

#### 4.0 Mitigating Factors for Interpretation of Clinical Data

None

#### 4.1 Other Discipline Reviews

##### 4.1.1 CMC – including product microbiology, EA, EER

See Dr. Zaremba's review

##### 4.1.2 Pharmacology /Toxicology

See Dr. Green's review

#### 4.2 Auditing Functions

##### 4.2.1 BIMO Outcomes

*The following review of Bioresearch Monitoring Inspection Results was conducted and provided in written format by Dr. Mary Andrich.*

Clinical investigator inspection assignments were conducted at three clinical sites for which the sponsor submitted data to BLA STN 125011 for protocol CP-98\_020: Expanded Access Study of Iodine-131 AntiB1 Antibody for Relapsed/Refractory Low-grade and Transformed Low-grade Non-Hodgkin's Lymphoma. An inspection of the sponsor was also performed. Data for subjects were taken from the BLA and compared to source data at the study sites. The assignment included specific questions about the studies.

Data audits were performed at three clinical trial sites.

| <u>Clinical Site</u>             | <u>Investigator</u> | <u>Date</u>   | <u>FDA Form 483 Classification</u> |     |
|----------------------------------|---------------------|---------------|------------------------------------|-----|
| Rush-Presbyterian Medical Center | Dr. Gregory         | 4/01          | Yes                                | VAI |
| Carolinas Medical Center         | Dr. Frenette        | 7/01 and 4/02 | Yes                                | OAI |
| University of Arkansas           | Dr. Maddox          | 8/02          | Yes                                | OAI |

## INSPECTIONAL FINDINGS—CLINICAL SITES

1. Failure to ensure that the investigation was conducted according to the protocol.
  - a. Enrollment of an ineligible patient. Dr. Maddox (1 subject).
  - b. Failure to calculate and administer the correct therapeutic doses of the investigational product. Dr. Gregory (4 subjects) and Dr. Maddox (3 subjects).
  - c. Failure to obtain follow-up laboratory tests required by protocol. Dr. Maddox (6 subjects).
  - c. Failure to ensure that the Form FDA 1572 listed all subinvestigators. Dr. Gregory.

2. Failure to assay the residual activity in the infusion set following the therapeutic dose, as required by the sponsor.

Dr. Frenette (8 subjects) and Dr. Maddox (7 subjects).

Dr. Frenette assumed a loss of 10% of the activity of the investigational product in the infusion set. However, when his staff performed the assay, the actual residual activity in the infusion set ranged from 0% to 19% of the original assayed dose. Dr. Maddox assumed a loss of 0% of the activity in the infusion set.

3. Failure to provide accurate data to the sponsor.

Reporting of estimated administered doses of the investigational product as actual administered doses. Dr. Frenette (12 subjects) and Dr. Maddox (7 subjects)

4. Failure to prepare and maintain adequate and accurate case histories.
  - a. Failure to maintain source documents to support adverse events reported to the sponsor on CRFs. Dr. Gregory (2 subjects).
  - b. Failure to ensure that data required on the CRFs was transcribed from the records. Dr. Maddox (4 subjects).

An inspection of the sponsor was conducted in 11/02. A Form FDA 483 was issued, and the inspection was classified as OAI.

INSPECTIONAL FINDINGS—SPONSOR

1. Failure to monitor the progress of all investigations conducted under the IND.

Failure to provide adequate monitoring for the following studies: RIT-II-000, RIT-II-001, RIT-II-002, RIT-II-003, RIT-II-004, CP-97-012, and CP-98-020.

- a. Failed to ensure that clinical investigators assayed infusion sets for residual milliCurie activity after administration of the investigational product.

**APPEARS THIS WAY  
ON ORIGINAL**

- b. Failure to ensure that clinical investigators documented changes of the infusion set filter between doses of the cold antibody and the radiolabeled antibody. The inspection revealed that it was not possible to determine when filters were changed during infusions of the study drug.
  - c. Failure to follow the sponsor's SOP for Protocol CP-98-020 entitled "Site Monitoring: Monitoring Visit." This SOP required that every active site be visited a minimum of once per year. There were no monitoring reports for 35 of 38 sites reviewed. Furthermore, the sponsor did not verify the laboratory data for this protocol.
2. Failure to ensure that the investigation was conducted according to the protocols contained in the IND.

