDS/AML in Patients Treated with Iodine I 131 Tositumomab: Integrated Safety Population

Group	N	No. MDS/AML	Crude Incidence (95% CI)	Post-Iodine I 131 Tositumomab Person-years	Median Follow-Up (yrs) (range)	Annualized Incidence	95% CI for Annualized Incidence
RIT-I-000	22	5	22.7% (7.8%–45.3%)	94	3.8 (0.2–8.2)	5.3%/yr	(2.2%–12.8%/yr)
RIT-II-001	47	5	10.6% (3.5%–23.1%)	144	2.8 (0.0–5.5)	3.5%/yr	(1.4%–8.3%/yr)
RIT-II-002	61	3	4.9% (1.0%–13.7%)	136	2.1 (0.2–4.9)	2.2%/yr	(0.7%–6.9%/yr)
RIT-II-004	59	4	6.8% (1.9%–16.5%)	135	2.6 (0.0–5.0)	3.0%/yr	(1.1%–7.9%/yr)
Other Studies	4	0	0.0% (0.0%–60.2%)	9	2.3 (1.2–3.6)	0.0%/yr	(0.0%–32.0%/yr)
CP-97-012	40	1	2.5% (0.1%–13.2%)	75	2.1 (0.1–3.3)	1.3%/yr	(0.2%–9.4%/yr)
TOTAL without EAP	**233**	**18**	**7.7% (4.6%–11.9%)**	**593**	**2.4 (0.0–8.2)**	**3.0%/yr**	**(1.9%–4.8%/yr)**
TOTAL without EAP (adjusted for independent review)	**229**	**13**	**5.7% (3.1%–9.5%)**	**591**	**2.6 (0.0–8.2)**	**2.2%/yr**	**(1.3%–3.8%/yr).**
Expanded Access	387	1	0.3% (0.0%–1.4%)	521	1.5 (0.0–2.9)	0.2%/yr	(0.0%–1.4%/yr)
Total with EAP	**620**	**19**	**3.1% (1.9%–4.7%)**	**1115**	**1.5 (0.0–8.2)**	**1.7%/yr**	**(1.1%–2.7%/yr)**

Therapeutic histories of the 19 patients with a diagnosis of MDS/AML are included in Appendix 6 and Appendix 7. All patients had been previously treated with multiple regimens that included repetitive courses of mustard-like alkylating agents (chlorambucil, melphalan, cyclophosphamide, nitrogen mustard), nitrosoureas, cisplatin, procarbazine, and inhibitors of topoisomerase II (etoposide, doxorubicin, mitoxantrone), and antimetabolites (fludarabine, ara-C, methotrexate). In addition, 9 of the 19 patients had received external beam radiotherapy involving major marrow-producing sites.

Dr. John Bennett performed a centralized, independent, masked review of the 16 available cases of MDS/AML. He determined that, in retrospect, 5 of the 16 patients (000-002-055, 001-003-002, 002-025-901, 004-020-007, and 020-038-022) had evidence of MDS prior to receiving iodine I 131 tositumomab, and that 1 patient (004-016-003) had no morphological evidence of MDS/AML either before or after treatment with iodine I 131 tositumomab.

Excluding the EAP and assuming central review confirms the other case, based on the masked independent review, 13/229 (5.7%, 95% CI: 3.1%–9.5%) patients developed MDS/AML after receiving iodine I 131 tositumomab therapy. This analysis yields an annualized incidence of MDS/AML of 2.2%/yr (95% CI: 1.3%/yr–3.8%/yr).

With additional safety follow-up through 13 September 2002, 5 additional patients have been reported to have developed MDS/AML.

With these 5 additional patients a total of 24 of the 620 (3.9%) patients have developed MDS/AML with an annualized incidence of 1.8%/yr. The 5 patients have not yet undergone central pathology review. Assuming that the central review confirms MDS/AML diagnosis, 18 of 620 (2.9%) patients have developed MDS/AML with an annualized incidence of 1.3%/yr.

Results from another study (RIT-II-003) are relevant when characterizing the possible risk of MDS/AML post iodine I 131 tositumomab treatment. Because study RIT-II-003 was in previously untreated patients, it was not included as a supportive study or detailed in this briefing document. However the results are relevant to overall interpretations of the risk of MDS/AML. Study RIT-II-003 was a Phase 2, single-arm, open-label study of Iodine I 131 tositumomab treatment for patients with previously untreated, advanced-stage (Stage III/IV), low-grade NHL. With a median follow-up of 32 months (range: 8–54 months), none of the 76 patients treated in the study have developed MDS or AML. The annualized incidence for myelodysplasia/AML in this study is 0.0%/year (95% CI: 0.0%–1.46%/year). Serial cytogenetic analyses of bone marrow aspirates were performed to assess the long-term effects of iodine I 131 tositumomab treatment on hematopoiesis (i.e., development of clonal chromosomal abnormalities) for 53 of the 76 (70%) patients. Chromosomal abnormalities were classified as being either “clonal” or “nonclonal” abnormalities using standard criteria. A chromosomal loss occurring in at least three cells or a gain or structural rearrangement in two cells was considered to be a clonal abnormality. None of these patients demonstrated any persistent or consistent abnormalities that might be ascribed to therapy. Although, ultimately, a long follow-up period will be required to assess the overall risk of MDS and secondary leukemia following iodine I 131 tositumomab treatment, these data do not suggest a substantial risk for MDS/AML in patients treated with iodine I 131 tositumomab who have not been treated with multiple prior marrow toxic therapies.

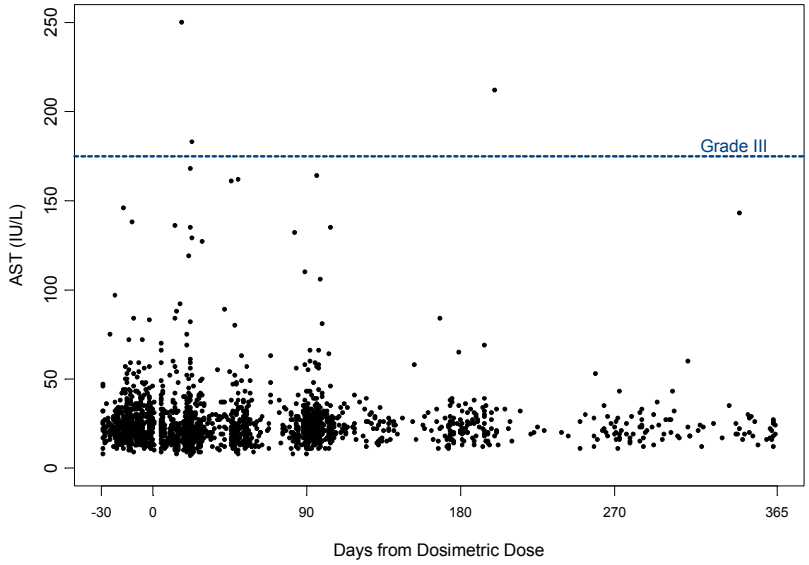
Extensive chemotherapy regimens and prior external beam radiotherapy treatments to marrow-producing regions have been well documented as risk factors for the development of MDS/AML. Patients who developed MDS/AML after iodine I 131 tositumomab treatment in these studies were typical of patients developing treatment-

related secondary MDS/AML. They had cytogenetic abnormalities (particularly deletions of all or parts of chromosomes 5 and 7). It is not possible, with the experience to date, to determine the extent to which iodine I 131 tositumomab may contribute to the incidence of myelodysplasia and acute leukemia in this patient population.

4.3.10 Liver and Renal Function Abnormalities

Serum chemistry data on AST, total bilirubin, and creatinine were collected in all studies except the single-patient studies. Time plots of the serum chemistry data for AST, total bilirubin, and creatinine are presented in Figure 30, Figure 31, and Figure 32, respectively. Figure 30 and Figure 31 demonstrate less than 1% of patients with hepatic toxicity, and Figure 32 demonstrates minimal apparent renal toxicity through the first 12 months following therapy.

Figure 30. Integrated Safety Population: AST (IU/L) Over Time[a]



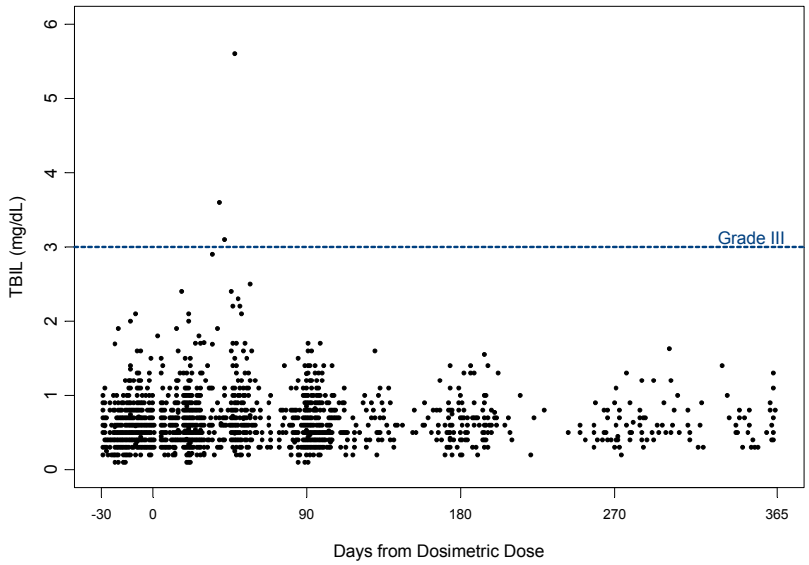
[a] The plot excludes three outlying values (see discussion).

Five patients experienced 6 Grade III AST values (3 of which are not included in Figure 30).

- Patient 001-008-002 had an AST of 8200 IU/L* on Day 3 related to disseminated intravascular coagulopathy and multi-organ failure. The patient died on Day 4 without receiving the therapeutic dose.
- Patient 002-011-020 had an AST of 350* IU/L on Day –6 and an AST of 695* IU/L on Day 6 related to reactivation of hepatitis B at study entry.
- Patient 002-011-003 had an unexplained, isolated AST of 212 IU/L on Day 200.
- Patient 020-054-214 had an AST of 183 IU/L on Day 23 and was withdrawn from study on Day 36 for progression of NHL in the liver.
- Patient 020-059-149 experienced an unexplained, isolated AST of 250 IU/L on Day 17.

* data not shown in Figure 30

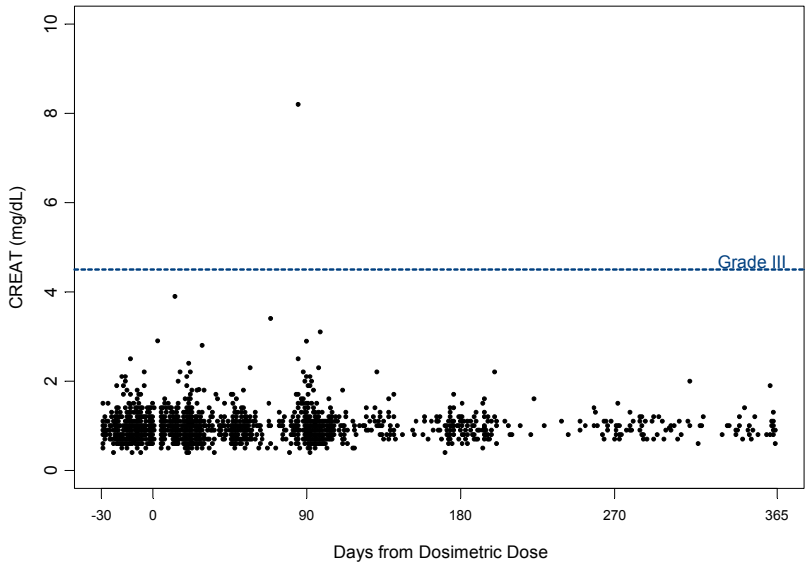
Figure 31. Integrated Safety Population: Total Bilirubin (mg/dL) over Time



One patient had 3 Grade III/IV bilirubin values (Figure 31).

Patient 000-002-046 had total bilirubin values of 3.1, 3.6 and 5.6 mg/dL on Days 39, 42, and 49, respectively, related to hemolytic anemia which developed on Day 39 and resolved by Day 77, requiring 6 transfusions of packed red blood cells (PRBC).

Figure 32. Integrated Safety Population: Serum Creatinine (mg/dL) over Time



One patient had a Grade III/IV creatinine value (Figure 32).

Patient 004-029-001 had a serum creatinine of 8.2 mg/dL on Day 85 secondary to bilateral hydronephrosis from progressive NHL.

4.3.11 Thyroid Function

Prior to 2001, TSH laboratory data were collected every 3 to 6 months for the first 2 years for all studies, except if patients progressed or died. Following progression and after 2 years on study, only information on thyroid medication was collected. In 2001, all protocols were amended to include semi-annual follow-up for TSH assessment until death for all patients.

4.3.11.1 Baseline Hypothyroidism

Ninety-six percent (598 of 620) of patients had TSH measured at baseline. Forty-eight of 598 (8%) patients had an elevated TSH prior to the therapeutic dose, and an additional 23 (3%) patients had a history of thyroid medication. Thus, 71 of 620 (11%) patients had evidence of hypothyroidism prior to receiving their therapeutic dose. These patients were excluded from analyses of post-treatment hypothyroidism.

4.3.11.2 Description of Available Data on Thyroid Assessment

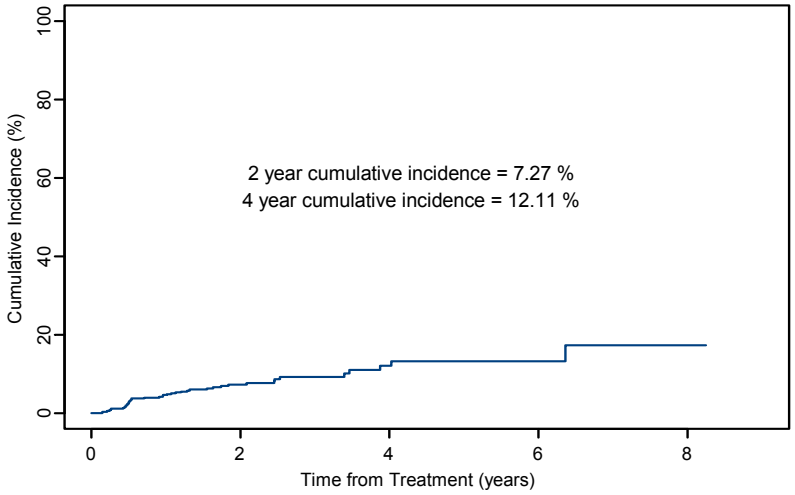
Both TSH laboratory data and thyroid medication data were collected in all studies. A conservative analysis was performed and a patient was classified at risk of hypothyroidism or as developing hypothyroidism if he/she developed an elevated TSH or initiated thyroid supplementation (with or without an elevated TSH).

4.3.11.3 Hypothyroidism Following Iodine I 131 Tositumomab

Follow-up TSH levels were obtained for 362 evaluable patients; 34 (9%) of these developed an elevated TSH. The median elevated TSH level was 6.09 µU/mL (range: 4.22–25.58 µU/mL). The textbook normal range for TSH is 0.5–5.0 µU/mL. An additional 8 patients had thyroid supplementation begun without documentation of elevated TSH level. Twenty-five of 505 (5%) patients with thyroid supplementation follow-up data had thyroid supplementation initiated. The median study day for the initiation of thyroid medication was 196 (range: 76–1415 days). Overall, 42 of 516 (8%) evaluable patients developed either an elevated TSH or initiated thyroid supplementation following iodine I 131 tositumomab.

The cumulative incidence for decrease in thyroid function (defined as either developing an elevated TSH or initiating thyroid medication) is presented in Figure 33. The 2-year and 4-year cumulative incidence rates (patients at risk) for decrease in thyroid function were 7.3% (170) and 12.1% (34), respectively.

Figure 33. Cumulative Incidence of Elevated TSH or Thyroid Supplementation



4.3.12 Detection of Human Anti-Murine Antibody (HAMA)

HAMA laboratory data were generally collected on all studies at baseline, prior to administration of the therapeutic dose, at Weeks 7 and 13 and at Month 6. In 2001 all protocols were amended to included semi-annual follow-up for HAMA assessment for two years following the dosimetric dose.

Serum samples were analyzed for HAMA using the individual assays of the clinical site(s) for studies RIT-I-000 and RIT-II-001. Serum samples from studies RIT-II-002 and RIT-II-004 were analyzed for HAMA by the clinical site and by the central reference laboratory using the ImmuSTRIP® ELISA for HAMA. Therapy was initiated based on the site assay and not the centralized assay. Serum samples collected in study CP-98-020 were analyzed for HAMA by the central laboratory; decisions for therapy were based on these results. Serum samples collected in study CP-97-012 were analyzed for HAMA by the clinical site only.

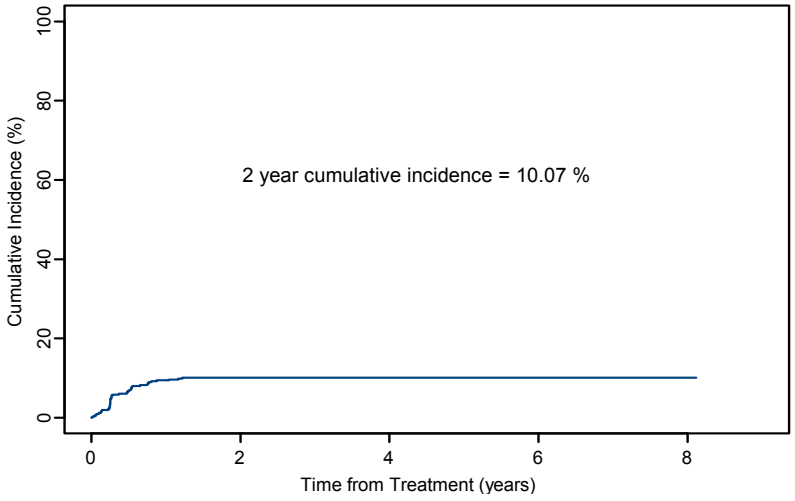
The concordance between the site and central HAMA assays was 95.6% with 417 of 436 blood samples assayed by both the site and central HAMA assays in agreement. The data were pooled and patients were classified as HAMA positive if they were positive on either the site or central assay.

4.3.12.1 Conversion to HAMA Positivity

A total of 51 of the 515 patients (10%) with a negative baseline HAMA assay and follow-up HAMA assay converted to HAMA positivity. The median time to a positive HAMA for patients who seroconverted was 96 days (range: 5–426 days). Forty-one of 51 (80%) patients converted to HAMA positivity on or prior to their Month 6 evaluation, and 10 of the 51 (20%) converted to HAMA positivity after the Month 6 evaluation. Only 3 of the 84 (4%) patients who were HAMA negative prior to 12 months became HAMA positive. No patient converted to HAMA positivity after 15 months.

The cumulative incidence for conversion to a positive HAMA is presented in Figure 34. The 1-, 2-, and 4-year cumulative incidences of HAMA positivity were 9.4%, 10.1%, and 10.1%, respectively. There was an apparent plateau in the cumulative incidence curve between 1 and 2 years.

Figure 34. Cumulative Incidence for Conversion to a Positive HAMA Result, Site or Central HAMA Assay: Integrated Safety Population (N=620)



4.3.13 Non-Hematologic Malignancies

A total of 32 non-hematologic malignancies were reported by 29 patients and are summarized in Table 37.

Table 37. Non-Hematologic Malignancies Reported: Integrated Safety Population (N=620)

Type of Malignancy		Number of Patients
Total patients with any malignancy		29 (5%)
Skin cancer	Basal cell carcinoma	6 (1%)
	Squamous cell	4 (1%)
	Unspecified	3 (<1%)
Lung cancer	Non small cell lung cancer	2 (<1%)
	Small cell carcinoma	1 (<1%)
Colorectal cancer	Colon	1 (<1%)
	Rectal (squamous)	1 (<1%)
Bladder cancer		2 (<1%)
Breast cancer		4 (1%)
Gastric cancer		1 (<1%)
Head and neck cancer	Laryngeal	1 (<1%)
	Throat	1 (<1%)
	Mucoepidermoid	2 (<1%)
Other (site unspecified)	Squamous cell carcinoma	2 (<1%)
	Omental carcinoma (ovarian/peritoneal)	1 (<1%)

Less than 5% of the patients experienced a second malignancy after drug administration. Half of the malignancies were skin cancers, either basal cell, squamous cell, or unspecified.

4.3.14 Deaths

No deaths occurred during or on the day of infusion of either tositumomab or iodine I 131 tositumomab.

Two hundred fifty-four of 620 (41%) patients expired as of the data cutoff dates. The median time from the dosimetric dose to death was 38.7 months with a 95% C.I. of 33.7–46.6 months. Death was most commonly attributed by the Investigator to a single cause, lymphoma progression, in 192 (76%) of the 254 patients. In the remaining 62 (24%) patients, 30 patients had deaths over 180 days from study drug following disease progression with or without additional NHL therapy; 7 patients died from complications not related to lymphoma (suicide, secondary malignancies, or surgery); 14 patients died with MDS/AML; and 12 patients died due to a cause not related to disease progression within 180 days of study drug. Of these 12 patients, 8 deaths occurred within 90 days of study drug and 4 deaths occurred between 90 and 180 days after study drug. The Investigator classified 3 of the 12 deaths as possibly related to study drug and 9 of the 12 deaths as not related to study drug. In a conservative analysis in which all 12 deaths are considered possibly related to study drug, study-related deaths were estimated at 1.9% (12 out of 620 patients). If one considers all MDS-related deaths as also possibly related to study drug then this increases the study-related deaths to 4.2% (26 out of 620 patients).

5. SUMMARY OF DOSIMETRY AND PHARMACOKINETIC RESULTS

5.1 DOSIMETRY

5.1.1 Tumor Dosimetry

Tumor doses were calculated based on regions of interest (ROIs) drawn on anterior and posterior gamma camera images over the tumors. Corrections for attenuation and background were performed as for normal organ dosimetry. Tumor volumes were calculated by outlining individual tumors slice-by-slice on CT scans. For tumors with estimated masses between 10 and 100 g, tumor dosimetry was performed using the table of absorbed fractions for spheres. For tumors greater than 100 g, a splenic mass adjusted model was used. The tumor dose represents the nonpenetrating (beta) and penetrating (gamma) doses from iodine 131 within the tumor plus the expected penetrating dose from the total body.

The mean tumor dose was 895.3 cGy/75 cGy total body dose (n=91). The mean tumor doses were relatively constant across study, gender, grade, patient weight, spleen size, bone marrow involvement, HAMA status or response to therapy. The only statistically significant difference was noted in patients with bulky disease (mean tumor dose = 762.4 cGy/75 cGy TBD) versus patients without bulky disease (mean tumor dose = 967.3 cGy/75 cGy TBD).

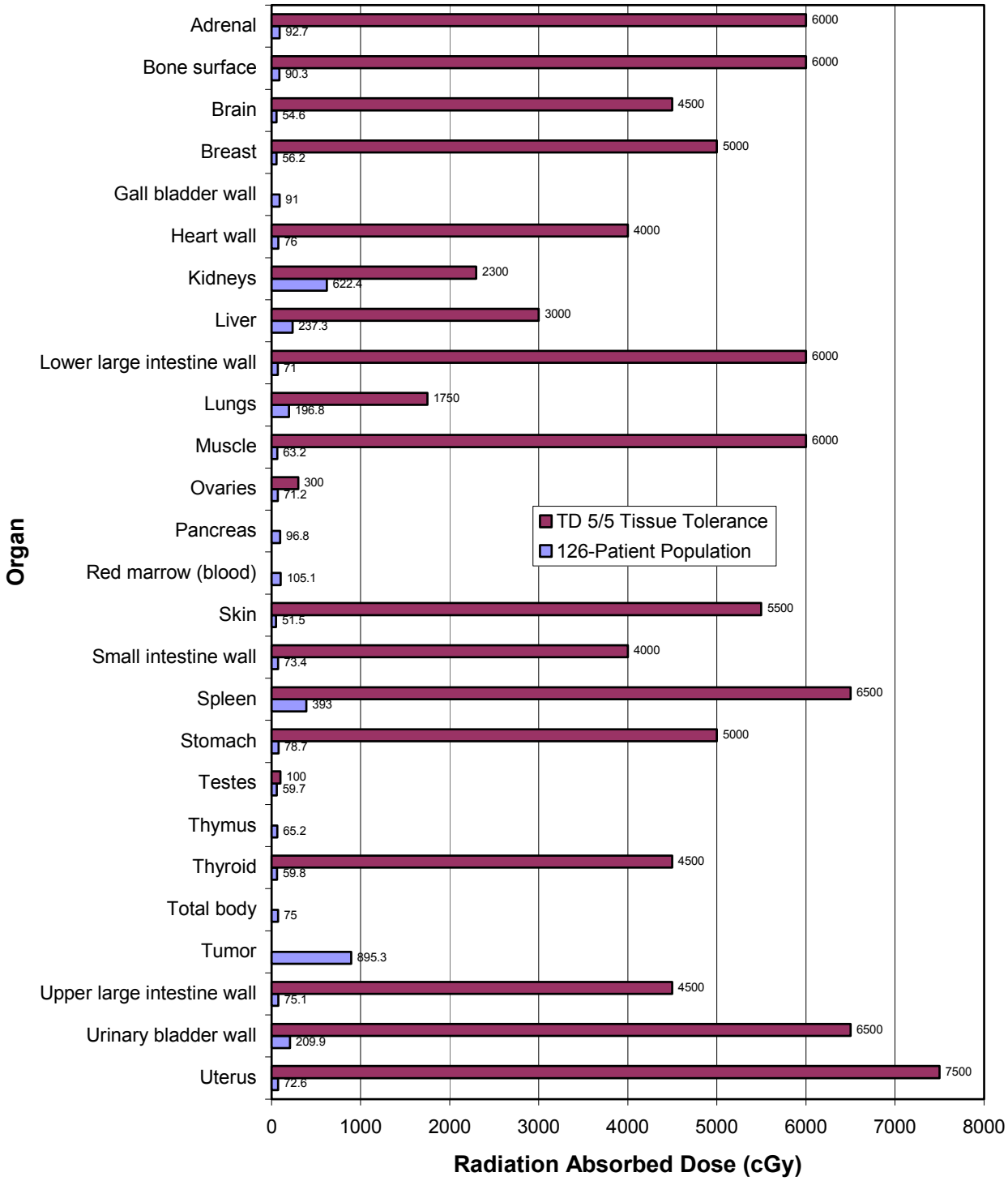
5.1.2 Organ Dosimetry

Organ dosimetry was performed after 126 infusions in patients based on ROI counts obtained daily after the dosimetric dose from the kidneys, liver, lungs, and spleen. Counts from blood samples were used to estimate red marrow absorbed dose; urinary bladder and remainder of the body were additional source organs. Mean radiation-absorbed doses (cGy) from iodine I 131 tositumomab to all organs and total body for the 126 patients are shown in Figure 35. In addition, the TD 5/5 tissue tolerance dose (the 5% probability of complication within 5 years after treatment) as determined for

conventional external beam fractionation are shown for comparison.[65] Although radiation from external and internal sources is not directly comparable, the tissue tolerances derived from experience with external beam radiotherapy represent the best available information.