Failure to ensure that clinical investigators performed accurate dosimetric calculations, according to the protocol, prior to administration of the therapeutic doses of the investigational product for Protocols RIT-II-004 and CP-98-020.

BIMO ADMINISTRATIVE FOLLOW-UP

A Warning Letter was issued to Dr. Frenette. Untitled letters were issued to Dr. Gregory, Dr. Maddox, and the sponsor.

PREVIOUS BLA INSPECTIONS

In support of BLA 99-0813, inspections of five clinical sites were performed for Protocol RIT-II-004, entitled "Multicenter, Pivotal Phase III Study of Iodine-131 Anti-B1 Antibody (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grade Histologies." In addition one of the sites (University of Nebraska) was also inspected for Protocol RIT-II-001, entitled "Multicenter, Phase II Dosimetry/Validation Study of 131Iodine-AntiB1(murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grades" after the sponsor told the FDA that data from this site was missing. The inspections were conducted in accordance with CPGM 7348.811, the Inspection Program for Clinical Investigators.

Data audits were performed at the following five sites:

| <u>Clinical Site</u> | <u>Investigator</u> | <u>Date</u> | <u>Form 483</u> | <u>Classification</u> |
|----------------------|---------------------|-------------|-----------------|-----------------------|
|----------------------|---------------------|-------------|-----------------|-----------------------|

|                     |                  |       |     |     |
|---------------------|------------------|-------|-----|-----|
| Kaiser/Vallejo      | Dr. Fehrenbacher | 8/99  | No  | VAI |
| Stanford University | Dr. Knox         | 8/99  | Yes | VAI |
| Univ. of Michigan   | Dr. Kaminski     | 9/99  | Yes | VAI |
| Univ. of Washington | Dr. Press        | 9/99  | Yes | VAI |
| Univ. of Nebraska   | Dr. Vose         | 11/99 | Yes | VAI |

A Form FDA 483 was issued to Dr. Knox, Dr. Kaminski, Dr. Press, and Dr. Vose.

**APPEARS THIS WAY  
ON ORIGINAL**

During the inspection of Dr. Fehrenbacher, it was discovered that none of the three subjects listed in the BLA for Kaiser/Vallejo were treated there. Instead, they were enrolled by Kaiser physicians and then sent to Dr. Knox to receive both the diagnostic and the therapeutic doses of the investigational product. Afterwards, they returned to the Kaiser system for follow-up care.

The clinical site inspectional findings are summarized below:

1. Failure to ensure that the investigation was conducted according to protocol and failure to protect the rights, safety, and welfare of a subject under the investigator's care.

One ineligible subject was enrolled by a subinvestigator of Dr. Fehrenbacher, and then sent to Dr. Knox for therapy. At the time of enrollment, Kaiser pathologists were uncertain of the correct diagnosis. They requested another opinion on the pathology from Stanford. However, Dr. Knox treated the subject prior to the correct diagnosis of mantle cell lymphoma, which made him ineligible for therapy.

2. Failure to ensure that the investigation was conducted according to protocol

a. Failure to obtain gamma camera background counts according to protocol.

Dr. Kaminski and Dr. Vose.

b. Failure to calculate and administer the correct therapeutic doses of the investigational product. Dr. Knox (2 subjects) and Dr. Press (3 subjects).

c. Failure to administer pre-treatment doses of potassium iodide according to the protocol. Dr. Kaminski (6 subjects).

d. Failure to assay the residual activity in the infusion set following the therapeutic dose, as required by the sponsor. Dr. Kaminski.

3. Failure to prepare and retain signed and dated consent forms. Dr. Knox (1 subject).

Untitled letters were issued to all five clinical investigators. As a result of these inspectional findings an inspection of the sponsor, Coulter Corporation, was performed in 11/00 and was classified NAI.