Additional organ doses were calculated for a subset of 10 patients with increased thyroid, stomach, and/or intestinal targeting. Organ doses were based on using kidneys, liver, lungs, spleen, urinary bladder, heart, lower and upper large intestine, small intestine, stomach, testes, thyroid, and red marrow as source organs. For these ten selected patients mean organ doses (cGy/75 cGy TBD) were 1044 for thyroid, 406 for upper large intestine wall, 393 for lower large intestine wall, 365 for heart wall, 225 for red marrow based on humerus ROI, 250 for testes, 151 for stomach, and 72 for small intestine wall.

Figure 35. Mean Radiation Absorbed Dose (cGy) for the 126-Patient Population Compared to the Tolerance of Normal Tissues to External Beam Radiation



5.2 PHARMACOKINETIC ANALYSIS

Systemic pharmacokinetics of iodine I 131 tositumomab were determined following the administration of the dosimetric dose. Counts of iodine 131 from whole blood samples were assayed and data were well fit by a two-compartment model.

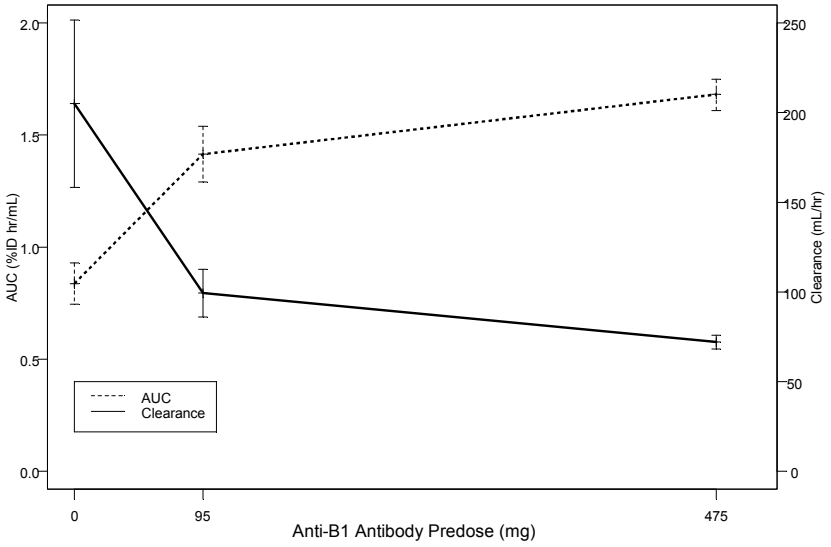
As part of the Phase 1/2 Study RIT-I-000 varying doses (0, 95, and 475 mg) of unlabeled tositumomab were administered prior to the iodine I 131 tositumomab administration. As anticipated from the preclinical models, protein dose dependent pharmacokinetics were observed and a pretreatment with the unlabeled tositumomab reduced the clearance rate of iodine I 131 tositumomab causing a longer terminal half-life ($t_{1/2}\beta$) and a significantly larger AUC (see Table 38 and Figure 36).

Table 38. Systemic Pharmacokinetics of Iodine I 131 Tositumomab Following a Predose of Unlabeled Tositumomab

	CL (mL/hr)	AUC (%ID hr/mL)	Cmax (%ID/g)	Vd_{ss} (mL)	$t_{1/2}\alpha$ (hr)	$t_{1/2}\beta$ (hr)
0 mg (n=24)						
Mean	205.04	0.838	0.0164	13026	6.151	63.16
SD	228.66	0.453	0.0046	12324	5.703	51.50
95 mg (n=35)						
Mean	99.38	1.415	0.0190	7743	6.005	72.63
SD	78.39	0.731	0.0042	4254	6.516	41.28
475 mg (n=102)						
Mean	72.11	1.682	0.0194	7076	6.743	84.47
SD	39.00	0.737	0.0041	2163	6.776	52.89

CL = Clearance; AUC = Area under the curve; Cmax = Maximum concentration;
Vd_{ss} = Volume of distribution at steady state; $t_{1/2}\alpha$ = Initial half-life; $t_{1/2}\beta$ = Terminal half-life.

Figure 36. Systemic Pharmacokinetics of Iodine I 131 Tositumomab Following 0, 95, and 475 mg Predose of Unlabeled Tositumomab



Following study RIT-I-000 all patients received 450 mg of tositumomab prior to the administration of iodine I 131 tositumomab.

As would be expected when a fixed total protein dose of 485 mg tositumomab and a fixed radioactivity of 5 mCi iodine I 131 tositumomab were administered to all patients, there were effects of blood pool volume on some of the pharmacokinetic parameters.

For example, patients with larger weights and patients with larger body surface areas had on average a more rapid clearance, lower maximum concentration, and larger volume of distribution at steady state.

Several readily identifiable disease-related parameters affected systemic pharmacokinetics. There was a significantly lower AUC and shorter terminal half-life in patients with either high tumor burden (>500 g), splenomegaly (spleen mass > 400 g), or bone marrow involvement as shown Table 39.

Table 39. Blood Pharmacokinetics by Disease Characteristics Related to the B-Cell Population (N=110)

	Median AUC (%ID hr/mL)	Median Cmax (%ID/mL)	Median $t_{1/2}\beta$ (hr)
Tumor burden ≤ 500 g (n=76)	1.66	0.0203	68.6
Tumor burden > 500 g (n=34)	1.15	0.0178	60.6
P-value[a]	<0.0001	0.0012	0.0011
Spleen mass ≤ 400 g (n=55)	1.70	0.0210	69.3
Spleen mass > 400 g (n=38)	1.19	0.0174	61.7
P-value[a]	<0.0001	0.0001	0.0004
No bone marrow involvement (n=54)	1.67	0.0190	73.5
Bone marrow involvement (n=55)	1.26	0.0188	61.4
P-value[a]	<0.0001	0.0839	<0.0001

[a] Tests based on one-way ANOVA on log transformed values.

5.3 URINARY EXCRETION OF IODINE 131 ACTIVITY

The route of excretion of iodine 131 was renal. Complete urine was collected following 49 dosimetric doses. Samples were collected and counted for the following intervals: 0–12 hours, 12–24 hours, 24–48 hours, 48–72 hours, 72–96 hours, and 96–120 hours. In the first 120 hours following the dosimetric dose, the whole body clearance of the iodine 131 was 67% ± 13% of the injected dose. The percent of the injected dose collected in the urine was 65% ± 13%. The percent of total body excretion that was captured in the urine over the 5-day time period was 98% ± 15%.

5.4 RADIATION DOSES TO INDIVIDUALS EXPOSED TO NHL PATIENTS RECEIVING RADIOIMMUNOTHERAPY

Recently, the Nuclear Regulatory Commission (NRC) and most state agencies have implemented new regulations regarding the release of patients who have been administered radioactive materials in various forms. The regulations allow the release of a patient who has received radioactive material if the maximum radiation dose to any other individual exposed to this patient is not likely to exceed 500 mrem. Based on these regulations, patient-specific calculations have indicated that 99% of patients treated with iodine I 131 tositumomab can be released the day of treatment without excess exposure to caregivers or family members.[66,67]

5.5 RELEASE OF PATIENTS AFTER TREATMENT

Based on these regulations from the NRC, a methodology was developed for determining when a patient could be released from the hospital following iodine I 131 tositumomab therapy. Dosimetry data were analyzed retrospectively from 157 administrations to 139 patients.[67] Based on current regulatory guidelines for release of patients, all patients were determined to be releasable on the day of treatment by comparing the dose rate at 1 m to a predetermined maximum releasable dose rate.

5.5.1 Exposure to Family Members

Although the NRC has provided patient release criteria, guidance is limited on instructions to patients on how to keep the radiation dose to others as low as is reasonably achievable. Therefore, guidelines were developed using a patient-specific calculation based on the measured total-body residence time and dose rate to limit exposure of others. These guidelines include restrictions on how long a patient should sleep alone, wait before returning to work or using public transportation, and avoid contact with infants/young children and pregnant women.

The appropriateness of the guidelines was verified by monitoring 26 family members exposed to 22 patients for periods ranging from 2 to 17 days after administration.[66] The administered dosages for the patients ranged from 25 to 129 mCi of iodine I 131 tositumomab therapy. The radiation exposure to caregivers ranged from 17 to 409 mrem. These radiation doses are below the 500-mrem limit recommended by the NRC.

6. JUSTIFICATION FOR ACCELERATED APPROVAL

The Code of Federal Regulations (21 CFR 601) states that biological products that have been studied for safety and effectiveness in the treatment of serious or life-threatening illnesses may receive marketing approval if they provide the ability to treat patients unresponsive to, or intolerant of available therapy, or if there is an improved response over available therapy. The regulations further state that such approval may be granted "on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely…to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."

Corixa believes that the data presented in this document and the underlying Biological Licensing Application provide ample, robust, clinical evidence that patients unresponsive to or intolerant of available therapy derive significant therapeutic benefit from Bexxar therapy. The data supporting accelerated approval exceed the usual standard (i.e., demonstration of response and adequate safety) and address all the requirements:

1. **Adequate and well controlled pivotal trial (study RIT-II-004):** Bexxar therapy resulted in patients having significantly longer durations of response when compared to the durations of the patient's previous response to chemotherapy ($p<0.001$). Similar results were achieved in 4 supportive trials.
2. **Effect on a surrogate endpoint:** Bexxar therapy induced a substantial number of durable responses (TTP of 1 year or more) in patients with relapsed or refractory low-grade or transformed low-grade NHL. Long-term durable responses were demonstrated in the pivotal trial and in each of 4 additional supportive trials. Long-term durable responses produce a meaningful clinical

benefit to this relapsed/refractory patient population whereby a single treatment lasting 1–2 weeks gives long-term progression-free survival for up to 8 years without the need for further therapy.

3. **Meaningful benefit over existing treatments:** Treatment with Bexxar has been shown to provide (a) an improved response (measured in duration of response) when compared to the patient's immediate prior therapy; (b) an improved response (measured in the incidence of durable responders with demonstrably longer durations of response) compared to data reported for Zevalin or Rituxan; and (c) a better defined benefit (based on substantially more data) in patients with transformed low-grade NHL than reported for Zevalin.

No other single treatment to date has been shown to induce durable responses of greater than several years in a significant percentage of patients with relapsed or refractory low-grade non-Hodgkin's lymphoma, with or without transformation.

Approval under these rules is subject to the requirement that additional studies be undertaken to verify and describe the clinical benefit. Corixa Corporation has committed to conduct additional trials to verify the apparent clinical benefit of this therapy.

The justification for accelerated approval is further elaborated below.

6.1 THE PIVOTAL TRIAL WAS ADEQUATE, WELL CONTROLLED, AND SUPPORTIVE OF ACCELERATED APPROVAL

The primary efficacy endpoint in the pivotal trial was the MIRROR Panel–assessed comparison of the number of patients who had a longer duration of response (i.e., more than 30 days longer) following Bexxar therapy compared to the number of patients who had a longer duration of response (i.e., more than 30 days longer) after their last qualifying chemotherapy (LQC). This study design (patient-as-own-control) was discussed with FDA and agreed upon as the pivotal trial design. Using the patient's LQC as the internal control and comparing the associated results to those with subsequent treatment with iodine I 131 tositumomab therapy is informative in this refractory, late-stage patient population.

The analysis of this study concluded that the number of patients with longer duration of response following Bexxar therapy was significantly greater ($p<0.001$) than the number of patients who had a longer duration of response from their last qualifying chemotherapy. A similar analysis was performed for studies CP-97-012 (Figure 15), RIT-II-002 (Figure 14), RIT-I-000 (Figure 16) and RIT-II-001 (Figure 17), all demonstrated consistent results with a number of patients having longer responses to Bexxar compared to their last therapy.

Planned analyses of secondary endpoints included a comparison of response rates and median duration of response observed after iodine I 131 tositumomab therapy to those observed after treatment with the last qualifying chemotherapy. The response rate to the last qualifying chemotherapy was 12%, confirming the late-stage, refractory nature of this patient population. In contrast, the response rate to subsequent Bexxar therapy was 47% ($p<0.001$). In addition, the median duration for response was 124 days after the last qualifying chemotherapy compared to 355 days after Bexxar therapy ($p<0.001$). Seven of the 60 (12%) patients are still in complete response with censored times to progression ranging from 40.9+ months to 48.5+ months.

6.2 BEXXAR THERAPY SHOWS A SIGNIFICANT BENEFIT IN DURABLE RESPONSES

Iodine I 131 tositumomab positively affected duration of response in the pivotal study and all other supportive studies. This suggests that the therapy will provide a meaningful clinical benefit to patients with low-grade lymphoma. The results obtained meet the requirements of the regulations. The results also exceed the usual standard (response rate only) that has been used for regulatory approval of other drugs used in refractory disease settings. Iodine I 131 tositumomab therapy has shown a significant therapeutic advantage over existing therapies by producing substantial numbers of durable responses in patients with relapsed or refractory low-grade or transformed low-grade NHL.

6.2.1 Durable Responses

Corixa believes that the significant number of long-term durable responders demonstrates that Bexxar provides a meaningful therapeutic benefit to patients with late-stage, relapsed, and refractory low-grade non-Hodgkin's lymphoma.

Seventy-eight patients who met this definition were identified in the Integrated Efficacy Population of 250 patients.

A summary of results demonstrating consistency over multiple studies is presented in Table 40 and Figure 37, respectively.

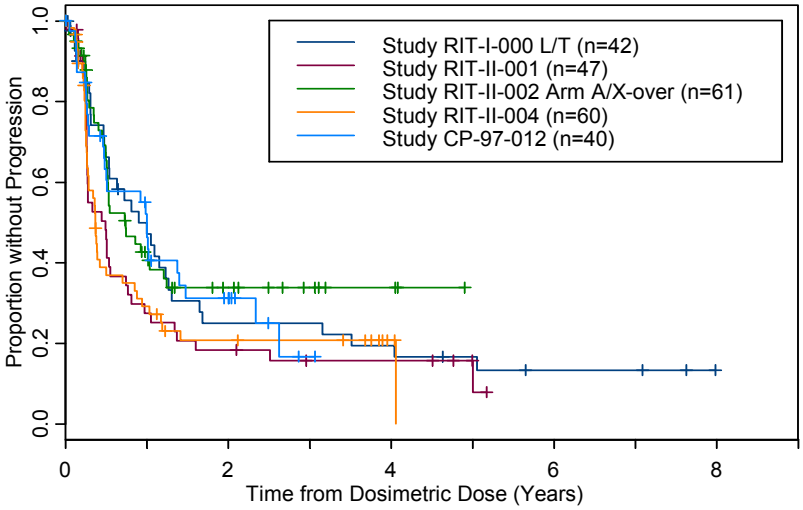
Table 40. Summary of Durable Responses Observed in Pivotal Study and Supporting Studies

Study Number	Durable Responders[a]	
	Number of Patients (%)	Median TTP (range) (months)
RIT-II-004 (N=60)	15/60 (25%)	48.7 (12.4 – 48.7)
RIT-II-002 (N=61)	20/61 (33%)	NR (12.1 – 58.9+)
CP-97-012 (N=40)	17/40 (43%)	31.5 (12.0 – 36.7+)
RIT-I-000 (N=42)	16/42 (38%)	40.0 (13.1 – 95.8+)
RIT-II-001 (N=47)	10/47 (21%)	60.1 (12.6 – 62.1+)

[a] Durable response was defined as patients with a TTP ≥ 1 year. All patients with a TTP ≥ 1 year were independently reviewed and validated by the MIRROR Panel. The MIRROR Panel TTP values are reported for all of the 78 patients (the two patients with confounding issues are included).

NR = Not reached.

Figure 37. Time to Progression for All Patients from the Integrated Efficacy Population



The durability of these responses in this patient population and the consistency across multiple studies strongly suggest that these observations represent a meaningful therapeutic benefit. No other treatment modality, other than stem cell transplant, has been shown to offer responses that are more durable than those achieved with previous chemotherapy. This observation provides justification for Accelerated Approval.

6.3 BEXXAR THERAPY PROVIDES A MEANINGFUL THERAPEUTIC BENEFIT OVER EXISTING PRODUCTS

Patients with late-stage, relapsed and refractory low-grade NHL, with or without transformation, are in need of novel therapies that offer not only a high rate of response, but also the opportunity of durable complete responses. Bexxar therapy uniquely fulfills this medical need.

There are 2 products approved for the treatment of patients with relapsed or refractory, low-grade or follicular CD20-positive, B-cell non-Hodgkin's lymphoma: Rituxan and Zevalin. Clinical trials with Bexxar therapy were ongoing or completed when these products were approved. Consequently, there are no direct comparisons of results. However, based on the available data, neither Rituxan nor Zevalin has demonstrated the long-term, durable responses comparable to those observed with Bexxar therapy.

6.3.1 Comparison of Pivotal Trial Data for Bexxar, Rituxan, and Zevalin

Corixa performed analyses of the differences in the patient populations enrolled in the pivotal studies for Bexxar, Rituxan, and Zevalin. The differences among the three pivotal studies are outlined in Table 41. Patients enrolled in Bexxar's pivotal study, RIT-II-004, had a higher incidence of bulky disease, greater number of prior chemotherapy regimens, higher incidence of elevated LDH, significantly higher incidence of transformed low-grade NHL, lower response to last prior chemotherapy, and shorter duration of response to last chemotherapy. These demographic characteristics are well-recognized, important, prognostic characteristics that have a negative impact on treatment outcomes.

Table 41. Comparison of Patient Populations Treated in Pivotal Studies Conducted for Rituxan, Zevalin, and Bexxar

Criteria	Rituxan Pivotal Study Protocol 102-05 (N=166)[a]	Zevalin Pivotal Study Protocol 106-04 (N=73)[a]	Bexxar Pivotal Study Protocol RIT-II-004 (N=60)
Bulky disease	No bulky disease (no mass >10 cm in greatest diameter)	45% (≥5 cm) 8% (≥10 cm)	70% (≥5 cm)[b] 17% (≥10 cm)
≤1 prior chemotherapy regimen	34%	47%	0%[b]
≥4 prior chemotherapy regimens	15%	11%	58%[b]
Transformed low-grade NHL	None	12%	38%[b]
Stage I/II	22%	11%	2%
Elevated LDH	NA	20%	44%[b]
Response (%) to last prior chemotherapy	73%	Not Reported	28%[c]
% with a CR to last prior chemotherapy	37%	Not Reported	3%[d]
Median duration of response to prior chemotherapy	12 mo.	Not Reported	3 mo.

[a] Data on Rituxan were obtained from the FDA Clinical Review of BLA reference number CP-0260 and CP-0244. Data on Zevalin were obtained from the FDA Clinical Review and the IDEC Briefing document for BLA reference number 125109.

[b] The entry demographic characteristics within the first section of the table were compared between the studies and statistically significant differences between Bexxar and the other studies are noted.

[c] Investigator-assessed unconfirmed response rate. The MIRROR Panel–assessed response rate was 12%.

[d] Investigator-assessed unconfirmed complete response rate. The MIRROR Panel–assessed complete response rate was 2%.

The response rates in the patients treated with Bexxar and those treated with Rituxan and Zevalin were compared (see Table 42).

Table 42. Comparison of Results from Pivotal Studies Conducted for Rituxan, Zevalin, and Bexxar

Criteria	Rituxan Pivotal Study Protocol 102-05 (N=166)[b]	Zevalin Pivotal Study Protocol 106-04 (N=73)[b]	Bexxar Pivotal Study Protocol RIT-II-004 (N=60)
Overall Response in pivotal trial[a]	48%	73%	47%
Complete Response in pivotal trial[a]	6%	18%	20%
% with TTP >24 months	None	3%	15%
Duration of response compared to last course of chemotherapy	Not statistically significant	Not Reported	Highly statistically significant (p<0.001)

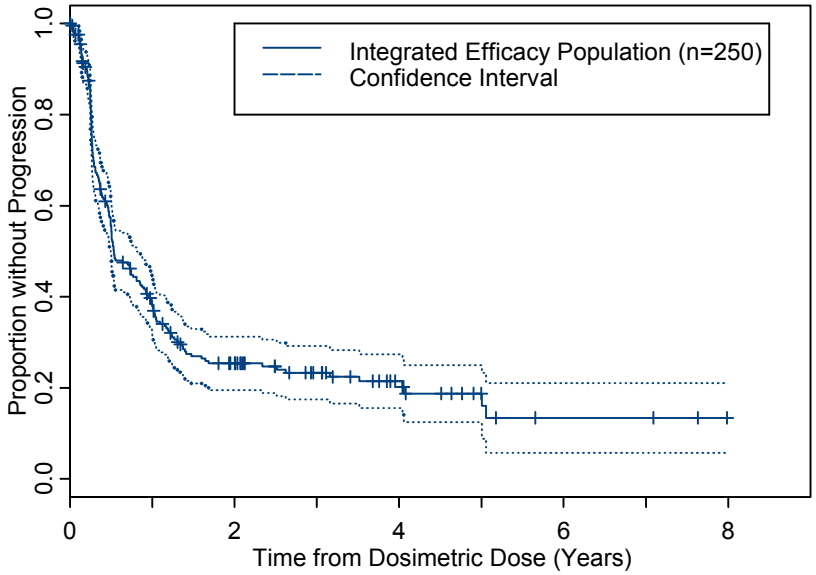
[a] Results based on protocol-defined response criteria.

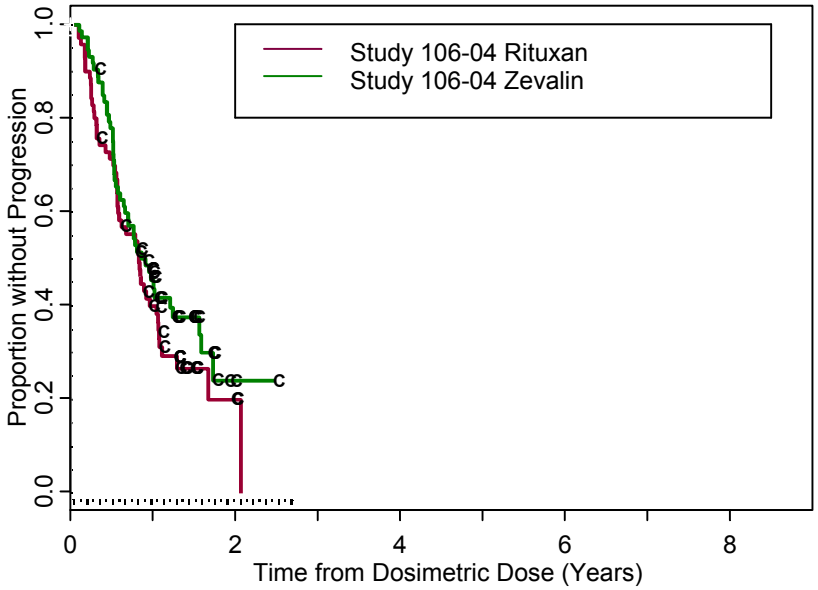
[b] Data on Rituxan were obtained from the FDA Clinical Review of BLA reference number CP-0260 and CP-0244. Data on Zevalin were obtained from the FDA Clinical Review and the IDEC Briefing Document for BLA reference number 125109.

The patients treated with Zevalin experienced a higher overall response rate than those given Bexxar; however, the complete response rates were similar. The percentage of patients with a time to progression of greater than 2 years was 15% in patients who received Bexxar therapy compared to 3% for patients given Zevalin. Duration of response following Bexxar exceeded that of the prior chemotherapy (p<0.001). Such a difference was not reported for Zevalin and was demonstrably absent for Rituxan. Data are not available to assess the durability of Zevalin responses beyond 32 months. The disparity in observed length of response is best demonstrated with data taken from the Zevalin pivotal trial, published in the FDA briefing document prepared at the time of ODAC presentation, that resulted in a recommendation for approval of Zevalin.

As Figure 38 illustrates, the Kaplan-Meier estimate of time to progression following Zevalin is approximately 25% at 30 months, but the patient with the longest ongoing response is at 32 months. For the Integrated Efficacy Population treated with Bexxar therapy, the Kaplan-Meier estimate of time to progression is 25% at 30 months, remains approximately 19% at 5 years, and continues at 13% at 8 years, with the last censored observation at 96 months.

Figure 38. Time to Progression for Bexxar, Rituxan, and Zevalin Therapies[a]





[a] Data taken from the Zevalin pivotal trial published in the FDA briefing document prepared at the time of ODAC presentation, that resulted in a recommendation for approval of Zevalin. The C on the curves for Zevalin and Rituxan represents the ongoing responders (censored patients). These data are represented by hash marks on the curve for iodine I 131 tositumomab.

Although the above observations can only be validated through long-term, prospective, randomized comparisons, differences between the two therapies are clinically and biologically plausible. Iodine 131 and yttrium 90 differ in many respects, including beta path length, half-life, biological clearance and uptake in normal tissue.

It is iodine I 131 tositumomab's ability (reproducible and independently validated) to produce durable remissions in patients for whom other therapies have failed that constitutes a meaningful benefit over existing therapies and provides the basis for the accelerated approval of this product requested at this time.

6.3.2 Comparison For Responses in Patients with Transformed Low-Grade NHL

In February 2002, Zevalin received accelerated approval for the treatment of patients with transformed low-grade NHL based on efficacy data from 9 patients (safety data were presented for 15 patients). Information has not been presented to determine whether these 9 patients were confirmed by central pathology review. Durable response data following Zevalin treatment in this patient population have not been reported.[68]

In contrast, the overall integrated efficacy analyses of the transformed low-grade NHL patient population treated with Bexxar include data on 71 patients who had an Investigator-assessed diagnosis of transformed low-grade NHL and who received treatment with Bexxar in the 5 studies comprising the Integrated Efficacy Population.