#### 4.2.2 Financial Disclosure

In this regard, investigators and consultants were asked to provide information pertaining to:

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

#### *Certification: Financial Interests and Arrangements of Clinical Investigators*

The sponsor has filed to the BLA certification (Form FDA 3454) of the collection of retroactive financial disclosure information from 21 principal/co-principal investigators, and 24 sub-investigators. By filing this form, the sponsor certifies the following:

1. the sponsor has not entered into any financial arrangement with these investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).
2. these clinical investigators are required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests.
3. no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

#### *Due Diligence Without Financial Disclosure*

The sponsor has filed to the BLA, and fully described the process, that due diligence was performed for the following 61 clinical sub-investigators who have not responded to the request for financial disclosure. The sponsor has verified that no financial arrangements occurred as defined in 21 CFR 54.2(a), (c) or (f).

**Table FD1: Sub-investigators Not Providing Financial Disclosure**

| Study                   | Firm/Organization | Investigator Name |
|-------------------------|-------------------|-------------------|
| <b>Study RIT-II-001</b> | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
| <b>Study RIT-II-002</b> | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |
|                         | _____             | _____             |

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| Study                     | Firm/Organization       | Investigator Name |
|---------------------------|-------------------------|-------------------|
| Study RIT-II-002 (cont'd) | _____                   | _____             |
| Study RIT-II-004          | _____<br>_____<br>_____ | _____<br>_____    |
|                           | _____                   | _____             |
|                           | _____                   | _____             |
|                           |                         | _____             |
|                           |                         | _____             |
|                           |                         | _____             |
|                           |                         | _____             |

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*Disclosure: Financial Interests and Arrangements of clinical Investigators*  
 Listed in the following table are investigators disclosing (Form FDA 3455) any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research,

compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

**Table FD2: Investigators Disclosing Any Significant Payments**

| Investigator With Financial Disclosure Information | Institution/Location | Comments   |
|--|----------------------|------------|
| [Redacted]   | [Redacted]           | [Redacted] |
| St.  | [Redacted]           | [Redacted] |
| [Redacted]   | [Redacted]           | [Redacted] |

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Listed in the following table are investigators disclosing (Form FDA 3455) the following:

1. Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study.

and

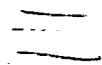
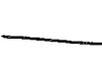
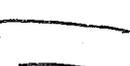
2. Any proprietary interest in the product tested in the covered study held by the clinical investigator.

**Table FD3: Investigators Disclosing Financial Arrangements with the Sponsor and Proprietary Interests in the Product**

| Investigator With Financial Disclosure Information                                   | Institution/Location | Comments |
|--|----------------------|----------|
|  |                      |          |

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**Table FD4: Investigators Disclosing Stock Positions in the Sponsor**

| Investigator With Financial Disclosure Information                                  | Institution/Location  | Comments  |
|---|---|---|
|  |  | Owns shares of stock that were worth over \$50,000. |
|  |  | Owns shares of stock that were worth over \$50,000. |

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*Independent Physician Reviewers: Financial Disclosure*

The sponsor has filed to the BLA certification of collection of retroactive financial disclosure information from the 11 participating physicians on the independent panel assessments including the MIRROR panel.

The sponsor has stated that none of these individuals have any of the following:

1. Financial interest whereby the value of their compensation could be influenced by the outcome of the study
2. Any proprietary interest
3. Any significant equity interest

The sponsor has provided information in the following table on any payments made to these individuals to determine if the payments made exceeded \$25,000 since February 2, 1999.

**Table FD5: Disclosure of Significant Payments to Independent Physician Reviewers**  
**Disclosure of Significant Payments**

| Name             | Significant Payment (≥\$25,000) | Amount    | Description      |
|------------------|---------------------------------|-----------|------------------|
| <del>_____</del> | Yes                             | \$57,700  | <del>_____</del> |
| <del>_____</del> | Yes                             | \$41,050  | <del>_____</del> |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | No                              | NA        | NA               |
| <del>_____</del> | Yes                             | \$104,875 | <del>_____</del> |
| <del>_____</del> | Yes                             | \$54,062  | <del>_____</del> |

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NA = Not applicable – no financial information to disclose.

*Sponsor Efforts to Minimize Bias*

The sponsor has described the following steps to minimize bias of the clinical study results by any of the disclosed arrangements or interests.

1. Clinical Site Monitoring
2. Clinical Audits
3. Independent Assessment of efficacy response data
4. Statistical Analysis of the contribution of clinical sites to detect introduction of bias at one or more clinical sites.