An independent central pathology review for confirmation of transformation was performed. Of the 71 patients, 53 patients had adequate slides or diagnostic material for reviewing both the original low-grade NHL diagnosis and the diagnosis for transformed histology. The results of the central pathology review of the 53 patients confirmed that 47 had histological transformation, 5 did not have confirmation of histological transformation, and 1 was classified as intermediate grade at diagnosis. The remaining 18 patients without histological specimens for both the low-grade and transformed low-grade diagnoses could not be confirmed for the following reasons: 15 patients were classified as having transformed low-grade NHL but did not have both specimens available for review, 1 patient was reclassified as low-grade, 1 patient's central review was non-diagnostic, and 1 patient's central review was not conducted. Some of these interpretations were re-reviewed as requested by FDA by a second independent reviewer, Dr. Elaine Jaffe, NCI.

Response was evaluated for the 47 patients with low-grade NHL whose histology was shown to have transformed to a higher grade in the central pathology review. The MIRROR Panel review of efficacy data for the 47 histologically confirmed transformed low-grade NHL patients is summarized in Table 43 and compared to results presented for the 9 patients treated with Zevalin.

Table 43. Comparison of the Data Obtained after Bexxar and Zevalin Treatment in the Transformed Low-Grade NHL Patient Population

	Zevalin Patients (N=9)	Bexxar Patients (N=47)
Overall Response	5/9 (56%)	19/47 (40%)
Median (95% CI) duration of response for responders (months)	6.8 (0.9–20.3)	14.4 (8.8–40.8)
Complete response	1/9 (11%)	11/47 (23%)
Median (95% CI) duration of response for complete responders (months)	Data not available	36.5 (14.4–59.1)
Median (95% CI) time to progression (months) for all patients	3.1 (0.8–21.7)	4.3 (3.3–10.2)
Median (95% CI) time to progression (months) for responders	Data not available	16.1 (10.2–42.2)

NR = Not reached as of the data cutoff date.

The median duration of response for all responders was 14.4 months following Bexxar therapy and 6.8 months following Zevalin therapy. Furthermore, the median duration of response for complete responders after treatment with Bexxar therapy was 36.5 months.

Individuals with transformed low-grade histology represent a particularly challenging patient population, with limited survival after currently available therapies. In a population of patients with histologic confirmation of transformation, treatment with Bexxar therapy produced MIRROR Panel–validated complete responses in 23% of the patients with a median duration of response of 36.5 months. Durations of response greater than 2 years have not been reported in patients with evidence of histological transformation who were treated with Zevalin.

6.4 SUMMARY OF POST APPROVAL COMMITMENTS

Following discussions with the FDA and clinical experts in the area of NHL, Corixa has proposed two post-marketing approval studies to confirm the benefit of Bexxar therapy. The first trial is already in progress and is being conducted by the Southwest Oncology Group (SWOG). The SWOG trial compares progression-free survival of patients with newly diagnosed, previously untreated CD20+ follicular lymphoma randomized to receive 6 cycles of CHOP chemotherapy alone, or 6 cycles of CHOP with rituximab, or 6 cycles of CHOP followed by Bexxar therapy. The second randomized trial under final review by the FDA is a 440-patient efficacy evaluation of Bexxar versus Rituxan therapy.

7. SUPPORT FOR CONVENTIONAL APPROVAL

7.1 COMPARISON OF EFFICACY FOR TREATMENT OF RITUXAN-REFRACTORY PATIENTS

On 11 September 2001, the Oncologic Drugs Advisory Committee discussed and recommended approval of Zevalin for the treatment of Rituxan-refractory patients with follicular lymphoma. Full approval for this indication was later granted by the FDA. The study was a single-arm study of 57 patients (54 patients included in efficacy analyses). The primary efficacy endpoint was the overall response rate (ORR). Approval was granted based on a secondary analysis that compared the duration of response after Zevalin to the duration of response to prior Rituxan using patients as their own control.

If the duration of response to Zevalin therapy was longer than the duration of response to prior Rituxan by greater than 30 days, the Zevalin therapy was considered beneficial. If the difference was less than or equal to 30 days, they were considered equivalent. If the duration of response to prior Rituxan was longer than the duration of response to the Zevalin therapy by more than 30 days, Zevalin was considered not beneficial.

Using this algorithm, 29 of the 32 patients with an objective response to Zevalin had a longer duration of response than to their prior Rituxan. Twenty of the patients had an equivalent response, and 5 had a longer response following prior Rituxan. The proportion of subjects with a longer duration of response to Zevalin was statistically significant.

Study CP-97-012, conducted by Corixa, is essentially identical to the study supporting approval of Zevalin. Forty patients with prior treatment with Rituxan were enrolled; all patients had a least 4 doses of Rituxan without an objective response or they progressed during or following treatment. Thirty-five of the 40 patients were refractory by the same definition used in the Zevalin trial. The primary endpoint was ORR and complete response (CR).

The demographics of patients enrolled in the Zevalin study 106-06 and in the Bexxar study CP-97-012 (n=35) were similar. For example, the 35 Rituxan-refractory patients enrolled in the Bexxar study CP-97-012 had received a median of 4 prior regimens for NHL and 24% had an International Prognostic Index (IPI) score of 3 or greater; while the 57 patients enrolled in the Zevalin study 106-06 had received a median of 4 prior regimens for NHL and 23% had an IPI score of 3 or greater.

Results are compared in Table 44.

Table 44. Independent Panel–Assessed Efficacy Endpoints: Comparison of Bexxar Study CP-97-012 and Zevalin Study 106-06

	Bexxar Study CP-97-012 (N=35)[a]	Zevalin Study 106-06 (N=54)[b]
Response (95% CI)	63% (45% – 79%)	59% (45% – 82%)
Median (range) duration (mo.)	25.3 (3.8+ – 35.2+)	7.7 (2.3 – 24.9+)
Complete Response (95% CI)	29% (15% – 46%)	4% (1% – 13%)
Median (range) duration of CR (mo.)	NR (4.1 – 35.2+)	NA
In Response at Data Cutoff (censored)	10 (29%)	10 (19%)
Time to progression		
Median (range) (mo.)	11.8 (0.1+ – 36.7+)	6.8 (1.1 – 25.9+)

[a] Restricted to patients with no response or duration of response of less than 6 months on last Rituxan therapy.

[b] Three patients with non-follicular histologies were excluded.

NR = Not reached as of data cutoff date.

NA = Not available.

Overall response rates were similar for the two treatments; however, Bexxar therapy produced a greater number of complete responses, a median duration of response three times larger than Zevalin, and longer times to progression.

The analysis of a secondary efficacy variable for the Zevalin study 106-06 comparing the duration of response after Zevalin therapy to the duration of response to the last prior Rituxan therapy was statistically significant. A similar analysis was performed for Bexxar study CP-97-012 and a similar conclusion was reached, with patients having a significantly longer duration of response on Bexxar therapy than on prior Rituxan ($p<0.001$).

7.2 COMPARISON OF SAFETY FOR HEMATOLOGIC TOXICITY

Hematologic toxicity was the most common severe (Grade III/IV) adverse experience reported for both products. Other severe adverse events reported for both products included: infections and bleeding events. Table 45 compares the results.

Table 45. Comparison of Severe Adverse Experience (Grade III/IV): Bexxar Therapy vs Zevalin Therapy

	Bexxar (N=620)		Zevalin (N=349)
	Reported (%)	Worst-Case Scenario[a] (%)	Package Insert (%)
Thrombocytopenia	36%	49%	63%
Neutropenia	42%	57%	60%
Anemia	11%	27%	17%
Infections	6%	NA	5%
Bleeding events	2%	NA	2%[b]

[a] See Section 4.3.8.2.2.

[b] IDEC Briefing Document, ODAC, 11 September 2001

NA = Not applicable.

In general the toxicities associated with Bexxar and Zevalin therapies are comparable even when comparing the results from Bexxar's worst-case analysis to the results in Zevalin's package insert.

Long-term follow-up will be required to fully assess the occurrence of MDS/AML in this patient population. At this point in time, data regarding MDS/AML are available for more patients over a longer period following Bexxar therapy. Therefore, patients and their physicians can make more informed decisions regarding this product.

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Appendix 1. List of Abbreviations

ACP	Doxorubicin, cyclophosphamide, and prednisone
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse experience
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the Curve
BACOP	Bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisone
BLA	Biologics License Application
CBC	Complete blood count
CCR	Clinical complete response
CDC	Complement-dependent cytotoxicity
CEPP	Cyclophosphamide, etoposide, procarbazine, and prednisone
CF	Cisplatin and 5-fluorouracil
CFR	Code of Federal Regulations
cGy	Centigray
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CHOP-Bleo	Cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
C-MOPP	Cyclophosphamide, mechlorethamine, vincristine, procarbazine, and prednisone
CNOP	Cyclophosphamide, mitoxantrone, vincristine, and prednisone
COMLA	Cyclophosphamide, vincristine, methotrexate, leucovorin, and cytarabine
COP-BLAM	Cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, and procarbazine
COP-Bleo	Cyclophosphamide, vincristine, prednisone, and bleomycin
COPP	Cyclophosphamide, vincristine, procarbazine, and prednisone
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CP	Cyclophosphamide and prednisone
CR	Complete response
CRF	Case report form
CRO	Clinical Research Organization
CT	Computed tomography
CTC	Common Toxicity Criteria
CVP	Cyclophosphamide, vincristine, and prednisone
DHAP	Dexamethasone, high-dose cytarabine, and cisplatin

DLT	Dose-limiting toxicity
EAP	Expanded Access Program
EFS	Event-free survival
ELISA	Enzyme-linked immunosorbent assay
EPOCH	Etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin
ESHAP	Etoposide, methylprednisolone, prednisone, cytarabine, and cisplatin
FDA	Food and Drug Administration
FND	Fludarabine, mitoxantrone, and dexamethasone
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GSK	GlaxoSmithKline
GVHD	Graft versus host disease
HAMA	Human anti-murine antibody
ICE	Ifosfamide, carboplatinum, and etoposide
IM-VP16	Ifosfamide, methotrexate, and etoposide
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	Intravenous
IWF	International Working Formulation
KPS	Karnofsky Performance Score
LDH	Lactate dehydrogenase
LQC	Last qualifying chemotherapy
MAb	Monoclonal antibody
MACOP-B	Methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin and leucovorin
m-BACOD	Methotrexate, leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone
mCi	Millicurie
mrem	Millirem
MDS	Myelodysplastic syndrome
MINE	Mesna, ifosfamide, mitoxantrone, and etoposide
MIRD	Medical internal radiation dose
MIRROR	Masked Independent Randomized Radiology and Oncology Review
MOPP	Mechlorethamine, vincristine, procarbazine, and prednisone
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin’s lymphoma
NRC	Nuclear Regulatory Commission
ORR	Overall response rate
PCR	Polymerase chain reaction
PET	Positron emission tomography

PD	Progressive disease
PR	Partial response
PRBC	Packed red blood cells
ProMACE-CytaBOM	Prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and leucovorin
ProMACE-MOPP	Prednisone, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
RAEB	Refractory anemia with effective blasts
RBC	Red blood cell
REAL	Revised European American Lymphoma Classification
RIT	Radioimmunotherapy
ROI	Region of interest
SAE	Serious adverse experience
SD	Stable disease
SPPD	Sum of the products of perpendicular diameters
SSKI	Saturated solution potassium iodide
SWOG	Southwest Oncology Group
$t_{1/2}\alpha$	Initial half-life
$t_{1/2}\beta$	Terminal half-life
TBD	Total body dose
TBI	Total body irradiation
TBRT	Total body residence time
TSH	Thyroid-stimulating hormone
TTD 5/5	Tissue tolerance dose (the 5% probability of complication within 5 years after treatment)
TTP	Time to progression
ULN	Upper limit of normal
USAN	United States Adopted Name
VAPEC-B	Vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide and bleomycin
Vd_o	Volume of distribution at time 0
Vd_{ss}	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

Appendix 2. List of Definitions

Response Definitions

Complete response (CR): Complete resolution of all disease-related radiological abnormalities and disappearance of all signs and symptoms related to the disease. For patients with a positive bone marrow biopsy at baseline, complete response requires that a bone marrow biopsy be performed and that it reveal no evidence of lymphoma.

Clinical complete response (CCR): Complete resolution of all disease-related symptoms but residual foci, thought to be residual scar tissue, are present. Generally, an unchanging lesion ≤2 cm diameter by radiographic evaluation or ≤1 cm diameter by physical examination can be considered scar tissue. The extent of disease must be unchanged or decreased on follow-up evaluations and, if unchanged or further decreases for 6 months or longer, the patient will then be classified as a complete response. For patients with a positive bone marrow biopsy at baseline, Clinical Complete Response requires that a bone marrow biopsy be performed and that it reveal no evidence of lymphoma.

Partial response (PR): ≥50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions with no new lesions.

Stable disease (SD): <25% increase and <50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions with no new lesions.

Progressive disease (PD): ≥25% increase from the nadir value of the sum of the products of the longest perpendicular diameters of all measurable lesions or the appearance of any new lesion. Individual lesions must be >2 cm diameter by radiographic evaluation or >1 cm diameter by physical examination.