**FDA Review Comment:**

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

**4.3 Other Factors (as necessary)**

**APPEARS THIS WAY  
ON ORIGINAL**

## **5.0 Summative Assessment**

### **5.1 Conclusion on Available Data**

The available safety and efficacy data indicate that Bexxar therapeutic regimen has a clinical benefit with acceptable safety profile in patients with Non-Hodgkin's lymphoma, with or without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. In this group of patients, the median duration of response was 16 months and overall response rate was 68%. The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months.

### **5.2 Recommendations for Regulatory Action**

Recommend approval of Bexxar therapeutic regimen for the treatment of patients with CD20 positive follicular, non-Hodgkin's lymphoma, with or without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.

### **5.3 Review of Labeling**

Please see the attached package label which was finalized and agreed upon after extensive review of the FDA team and the sponsor.

### **5.4 Comments to Sponsor**

None

#### **5.4.1 Comments Regarding Labeling**

None

#### **5.4.2 Comments Regarding Need for Additional Data**

Although the current recommendation of approval is entirely based on the existing data and is deemed sufficient for approval, the sponsor has agreed to perform several post-marketing studies with specific timelines as noted below:

**Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:**

1. To conduct an open-label efficacy trial of Rituximab versus the Bexxar<sup>®</sup> therapeutic regimen in patients with lymphoma who have received at least one, and no more than two prior chemotherapy regimens, and who are appropriate candidates for systemic therapy (Study CCBX001-049). The primary objective of this study is demonstration of a longer event free-survival in patients treated with the Bexxar<sup>®</sup> therapeutic regimen as compared to those receiving Rituximab.

The final protocol will be submitted for special protocol assessment review  
by

August 15, 2003, patient accrual will be initiated by January 2, 2004, patient accrual will be completed by March 3, 2006, and the final study report will be submitted by May 9, 2008.

**APPEARS THIS WAY  
ON ORIGINAL**

2. To conduct an open-label trial of Zevalin versus the Bexxar® therapeutic regimen in patients with lymphoma who have failed at least 3 regimens, one of which was Rituximab (Study CCBX001-053). The primary endpoint of the trial is overall safety. The trial will be designed to demonstrate non-inferiority with regard to efficacy.

The final protocol will be submitted for special protocol assessment review by September 15, 2003, patient accrual will be initiated by January 1, 2004, patient accrual will be completed by July 1, ~~2004~~, and the final study report will be submitted by February 1, 2007.

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3. To conduct a single arm, open label, multicenter, Phase 2 trial evaluating the pharmacokinetics, safety, and efficacy of retreatment with the Bexxar® therapeutic regimen in patients who have had duration of response of at least 6 months in the studies CCBX001-049 and CCBX001-053. The primary objective of the study (Study CCBX001-054) is to compare the pharmacokinetics associated with retreatment and with initial treatment. In addition, the study will assess the safety and efficacy of retreatment with the Bexxar® therapeutic regimen.

The final protocol will be submitted by October 16, 2003, patient accrual will be initiated by March 29, 2004, patient accrual will be completed by October 2, 2006 and the final study report will be submitted by September 29, 2008.

4. To conduct a companion study (Study CCBX001-055) to evaluate the use of prophylactic vaccines in patients with relapsed, follicular, B-cell non-Hodgkin's lymphoma receiving the Bexxar® therapeutic regimen or Rituximab while participating in the trial described in Study CCBX001-049). This study will assess the impact of the anti-lymphoma therapies on development of protective antibody titers to recall and new antigens.

The final companion protocol will be submitted by August 29, 2003, and the patient accrual will be initiated by January 2, 2004, patient accrual will be completed by March 3, 2006, and submission of a final study report will be initiated by May 9, 2008.

5. To collect information on patients who become seropositive for human anti-mouse antibody (HAMA) after treatment on studies CCBX-001-049 and CCBX001-053. The impact of HAMA on the following will be evaluated: ability of patients to receive subsequent therapy in which a component of the therapy was a murine or partially murine protein; alteration in the safety and/or efficacy of subsequent therapy; interference with *in vivo* or *in vitro* diagnostic assays that utilize murine monoclonal antibodies; and ability of patients to undergo *in vivo* diagnostic procedures.