Confirmed response: Responses that were confirmed by two separate response evaluations at least 4 weeks apart. **Only confirmed responses for iodine I 131 tositumomab are reported in this briefing document.**

Long-term or durable responder: A responding patient with a MIRROR Panel-assessed time to progression of 12 months or more.

Somewhat more conservative response definitions were employed in the MIRROR2 review of selected long-term durable responders. These were:

Complete response (CR): Complete resolution of all disease related radiological abnormalities (i.e., no residual radiographic evidence of disease) and disappearance of all signs and symptoms related to the disease. For patients with a positive bone marrow biopsy at baseline, complete response requires that a bone marrow biopsy be performed and that it reveal no evidence of lymphoma.

Clinical Complete Response (CCR): Complete resolution of all disease related symptoms but residual lesion(s) by radiographic evaluation. When such lesion(s) remain unchanged for 6 months or longer, the patient will then be classified as a Clinical Complete Response (CCR). For patients with a positive bone marrow biopsy at baseline, Clinical Complete Response requires that a bone marrow biopsy be performed and that it reveal no evidence of lymphoma.

Partial Response (PR): Greater than or equal to a 50% reduction in the SPD of all measurable lesions defined at baseline, no significant change in evaluable lesions, and no new lesions.

Stable Disease (SD): Less than a 25% increase and less than a 50% decrease in the SPD of all measurable lesions defined at baseline, no significant change in evaluable lesions, and no new lesions.

Progressive Disease (PD): Greater than or equal to a 25% increase from the nadir value of the SPD of all measurable lesions, a significant change in evaluable lesions, or the appearance of any new lesion.

Duration Measures

Time to progression: The time from the start of treatment (i.e., dosimetric dose of iodine I 131 tositumomab) to the first documented progression. To maintain the masking of the Masked Independent Randomized Radiology and Oncology Review (MIRROR) Panel, death information was not included in their review. Accordingly, MIRROR Panel data were used to determine time to progression, which was defined as the time from the start of treatment to the first documented progression.

Progression-free survival: The time from the start of treatment (i.e., dosimetric dose of iodine I 131 tositumomab) to the first documented progression or death.

Event-free survival: The time from the start of treatment (i.e., dosimetric dose of iodine I 131 tositumomab) to the first documented progression, subsequent therapy for NHL, or death.

Duration of response: The time from the first documentation of response to the first documented progression for all patients with confirmed CR, CCR, or PR.

Time to death: The time from the start of the dosimetric dose to the date of death from any cause.

Duration of Grade III/IV toxicity: The duration of Grade III/IV toxicity is defined as the number of days from the last Grade 0/I/II value prior to Grade III/IV toxicity to the first Grade 0/I/II after the Grade III/IV toxicity.

Duration of Grade IV toxicity: The duration of Grade IV toxicity is defined as the number of days from the last Grade 0/I/II/III value prior to Grade IV toxicity to the first Grade 0/I/II/III after the Grade IV toxicity.

Other

Modified IPI score: Modified IPI is defined by the following risk factors (age > 60, Stage III/IV, elevated LDH, KPS ≤ 60, extranodal disease). Standard IPI is defined by the following risk factors risk factors (age > 60, Stage III/IV, elevated LDH, KPS ≤ 70 [i.e., ECOG ≥ 2], 2 or more extranodal sites).[69] Patients were considered low-risk (0–1 factor), low-intermediate risk (2 factors), high-intermediate risk (3 factors), and high-risk (4–5 factors).

Grades of hematologic toxicity (NCI CTC toxicity grades):

ANC (1000 cells/mm^3): Grade II = 1.0 to <1.5, Grade III = 0.5 to <1.0, Grade IV = <0.5.

Platelets (1000/mm^3): Grade II = 50 to <75, Grade III = 25 to <50, Grade IV = <25.

Serious Adverse Experience: An event is considered to be a serious adverse experience (SAE) if:

- a patient's death is suspected as being a direct outcome of the adverse experience
- the patient was at substantial risk of dying at the time of the adverse experience or it is suspected that the use or continued use of the product would result in the patient's death
- the patient was admitted to the hospital or a hospital stay was prolonged because of the adverse experience
- the adverse experience resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life
- there are suspicions that exposure to the product prior to conception or during pregnancy resulted in an adverse outcome in the child
- the use of the product resulted in a condition which required medical or surgical intervention to preclude permanent impairment or damage

Appendix 3. Regulatory History of the Iodine I 131 Tositumomab BLA

Date	Event
13 Oct 1989	Original IND filed by Coulter Corporation
1990	Clinical trials initiated
30 Jun 1999	First Coulter Pharmaceuticals BLA submission
27 Aug 1999	Refusal to file received
14 Sep 2000	BLA resubmitted
11 Jan 2001	IND and BLA transferred to Corixa
16 Mar 2001	Complete Review letter: Additional data requested
10 Sep 2001	Submitted response to Complete Review letter: additional data completed
12 Mar 2002	2nd Complete Review letter: Not approvable
31 May 2002	Dispute Resolution requested by Corixa
26 Jun 2002	Appeal granted
30 Oct 2002	Submitted response to Complete Review letter
08 Nov 2002	ODAC meeting scheduled
14 Nov 2002	FDA accepted response to Complete Review letter

Appendix 4. Clinical Studies Evaluating Iodine I 131 Tositumomab for the Treatment of B-Cell Lymphomas

Study No.	Title	Sites
	Integrated Studies	
RIT-I-000	Phase I/II Study of Radiolabeled Monoclonal Antibody Anti-B1 for the Treatment of B-Cell Lymphomas	University of Michigan Medical Center
RIT-II-001	Multicenter, Phase II Dosimetry/Validation Study of ^{131}Iodine Anti-B1 (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that Have Transformed to Higher Grade Histologies	Christie Hospital (UK), Memorial Sloan-Kettering Cancer Center, St. Bartholomew's Hospital (UK), Stanford University Medical Center, University of Alabama at Birmingham, University of Michigan Medical Center, University of Nebraska Medical Center
RIT-II-002	A Randomized Study of Iodine I 131 Tositumomab versus Tositumomab in Chemotherapy-Relapsed/Refractory Low-Grade or Transformed Low-Grade Non-Hodgkin's Lymphoma (NHL)	Cornell Medical Center, Dana-Farber Cancer Institute, Fairfax Hospital, Georgetown University, Memorial Sloan-Kettering Cancer Center, Rush-Presbyterian-St. Luke's Medical Center, Stanford University Medical Center, University of Michigan Medical Center, University of Miami Hospital and Clinic, Yale University School of Medicine
RIT-II-003	Phase II Trial of Iodine I 131 Tositumomab for Previously Untreated, Advanced-Stage Low-Grade Non-Hodgkin's Lymphoma	University of Michigan Medical Center
RIT-II-004	**Multicenter, Pivotal Phase III Study of Iodine I 131 Tositumomab (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that Have Transformed to Higher Grade Histologies**	Cornell Medical Center, Kaiser Permanente Medical Center, Memorial Sloan-Kettering Cancer Center, St. Bartholomew's Hospital (UK), University of Alabama at Birmingham, University of Michigan Medical Center, University of Nebraska Medical Center, University of Washington
	Expanded Access Study	
CP-98-020	Expanded Access Study of Iodine I 131 Tositumomab for Relapsed/Refractory Low-Grade and Transformed Low-Grade Non-Hodgkin's Lymphoma	89 sites
	Rituxan-Failure Study	
CP-97-012	Phase II Study of Iodine I 131 Tositumomab for Non-Hodgkin's Lymphomas Patients Who Have Previously Received Rituximab	MD Anderson Cancer Center, Stanford University Medical Center, US Oncology Center

Study No.	Title	Sites
Single-Patient, Open-Label, Studies of Iodine I 131 Tositumomab for Low-Grade or Low-Grade Transformed B-Cell NHL		
CP-97-014c		University of Michigan Medical Center
CP-97-016c		University of Michigan Medical Center
CP-98-023c		University of Michigan Medical Center
CP-98-024c		Memorial Sloan-Kettering Cancer Center
CP-98-029c		Memorial Sloan-Kettering Cancer Center
CP-00-039c		Stanford University Medical Center
	Other Clinical Studies	
CP-97-011	Phase II Study of Iodine I 131 Tositumomab for the 1st or 2nd Relapsed Indolent B-Cell Lymphomas or B-Cell Lymphomas that Have Transformed to a More Aggressive Histology	Christie Hospital (UK), St. Bartholomew's Hospital (UK)
CP-98-018	A Phase I, Dose-Escalation, Open-Label, Multicenter Study of Iodine I 131 Tositumomab for Intermediate- and High-Risk B-Cell Chronic Lymphocytic Leukemia	Long Island Jewish Medical Center, Stanford University Medical Center
CP-98-021	Retreatment Study of Patients with Non-Hodgkin's Lymphoma Who Have Previously Responded to Iodine I 131 Tositumomab	Christie Hospital (UK), Cornell Medical Center, Rush-Presbyterian-St. Luke's Medical Center, Stanford University Medical Center, University of Michigan Medical Center
CP-98-025	Fludarabine Monophosphate Followed by Iodine I 131 Tositumomab for Untreated Low-Grade and Follicular Non-Hodgkin's Lymphoma	Cornell Medical Center
CP-98-026i	A Phase II Pilot Trial of CHOP followed by Iodine I 131 Labeled Monoclonal Anti-CD20 Antibody for Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphomas	42 sites[a]
CP-98-027n	Named Patient Study: Christie Hospital	Christie Hospital (UK)
CP-98-028	Phase I, Dose-Escalation Study of Iodine I 131 Tositumomab for Patients with Previously Treated Non-Hodgkin's Lymphoma with More than 25% Bone Marrow Involvement	Cornell Medical Center
CP-99-032	Phase II, Multicenter Study of Iodine I 131 Tositumomab Consolidation for Patients with Diffuse Large B-Cell Non-Hodgkin's Lymphoma Following CHOP	Cornell Medical Center, Rush-Presbyterian-St. Luke's Medical Center, New England Medical Center
CP-99-035skb	Named Patient Study: St. Bartholomew's Hospital	St. Bartholomew's Hospital (UK)

Study No.	Title	Sites
CP-99-036	Phase II, Multicenter Study of CVP Followed by Iodine I 131 Tositumomab for Patients with Untreated Low-Grade Non-Hodgkin's Lymphoma	Cornell Medical Center, University of Iowa Hospital and Clinic, University of Michigan Medical Center
CP-00-043n	Named Patient Study: Christie Hospital	Christie Hospital (UK)
CP-00-047n	Named Patient Study: Centre Hospitalier Lyon	Centre Hospitalier Lyon (France)
	Integrated Myeloablative Studies	
RIT-I-013	Treatment of B-Cell Lymphomas with Radiolabeled Monoclonal Antibodies Directed against the CD20 ("B1") Antigen	University of Washington
RIT-II-008	Treatment of B-Cell Lymphomas with Radiolabeled Monoclonal Antibodies Directed against the CD20 ("B1") Antigen: A Phase II Study	University of Washington
RIT-II-009	Radioiodinated B1 Antibody, VP-16, Cyclophosphamide, and Autologous Transplantation for Relapsed Non-Hodgkin's Lymphoma: A Phase I/II Study	University of Washington
	Other Myeloablative Clinical Studies	
CP-97-010i	BEAM + ^{131}Iodine-Anti-B1 Radioimmunotherapy and Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Recurrent Non-Hodgkin's Lymphoma	University of Nebraska Medical Center
CP-99-033i	A Phase II Trial Evaluating Radioiodinated Anti-B1 (Anti-CD20) Antibody with Autologous Stem Cell Transplantation for Relapsed or Refractory Non-Hodgkin's Lymphoma in Patients 60 Years of Age and Older	University of Washington
CP-99-034i	A Phase II Trial Evaluating the Efficacy of Radioiodinated Anti-B1 (Anti-CD20) Antibody, Etoposide and Cyclophosphamide Followed by Autologous Transplantation for Relapsed of Refractory Non-Hodgkin's Lymphoma	University of Washington
CP-00-040i	Phase II Trial of BEAM + Iodine I 131 tositumomab with Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Recurrent Diffuse Large B-Cell Non-Hodgkin's Lymphoma	University of Nebraska Medical Center

[a] List of CP-98-026i sites: Arizona Cancer Center, Akron General Medical Center, Benefis Health Care West, California Pacific Medical Center, Cancer Center of Santa Barbara, Cancer Research of the Ozarks, Carilion Roanoke Hospital, City of Hope National Medical Center, Deaconess Medical Center, Good Samaritan Hospital, Grant Medical Center, Holy Family Hospital, Hillcrest Hospital Cancer Center, Integris Oncology, Kettering Medical Center, Loyola University School of Medicine, Mount Carmel East Hospital, North Idaho Cancer Center, Oregon Health Sciences University, Phoebe Cancer Center, Providence Anchorage Medical Center, Providence Hospital Medical Center, Providence St. Vincent Medical Center, Redwood Regional Oncology Group, Research Medical Center, St. Alphonsus Regional Medical Center, St. Francis Hospital Medical Center, St. John's Mercy Medical Center, St. Vincent Hospital, San Juan Regional Medical Center, Spartanburg Regional Medical Center, Thibodaux Regional Medical Center, University of Arkansas Medical Center, University of Hawaii St. Francis Medical Center, University of Hawaii Tripler Army Medical Center, University of Utah School of Medicine, University of Washington, Via Christi Regional Medical Center, Virginia Mason Medical Center, Washington Regional Medical Center, Wesley Regional Medical Center, West Florida Regional Medical Center

Appendix 5. Serious Infections: Integrated Safety Population (N=620)

Patient ID	Infection	Study Day of Infection	Pre-infection[a]		Nadir		Outcome
			ANC	Study Day	ANC	Study Day	
000-002-055	Necrotizing panniculitis	59	11880	57	378	46	Recovered
001-003-004	Infected port-a-cath	5	2465	5	450	47	Recovered
001-005-003	Sepsis due to central line infection	14	4410	14	1888	16	Recovered
	Streptococcal pneumoniae bacteremia	1	3953	1	1888	16	Recovered
001-005-005	Urinary tract infection	82	3784	82	1416	91	Recovered
001-006-003	Catheter-related sepsis	56	1476	56	852	62	Recovered
001-008-006	Infection (shingles)	40	3621	34	504	51	Recovered
002-026-004	Septicemia	–19[b]	NA	NA	5360	41	Recovered
002-030-019	Anaerobic gram-negative rod bacteremia	75	1428	75	217	97	Recovered
002-030-024	Suspected bacteremia	66	737	60	737	60	Recovered
002-034-912	Pneumonia	117	885	98	420	54	Recovered
	Bronchitis	54	420	54	420	54	Recovered
004-013-001	Pneumonia	68	1763	68	680	47	Recovered
004-013-002	Acute bronchitis	85	3650	54	2508	22	Recovered
004-013-005	Aspiration pneumonia	30	9065	30	639	38	Persists[c]
004-013-010	*Pneumocystis carinii* pneumonia (PCP)	23	3139	20	500	44	Recovered
	Catheter-related sepsis	16	4165	0	500	44	Recovered
004-014-002	Cough	13	6552	13	6552	28	Death[d]
004-015-005	Pneumonia	0	2208	–7	840	99	Recovered
012-037-005	Blood Staphylococcus	19	6688	19	3332	28	Death[e]
	Pneumonia	21	6840	21	3332	28	Death[e]

[a] ANC at time of infection or last ANC prior to infection.

[b] Infection occurred prior to the therapeutic dose.

[c] SAE secondary to progressive disease; death due to progressive disease on [redacted] (36 days post therapeutic dose; 14 days post SAE).

[d] Death due to progressive disease on [redacted] days post therapeutic dose; 29 days post SAE).

[e] Death due to respiratory failure due to aspiration pneumonia [redacted] (20 days post therapeutic dose; 16 days post blood staphylococcus and 14 days post pneumonia).

Patient ID	Infection	Study Day of Infection	Pre-infection[a]		Nadir		Outcome
			ANC	Study Day	ANC	Study Day	
012-037-006	Pneumonia	5	4150	–16	740	67	Recovered
020-013-467	Coughing	9	5560	–14	NA	NA	Persists[b]
020-014-350	Sore throat	10	3600	–21	0	53	Persists[c]
020-014-399	Pseudomonas sepsis	6	7410	–14	455	46	Recovered
020-017-430	Probable sepsis	29	210	28	210	28	Persists[d]
020-020-047	Staph sepsis	8	5890	–16	4690	44	Persists[e]
020-028-143	Cellulitis in right axilla	27	2200	21	1400	41	Recovered w/sequelae
020-034-083	Neutropenic sepsis	59	5640	40	5640	40	Death[f]
020-038-022	Pneumonia	150	7800	91	5200	36	Death[g]
	Sepsis	150	7800	91	5200	36	Death[g]
020-038-087	Sepsis	38	500	36	500	36	Recovered w/sequelae
020-038-209	Infectious wound	21	8270	21	2740	42	Recovered w/sequelae
020-038-347	Pneumonia	42	700	42	700	42	Recovered
020-041-032	Pneumonia	51	7300	35	5500	53	Persists[h]
020-042-101	Infection in left groin tumor	22	2146	14	2146	14	Persists[i]
020-046-212	Pneumonia	9	2900	0	2100	48	Recovered
020-052-147	Right upper extremity cellulitis	44	1500	41	51	45	Recovered w/sequelae
020-063-325	Pneumonia	9	2018	–15	1226	97	Recovered
020-065-233	Sepsis	28	3100	21	1200	29	Death[j]
020-075-289	Sepsis	53	630	53	330	43	Death[k]
023-013-151	Pneumonia	98	2650	96	400	82	Recovered

[a] ANC at time of infection or last ANC prior to infection.

[b] Death due to progressive disease on [redacted] 3 days post therapeutic dose; 1 day post SAE).

[c] Death due to progressive disease on [redacted] days post therapeutic dose; 47 days post SAE).

[d] Death due to progressive disease on [redacted] (28 days post therapeutic dose; 6 days post SAE).

[e] Death due to progressive disease on [redacted] days post therapeutic dose; 45 days post SAE).

[f] Death due to neutropenic sepsis, most likely related to subsequent chemotherapy, on [redacted] 45 days post therapeutic dose; day of SAE).

[g] Death due to sepsis, pneumonia, and respiratory failure on [redacted] (161 days post therapeutic dose, 18 days post SAE).

[h] Death due to progressive disease on [redacted] 47 days post therapeutic dose, 10 days post SAE)

[i] Death due to progressive disease on [redacted] 74 days post therapeutic dose; 59 days post SAE).

[j] Death due to septic shock on [redacted] (25 days post therapeutic dose; 4 days post SAE).

[k] Death due to progressive disease on [redacted] (65 days post therapeutic dose; 19 days post SAE).

Appendix 6. Therapeutic History of Patients Treated with Iodine I 131 Tositumomab Therapy Who Developed MDS/AML as Reported by Investigators

Patient ID (Age at Study Entry/Gender)	MDS/AML	Total # ChemoTx Agents Received	Chemotherapeutic Agents Prior to MDS/AML				Total # ChemoTx Regimens Received	No. Sites Treated with Radiation	Total # ChemoTx+ Radiation Regimens Received	Time to MDS/AML (yr)	
			Alkylating Agents	Topo-isomerase-II Inhibitors	Anti-metabolites	Other				From Initial Alkylating Agent	From Iodine I 131 Tositumomab
Study RIT-I-000											
000-002-019 (58F)	AML	9	M, C, L, P	D	M	B, V, S	11	2 - Th, Ing	13	25.4	7.1
000-002-050 (49F)	RAEB-1	8	C	E, D	M, F	V, S, I	9	1 - Abd	10	15.5	2.7
000-002-055 (68M)[a]	CMML	9	C, Cp	D, E, M	A, F	V, S	4	0	4	3.2	0.3
000-002-056 (66F)	RAEB-1	9	L, C	D, E, M	M	S, V, I	9	1 - S	10	9.9	3.1
000-002-031(49M)	AML	11	C, I, CB	D, E	A, F	V, S, R	11	2 – M,N	12	17	7.7
Median		9					9		10	12.7	3.1
Study RIT-II-001											
001-003-002 (59F)[a]	RAR/RARS	9	C, L, P	D, M, E	F	V, S	8	6 - Abd, I, Sup, O, Cer, Ch	14	8.3	0.8
001-006-001 (51M)	RAEB-II	6	C	D	F	V, S, I	6	1 - A	7	3.5	1.8
001-006-004 (69F)	AML	7	C, A, N	D	F	V, S	3	2 - S,S	5	4.3	1.7
001-009-002 (56F)	Atypical CML	10	L, C	D, M, E	F	I, V, S, H	7	0	7	7.1	2.3
001-005-005 (78F)	MDS	8	L, C, Cp	D,E	A	S, V	8	1	5	9	4.4
Median		8					7		7	5.7	1.8
Study RIT-II-002											
002-011-917 (50F)	CMML	11	C, I, Cp	D, M, E	A, F	T, S, V	6	0	6	3.8	1.2
002-025-901 (81M)[a]	AML (M6)	3	L, P		F		2	0	2	3.4	1.2
002-030-019 (52M)	RAEB-II	6	L, C	M	F	V, S	4	0	4	3.5	0.4
Median		6					4		4	3.5	1.2

[a] Onset was prior to treatment with iodine I 131 tositumomab.

Patient ID (Age at Study Entry/Gender)	MDS/AML	Total # ChemoTx Agents Received	Chemotherapeutic Agents Prior to MDS/AML				Total # ChemoTx Regimens Received	No. Sites Treated with Radiation	Total # ChemoTx+ Radiation Regimens Received	Time to MDS/AML (yr)	
			Alkylating Agents	Topo-isomerase-II Inhibitors	Anti-metabolites	Other				From Initial Alkylating Agent	From Iodine I 131 Tositumomab
Study RIT-II-004											
004-016-003 (44F)[b]	None	9	C	D, E	F, A, M	S, B, V	3	0	3	5.8	2.5
004-016-007 (61M)	RAEB-T	8	C, I, Cp	D, E	F	S, IV	6	0	6	5.6	3.4
004-020-007 (45M)[a]	RA/RARS	8	C, Cp	D, M	F, A	S, V	5	0	5	4.6	1.8
004-020-008 (71M)	RAEB	6	C	M, D	F	V, S	4	0	4	4.6	3.0
Median		8					4.5		4.5	5.1	2.75
Study CP-98-020											
020-038-022 (53M)[a]	MDS	7	L, C	D	F	V, S, U	3	0	3	4.7	0.4
Study CP-97-012											
012-035-002 (63M)	AML	3	C		F	R	2	1	3	4.3	2.1

[a] Onset was prior to treatment with iodine I 131 tositumomab.

[b] Patient had a normal marrow before and after treatment with iodine I 131 tositumomab.

Alkylating Agents:
A = Melphalan (Alkeran)
C = Cyclophosphamide
Cp = Cisplatin
I = Ifosfamide
L = Chlorambucil (Leukeran)
M = Nitrogen mustard
N=Nitrosourea
P = Procarbazine

Topoisomerase II Inhibitors
E = VP - 16 (Etoposide)
D = Doxorubicin
M = Mitoxantrone

Antimetabolites
A = Cytosine arabinoside
F = Fludarabine
M = Methotrexate

Other
B = Bleomycin
H = Hydroxyurea
I = Interferon
IV = Idiotypic vaccine
M = Mitoguazone
T = Taxol
R = Rituximab
S = Corticosteroid (Prednisone, dexamethasone)
U = Unknown
V = Vincristine
Vr = Vinorelbine

Radiation
A = Axilla
Abd = Abdomen
Arm = Arm
C = Chest wall
Cer = Cervical nodes
Ch = Cheek
I = Inguinal/groin
IL = Iliac nodes
Ing = Inguinal nodes
M = Mediastinum
N=Nasopharynx
O = Orbit
Pe = Periaortic nodes
S = Spine
St = Sternum
Sup = Supraclavicular nodes
Th = Thigh

Appendix 7. Patient Characteristics and Therapeutic History for Patients Who Developed MDS/AML

Study	MDS (N)	Patient Characteristics	Median No. Chemo Agents	Median No. Treatment Regimens	Median No. Chemo Regimens	Median No. Radiation Therapies	Cytotoxic Regimens (Range)	Annualized Incidence
RIT-I-000	5	Relapsed/refractory Any histology	9	10	9	1	4–13	4.6%
RIT-II-001	5	Relapsed/refractory LG/T-LG	8	7	6.5	1.5	5–14	3.1%
RIT-II-002	3	Relapsed/refractory LG/T-LG	6	4	4	0	2–6	2.7%
RIT-II-003	0	Previously untreated LG/T-LG	0	0	0	0	0	0.0%
RIT-II-004	4	Refractory LG/T-LG	8	4.5	4.5	0	3–6	3.2%
CP-97-012	1	Rituxan Failures	3	3	2	1	3	2.0%
CP-98-020 (EAP)	1	Relapsed/refractory	7	3	3	0	3	0.4%

LG = Low-grade; T-LG = Transformed low-grade.

Appendix 8. Qualifying Prior Chemotherapy

CVP	MINE*	CHOP-Bleo + Alpha Interferon*
C-MOPP*	ESHAP*	COMLA*
BACOP*	DHAP*	Fludarabine
COP-Bleo	EPOCH*	ACP*
CHOP*	CEPP*	Cladribine
CHOP-Bleo*	Pro-MACE-CytaBOM*	MACOP-B*
CP	ICE*	m-BACOD*
Cytoxan or Chlorambucil	COP-BLAM*	VAPEC-B*
COPP*	CNOP*	IM-VP16*
ProMACE-MOPP*	FND*	CF

Single agents of the same class (e. g., alkylating agent or anthracycline) may be substituted within a qualifying regimen. A single drug may be deleted from a 3 or 4 drug qualifying regimen if the patient's lymphoma has previously progressed following receipt of the agent or an agent from the same class or the patient has previously been intolerant to the agent. Additional drugs may be added to a qualifying regimen. Patients must have received at least two cycles (or 6 weeks of a single agent, such as chlorambucil) of the regimen in order to qualify as a failure, unless the patient has clearly progressed during the first cycle of therapy. If the patient received a single course of two qualifying regimens sequentially, this will constitute 2 courses of a qualifying regimen. If a patient received less than 2 cycles (or 6 weeks of a single agent) of a qualifying regimen and did not progress during therapy, this regimen will be considered a non-qualifying therapy.