Data will be integrated from studies CCBX001-049 and CCBX001-053 and submitted as a separate stand-alone report, CCBX001-056. This final study report will be submitted by September 9, 2008.

6. To conduct a retrospective study, CCBX001-0057, and a prospective sub-study, CCBX001-058, to determine the prevalence of interference of HAMA with diagnostic *in vitro* assays and the relationship, if any, between interference and level of HAMA.

In the retrospective study, CCBX001-0057, stored sera samples will be assayed from patients who became HAMA seropositive following initial therapy with the Bexxar® therapeutic regimen as initial therapy. The final protocol for the retrospective study will be submitted by September 30, 2003, assay development will be completed by

December 31, 2003, assay of sera will be completed by February 28, 2004, data analysis will be completed by March 31, 2004, and the final study report will be submitted by June 3, 2004.

The prospective sub-study, CCBX001-058, will be conducted on sera from patients in the trials described in studies CCBX001-049 and CCBX001-053 who become HAMA seropositive following treatment. The final protocol for the prospective sub-study will be submitted by October 30, 2003, patient accrual will be completed by February 1, 2005, and the final study report will be submitted by January 1, 2006.

7. To collect information regarding the occurrence of myelodysplasia/acute leukemia in studies involving the Bexxar® therapeutic regimen, including studies in your BLA, BL 125011/0; other studies not contained in the BLA; and those studies that are being designed to address post-marketing commitments or other regulatory requirements. You will submit this information as an integrated analysis designated as CCBX001-059.

The integrated analysis plan, CCBX001-059, for the annual progress report will be submitted by September 30, 2003. On an annual basis, you will submit analyses of the incidence of MDS/AML across all studies based on the plan, CCBX001-059 for 10 years of follow-up period.

8. The sponsor has developed policies and procedures, such that the Corixa/GSK will accept orders for the Bexxar® therapeutic regimen only from sites where both the site and the physician have successfully completed the on-site training for qualification or have completed the certification program. You will conduct a quality assurance (QA) assessment after approval to determine the effectiveness the training program for clinical sites and compliance of the Bexxar Service Center with required procedures.

A complete plan for the quality assurance program (CCQA001-01) will be submitted by September 30, 2003 and a report will be provided at the time of the annual update on postmarketing commitments.

#### **5.4.3 Comments Regarding Other Topics**

None

**APPEARS THIS WAY  
ON ORIGINAL**

## 6.0 Individual Trial / Study Reports

### 6.1 Major Efficacy and Safety Trials

#### *Study CP-97-012*

Title: Phase II Study of Iodine I 131 tositumomab for Non-Hodgkin's Lymphoma Patients who Have Previously Received Rituximab.

Design: Phase 2, single-arm, open-label, multicenter study of iodine I 131 tositumomab in the treatment of non-Hodgkin's lymphoma patients who were previously treated with rituximab therapy without an objective response or who relapsed/progressed during or within 6 months following therapy.

Accrual initiated – July 17, 1998

Closed to enrollment - November 19, 1999

Data-cutoff – December 17, 2000

Final study report: August 17, 2001

Data cut-off: February 8, 2002

#### Principal investigators and study sites

- Stanford University Medical Center- Sandra Horning, M.D.
- M.D. Anderson Cancer Center - Anas Younes, M.D.
- US Oncology Center/Baylor Hospital - Vinay Jain, M.D.

#### Objectives

3. To assess the response rate and duration of response of iodine I 131 tositumomab therapy in patients who were previously treated with at least 4 doses of rituximab and failed to achieve a response (CR, CCR, or PR) or relapsed/progressed during treatment or following completion of rituximab therapy.
4. To assess the safety of Iodine I 131 -tositumomab therapy in patients who were previously treated with at least 4 doses of Rituximab and failed to achieve a response (CR, CCR, or PR) or relapsed/progressed during treatment or following completion of rituximab therapy.

#### Inclusion Criteria (verbatim from protocol after the inclusion of amendments 1-4)

10. Patients must have a histologically confirmed initial diagnosis of low grade non-Hodgkin's B-cell lymphoma according to International Working Formulation (i.e., small lymphocytic [with or without plasmacytoid differentiation]; follicular, small-cleaved; or follicular, mixed small-cleaved lymphoma), low-grade lymphoma that has transformed to higher grade histology, or *de novo* follicular large cell lymphoma.
11. Patients must have evidence that their tumor tissue expresses the CD20 antigen. Immunoperoxidase stains of paraffin-embedded tissue showing positive reactivity with L26 antibody or immunoperoxidase stains of frozen tissue showing positive reactivity with Anti-B1 Antibody or evidence of CD20 positivity by flow cytometry are acceptable evidence of CD20 positivity.

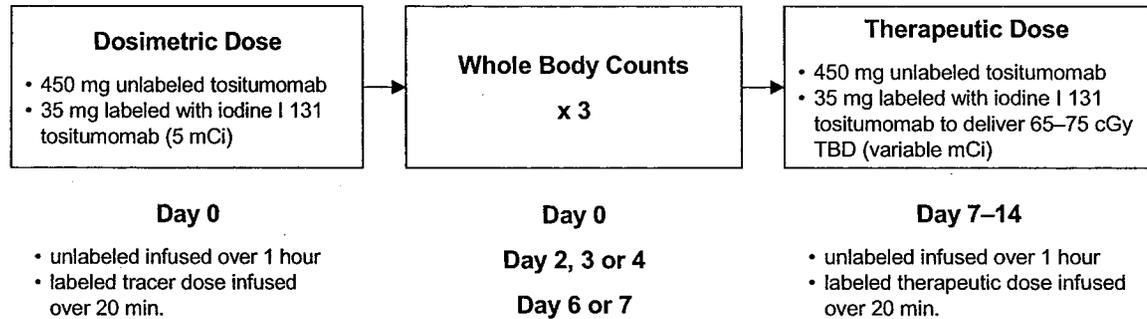
12. Patients must have been treated with at least 4 doses of rituximab at any time and failed to achieve an objective response (CR, CCR, PR), or relapsed/progressed during treatment or following the completion of rituximab therapy.
13. Patients must have a performance status of at least 60% on the Karnofsky Scale and an anticipated survival of at least three months.
14. Patients must have an absolute granulocyte count  $>1500/\text{mm}^3$  (US) or  $>1500 \times 10^9/\text{l}$  (UK) and a platelet count  $>100,000/\text{mm}^3$  (US) or  $>100,000 \times 10^9/\text{l}$  (UK) within 14 days of study entry. These blood counts must be sustained without support of hematopoietic cytokines or transfusion of blood products.
15. Patients must have adequate renal function (defined as serum creatinine  $<1.5 \times$  upper limit of normal) and hepatic function (defined as total bilirubin  $<1.5 \times$  upper limit of normal and hepatic transaminases [AST and ALT]  $<5 \times$  upper limit of normal) within fourteen days of study entry.
16. Patients must have bi-dimensionally measurable disease. At least one lesion must be  $2 \times 2$  cm (by CT scan).
17. Patients must be at least 18 years of age.
18. Patients must give written informed consent and sign an Institutional Review Board/Ethics Committee (IRB/EC)-approved informed consent form prior to study entry.

Exclusion Criteria (verbatim from final protocol which includes amendments 1-4)

16. Patients with more than an average of 25% of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens as assessed microscopically within 42 days of study entry. Bilateral posterior iliac crest core biopsies are required if the percentage of intratrabecular space involved exceeds 10% on a unilateral biopsy. The mean of bilateral biopsies must be no more than 25%.
17. Patients who have received cytotoxic chemotherapy, radiation therapy, immunosuppressants, or cytokine treatment within 4 weeks prior to study entry (6 weeks for nitrosourea compounds) or who exhibit persistent clinical evidence of toxicity. The use of systemic steroids must be discontinued at least 1 week prior to study entry.
18. Patients with prior hematopoietic stem cell transplant following high dose chemotherapy or chemo/radiotherapy.
19. Patients with active obstructive hydronephrosis.
20. Patients with evidence of active infection requiring intravenous (IV) antibiotics at the time of study entry.
21. Patients with New York Heart Association class III or IV heart disease (see Appendix D) or other serious illness that would preclude evaluation.
22. Patients with prior malignancy other than lymphoma, except for adequately treated skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for 5 years.
23. Patients with known HIV infection.
24. Patients with known brain or leptomeningeal metastases.
25. Patients who are pregnant or breastfeeding. Patients of childbearing potential must undergo a pregnancy test within 7 days of study entry and radiolabeled antibody is not to be administered until a negative result is obtained. Males and females must agree to use effective contraception for 6 months following the radioimmunotherapy.
26. Patients with previous allergic reactions to iodine. This does not include reacting to IV iodine-containing contrast materials.
27. Patients who previously received radioimmunotherapy.