* Signifies regimen acceptable as treatment for intermediate-grade lymphoma.

Appendix 9. Review of Durable Responders

Patient Number	Issue & TTP (days)	Comments/Recommendation/Resolution
000-002-058	Question of PD on 25 Jan 1999 rather than on 29 January 2001. TTP Assessments Investigator: 1848 MIRROR: 1848 FDA: 1113	Study entry: The MIRROR Panel identified 11 lesions. Study day 48: All lesions had regressed and the patient was classified as a PR. Study day 748: Patient classified as CCR. Study day 1112: a left axillary lesion was reported as having increased from 1.2 x 1.4 cm (1.5 cm^2) to 2.0 x 1.1 cm (2.2 cm^2). This increase did not meet the MIRROR Panel Charter definition of PD. Study day 1847: The MIRROR Panel noted PD. Conclusion: The MIRROR Panel assessment was appropriate.
001-005-008	No baseline lesions at least 2 x 2 cm (i.e., ≥4 cm^2) TTP Assessments Investigator: 1773+ MIRROR: 1080+ FDA: NA	Study entry: By physical examination two nodes in the right neck measuring 1 x 1.5 cm, and 2.2 x 3 cm were identified. Biopsy of one of the nodes confirmed the diagnosis of lymphocytic lymphoma with plasmacytic differentiation. MIRROR Panel identified 5 evaluable lesions ranging from 1.0 cm^2 to 2.52 $cm^{2,}$ with a SPPD of 7.49 cm^2. The RIT-II-001 protocol did not require at least one lesion to be 2 x 2 cm. Study day 50: All lesions decreased to below detectable limits (< 1 x 1 cm) Conclusion: Patient had biopsy proven relapsed NHL at entry and should be included as durable responder. The patient continues in CR on study day 1772.
002-011-009	No baseline lesions at least 2 x 2 cm (i.e., ≥4 cm^2) TTP Assessments Investigator: 993+ MIRROR: 371+ FDA: NA	The patient presented with follicular small-cleaved cell lymphoma, which later transformed to a higher-grade histology on a biopsy performed for rapidly enlarging adenopathy. An FNA was performed prior to study entry was consistent with low-grade lymphoma (small cleaved cell type). Study entry: Investigator reported a 3.2 x 2.1 cm submandibular lesion on MR and 2.5 x 2.0 cm on physical exam. MIRROR Panel identified two evaluable lesions on baseline CT scans: a right jugular node with a PPD of 1.12 cm^2 and a right submandibular node with a PPD of 3.52 cm^2. At entry the protocol did not require at least one lesion to be 2 x 2 cm. Study day 46: All lesions decreased to below detectable limits (< 1 x 1 cm) Conclusion: Patient had biopsy proven relapsed NHL at entry and should be included as durable responder.

Patient Number	Issue & TTP (days)	Comments/Recommendation/Resolution
002-011-016	Two MIRROR Panel reviews followed measurable disease in an area different than the investigator and the patient had a complex medical course potentially confounding assessment of response. TTP Assessments Investigator: 1647+ MIRROR: 1480+ FDA: NA	Eighteen months prior to study entry an open lung biopsy was positive for follicular small cell lymphoma. After chemotherapy failed, repeat bronchoscopy was positive for lymphoma. Study entry: The Investigator noted disease in the lung plus a "midline abdominal lesion anterior to the liver and superior to the kidney"; but stated the only measurable disease was in the right base. MIRROR and MIRROR2 Panels noted disease in the same areas, but stated the only measurable disease was in abdomen. MIRROR2 Panel states at baseline: "condensations of both the lungs probably sequelae". MIRROR Panel and MIRROR2 Panel and the investigator all reported tumor response to therapy and no PD despite following different measurable lesions. Study day 83 The patient was admitted for acute abdominal pain secondary to ascending cholangitis. Cholecystectomy was performed with full resolution of the problem. Study day 1646: The patient had a hemicolectomy and partial omentectomy that identified poorly differentiated adenocarcinoma, most compatible with Stage III ovarian carcinoma. The patient was withdrawn from study for treatment of ovarian carcinoma with chemotherapy. Conclusion: Corixa does not believe that the medical conditions interfered with response assessments.
002-011-915	Question of a PD with a reported 1 cm cervical node in medical notes. TTP Assessments Investigator: 1107 MIRROR: 441 FDA: 131	Study entry: The Investigator identified a right posterior cervical node at baseline measuring 2.0 x 1.2 cm. The MIRROR Panel identified 10 evaluable jugular, supraclavicular or subclavicular lesions. 1.5–2.0 cm cervical nodes were reported in medical notes. Study day 62: On physical exam, Investigator identified regressed 1.0 cm cervical nodes. Study day 105: On physical exam, Investigator identified a 0.5 cm cervical node. Study day 132: On physical exam, the local oncologist identified a 1 cm cervical node. The node does not appear to be a new node. Study day 163: On physical exam, the local oncologist reports the absence of adenopathy. Study day 440: MIRROR Panel determines PD based on a 1 cm supraclavicular node reported by local oncologist. Conclusion: Although the MIRROR Panel did not track the posterior cervical node, they reported that by radiographs the patient had all lesions below detectable level from study day 56 to study day 440. The identified cervical node did not represent PD.

Patient Number	Issue & TTP (days)	Comments/Recommendation/Resolution
002-032-001	Question of PD on study day 349. TTP Assessments Investigator: 694+ MIRROR: 706+ FDA: 350	Study entry: The MIRROR Panel identified 19 evaluable lesions including bilateral inguinal nodes of 6 and 9 cm^2. Study day 90: All lesions are reported to be < 1 x 1 cm on radiographs. Study day 349: "Stable left inguinal adenopathy" was reported in medical notes (no measurements were reported). Study day 433: "1 cm bilateral inguinal lymph nodes" are reported in medical notes. Study day 531: "No palpable adenopathy" is reported in medical notes. Conclusion: The MIRROR Panel radiologist tracked the bilateral inguinal nodes, which were reported on CT scan as <1 x <1 cm on study day 90 to study day 705 and the patient continues in CR. The inguinal adenopathy did not represent PD.
004-013-008	Question of PD on study day 425. TTP Assessments Investigator: 1443+ MIRROR: 1443+ FDA: 426	Early versions of the MIRROR Panel Charter defined measurable disease as any lesion ≥ 2 x 2 cm. This was interpreted operationally by the MIRROR Panel as any lesion with a product of perpendicular diameters (PPD) ≥ 4.0 cm^2. Study entry: The MIRROR Panel radiologist identified 11 evaluable lesions: Study day 425: A 1.8 cm^2 inguinal node and 3.96 cm^2 lower back node that previously had been below detectable limits were identified. Study day 971: Both lesions are reported as below detectable limits. Conclusion: The nodes identified on study day 425 did not meet the MIRROR Panel criteria for PD. Subsequent exams demonstrated the lack of progression. The lesions did not represent PD. The patient remains in CR on study day 1442.
004-014-008	Question of PD on study day 285. TTP Assessments Investigator: 286 MIRROR: 377 FDA: 286	Study entry: The MIRROR Panel identified 19 evaluable lesions of up to 49 cm^2, including a 2 x 3 cm left axillary lesion. Study day 47 to study day 180: The left axillary lesion is reported to be below detectable limits. Study day 285: The SPPD showed no increase from the nadir SPPD. The left axillary lesion is reported as 1.0 x 2.2 cm (2.2 cm^2). This increase did not constitute PD as defined by the MIRROR Panel Charter which required a lesion ≥ 4.0 cm^2. Study day 376: The MIRROR Panel declares PD based on a 48% increase in SPPD, primarily due to an increase in a mesenteric lesion. Conclusion: PD should be based on the SPPD increase on study day 376.

Patient Number	Issue & TTP (days)	Comments/Recommendation/Resolution
004-016-001	Two issues identified: Question of PD on study day 167. TTP Assessments Investigator: 1569+ MIRROR: 1442+ FDA: 168 or 805	Study entry: The MIRROR Panel identified 3 evaluable lesions with PPD of up to 27 cm^2. The patient had documented left axillary adenopathy on physical examination. Study day 167: The MIRROR Panel Oncologist called PD based on a left axillary node, which was interpreted as new disease. Upon the Joint MIRROR Panel Review by the Oncologist and Radiologist (as per Charter), the left axillary node was noted not to have been a new lesion. The Oncologist revised his assessment and documented his reasoning on the case report form: "palpable (L) axillary node also seen on old CT. Therefore, not progression." Study day 804: Investigator withdraws patient from study for PD. CRF states, "patient had a biopsy of a colonic polyp demonstrating a diffuse large cell lymphoma (DLCL)." The Investigator then re-entered patient on study at a later date, when patient records were obtained which noted: "During a routine screening colonoscopy, a lesion was found on the ileocecal valve that was biopsied and came back with a diagnosis of B cell lymphoma. But a CT scan failed to demonstrate any evidence of disease. In addition, the pathology report from the hemicolectomy revealed only lymphoid hyperplasia associated with the villous adenoma which was completely resection." The outpatient progress note stated: "the findings of DLCL within the villous adenoma may have been artifactual secondary to evaluation of a small biopsy sample." Conclusion: On pathology the apparent new lesion did not represent relapsed NHL. The patient continues in CR on study day 1568.
004-016-003	Questioned a change in response by the MIRROR Panel from PD to SD. TTP Assessments Investigator: 1541+ MIRROR: 1477+ FDA: NA	The original MIRROR Panel review that was conducted in 1998 based radiographic response on up to 8 indicator lesions. Per FDA request the MIRROR Panel was reconvened in 1999 and radiographic response was based on all lesions $\geq$ 1 x 1 cm. With the additional of all lesions some of the MIRROR Panel assessments changed. Study entry: The MIRROR Panel identified 3 evaluable lesions of up to 15 cm^2. Study day 130: A change in SPPD that had resulted in an assessment of PD based on indicator lesions, now resulted in an assessment of SD (16% increase in SPPD). Study day 255: All lesions are reported below detectable limits. Study day 1476: All lesions continue to be reported below detectable limits and the patient remains in CR. Conclusion: The change in MIRROR Panel response was due to the inclusion of all lesions (not just indicator lesions).

Patient Number	Issue & TTP (days)	Comments/Recommendation/Resolution
012-035-006	Question of PD on study day 186. TTP Assessments Investigator: 930+ MIRROR: 370 FDA: 187	Study entry: The MIRROR Panel identified 13 lesions, including a 3.8 x 2.8 cm right neck lesion. Study day 46: The right neck lesion was 1.0 x 1.2 cm. Study day 99: No neck CT was available. The eight non-neck lesions are reported below detectable limits. Study day 186: The right neck lesion was reported as 1.0 x 2.5. Per the MIRROR Panel Charter, a lesion had to be >4.0 cm^2 to be considered PD. Study day 369: The neck lesion was reported to be 2.7 x 1.8 cm and the MIRROR Panel reported PD. Conclusion: The MIRROR Panel assessment was appropriate. The Investigator reports the patient in ongoing CR.
012-036-007	Question of PD on study day 475. TTP Assessments Investigator: 510 MIRROR: 510 FDA: 476	Study entry: The MIRROR Panel identified 6 lesions. Study day 475: A 0.5 cm palpable lymph node was identified on physical examination. A 0.5 cm lesion did not represent PD based on the MIRROR Panel Charter, which required a node ≥ 1 cm by physical examination. Study day 509: The MIRROR Panel reported the patient to have PD based on a new supraclavicular lesion. Conclusion: The MIRROR Panel assessment was appropriate.
012-037-001	Question of PD on study day 629. TTP Assessments Investigator: 958 MIRROR: 958 FDA: 630	Study entry: The MIRROR Panel identified 3 lesions, including a 1.7 x 1.5 cm right lower lobe lesion. Between study 49 and study day 629: At the following five assessments the right lower lobe lesion was recorded as 1.5 x 2.3 cm (3.45 cm^2), 2.5 x 2.0 cm (5.0 cm^2), 2.2 x 1.7 cm (3.74 cm^2), 2.0 x 1.5 cm (3.0 cm^2), and 2.5 x 2.0 cm (5.0 cm^2) Study day 629: The increase from 3.0 cm^2 to 5.0 cm^2 met the MIRROR Panel Charter definition of PD. However, employing clinical judgment, the Oncologist documented in a Joint Response Review: "please note that the RLL lesion is unchanged within error of radiographic measurement." Study day 957: MIRROR Panel documented PD, based on the appearance of a new preauricular lymph node. The right lower lobe lesion was reported below detectable limits. Conclusion: The MIRROR Panel assessment was appropriate.

Patient Number	Issue & TTP (days)	Comments/Recommendation/Resolution
012-037-002	Question of eligible histology. TTP Assessments Investigator: 510 MIRROR: 502 FDA: NA	The initial biopsy at diagnosis was read as DLC lymphoma. A BM biopsy 3 days later was interpreted as FSC. Thus, the patient was classified with a diagnosis of transformed low-grade NHL based on multiple biopsies, with one site of low-grade histology (FSC) and one site of intermediate grade histology (DLC) (discordant histologies). The case was reviewed as part of the central pathology review of patients with transformed NHL. The central pathologist confirmed both histologies. Conclusion: The patient was eligible for the study.