28. Patients with progressive disease within 1 year of irradiation arising in a field that has been previously irradiated with >3500 cGy.
29. Patients who are HAMA positive.
30. Patients who are concurrently receiving either approved or non-approved (through another protocol) anti-cancer drugs or biologics.

### Treatment Plan



### Patient Monitoring Plan

Data were collected in three different phases.

2. During the initial study period, patients had data collected during outpatient visits
  - Imaging at several time points over days 0-7 to collect dosimetry data
  - AE data was collected at each visit.
  - Hematologic values were required to be obtained at baseline, weeks 3 though 9, weeks 13 and 25 and thereafter every 26 weeks during the follow-up phase.
  - HAMA values were obtained at baseline, day 5, weeks 7, 13, and 25.
  - Thyroid function (including TSH) data were obtained at baseline, week 25 and during follow up and long-term follow up (after amendment 4) visits.
  - Tumor response was evaluated at baseline and at weeks 7, 13, 25, and during follow-up visits.
4. At week 52, the follow up [FU] phase of visits began every 26 weeks until two years or until the patient withdrew from the study or two years elapsed. Follow up visits included physical examination and history, hematology and serum chemistry and thyroid function tests, radiographic evaluations, information on AEs and medication experience, and bone marrow studies if baseline biopsy was positive for lymphoma.
5. The last phase of monitoring was long-term follow up [LTFU]. LTFU began either after a patient withdrew from study for progressive disease or concomitant therapy or after two years post therapeutic dose. Data was collected every six months. LTFU data initially included only vital status, cancer status, and thyroid function but was expanded in amendment four to include HAMA, TSH sampling and thyroid disease information, second malignancy information and subsequent therapy for NHL by history.

### Original Analytic plan

*No primary endpoint was identified. The following endpoints were listed: response rate, complete response rate, response duration, time to progression, time to treatment failure, and survival. The sample size of 20 patients was selected to enable the response rate to be estimated with a maximum standard error of 0.112 and an expected standard error of 0.10. Point estimates with two-sided 95% confidence intervals would be generated for response rates; patients withdrawing due to death or toxicity before their [response] status could be assessed were considered to have progressive disease (intent-to-treat analysis). Additional analyses of response rates in patients who completed protocol-specified therapy would also be conducted. Kaplan-Meier curves would be generated for time to event analyses (response duration, time to progression, time to treatment failure and overall survival) and mean and median durations for the time to event analyses reported. Adverse events would be summarized by relationship to study drug, organ system and severity. Summaries of patient discontinuations would be provided. The use of supportive care such as CSFs and transfusions would be provided.*

Amendments to the Protocol and amendment date

**Amendment # 1 April 24, 1998**

- Sample size increased from 20 to 40 patients.
- Eligibility (Section 3.1 of protocol) - granulocyte (>1500/ mm<sup>3</sup>) and platelet (>100,000/ mm<sup>3</sup>) counts may be obtained within 14 days prior to study entry rather than within 7 days of study entry (inclusion criteria # 5).
- Eligibility- (Section 3.1 of protocol)- renal and hepatic function times of collection not specified in initial submission. Amendment specifies renal and hepatic function studies be obtained within 14 days of study entry.
- Definition of duration measures changed from start of treatment (i.e., administration of dosimetric dose) to date of enrollment.
- Stratified analysis of response by prior response to rituximab was added to the statistical plan.

**Amendment #2 January 21, 1999**

- Inclusion criteria for CD20 positive tumor modified to remove requirement that  $\geq 50\%$  malignant cells are CD20 positive.
- Removed sentence from evaluations (Section 4 of original submission) which stated that patients who achieved a response had to have a confirmatory evaluation 4 weeks later.
- Follow up defined as starting week 52. As in original submission, visits were scheduled every 26 weeks until two years or progressive disease (withdrawal of patient).
- HAMA assay was previously listed as performed at site and now may be done at either on-site or in a Central laboratory.
- Guidelines for Use of CSF found in Appendix E of protocol modified to read "In adults , the recommended CSF doses are 5 micrograms/kg/d of granulocyte-CSF (G-CSF; filgrastim or lenograstim) or 250 micrograms/m<sup>2</sup>/d of granulocyte-macrophage-CSF (GM-CSF; sargramostim or molgramostim)".

- Added sites in the United Kingdom as additional study sites.

**Amendment 3            May 18, 1999**

- New address for sponsor and change in vial size.

**Amendment 4            August 17, 2001**

- Time to treatment failure deleted from study endpoints
- Masked Independent Randomized Radiographic and Oncologic Review Panel (MIRROR panel) was not included in original submission. The MIRROR panel was added to protocol and will consist of two reviewers (radiologist and an oncologist) as described in other studies. Panel will determine response, confirmed response, CR, confirmed CR, duration of response, confirmed duration of response, TTP, time to death.
- Long term follow-up (LTFU) in original submission included only disease status, vital status and thyroid function. Additional data to be collected now include history of myelodysplastic disease or other malignancies, history thyroid medication, subsequent medications for NHL, TSH and HAMA.
- Administrative changes as a result of merger between Coulter and Corixa.

**Results**

**Patient Enrollment and Disposition**

Forty-three patients were enrolled between July 17, 1998 and November 19, 1999.

Three patients did not receive either the dosimetric or therapeutic dose (012-035-005; 012-036-011; and 012-037-013). Forty patients received both the dosimetric and therapeutic dose.

**ENROLLMENT BY PROTOCOL AMENDMENT**

|                   | Amendment date   | Effective date   | Cumulative enrollment |
|-------------------|------------------|------------------|-----------------------|
| Original protocol | January 8, 1998  | January 9, 1998  | 0                     |
| Amendment 1       | April 24, 1998   | May 6, 1998      | 0                     |
| Amendment 2       | January 21, 1999 | January 22, 1999 | 23                    |
| Amendment 3       | May 18, 1999     | June 3, 1999     | 29                    |
| Amendment 4       | August 17, 2001  | August 24, 2001  | 43                    |

Six patients withdrew from the study in the first 90 days. These six patients included three patients who died before day 90 (012-035-008 died day 51; 012-036-005 died day 66 and 012-037-005 died day 35 [see patient précis at end report]). Four of the six patients had chemotherapy within a short period of time. The reason cited for removal from study was disease progression in all 6 patients.

- 012-035-005: Patient withdrew for progressive disease after registration and prior to receipt of dosimetric or therapeutic dose.
- 012-036-011: Patient withdrawn because he was still responding to prior rituximab therapy
- 012-037-013: patient withdrew to seek alternative therapy

#### DEATHS WITHIN THE FIRST 90 DAYS OF STUDY ENTRY

- 012-035-008: Tumor lysis syndrome, hypoxia, hypercalcemia, death (study day 51)
- 012-036-005: Death on study day 66
- 012-037-005: Death on study day 35 due to aspiration pneumonia

#### Conduct of the Study

##### BioResearch Monitoring

FDA did not conduct on-site audits of the clinical data obtained under this study at any of the study sites

##### Financial Disclosures:

None of the principal investigators for this study had financial arrangements with the sponsor that required reporting.

##### Protocol Violations:

Twenty-one of the 43 patients enrolled (49%) had one or more protocol violations (total of 29 separate protocol violations). Protocol violations were classified by the sponsor in the following categories as entry, concomitant medication, withdrawal and treatment violations. The 8 treatment and 21 entry violations are listed in the table below.

Entry violations compromised the ability to assess the tositumomab therapeutic regimen activity in 5 patients. These included 2 patients who lacked measurable lesions, two patients without radiographic baseline studies, and one patient who was still responding to prior rituximab therapy.

Among the most serious treatment violations were two patients (012-037-003 & 012-036-005) who were seropositive for HAMA on study day 5 and received the therapeutic dose of I 131 tositumomab despite the HAMA results and two patients who were non-compliant for Lugol's solution (012-037-005 & 012-35-007) administration. The two patients who were seropositive for HAMA died on day 112 and 66 respectively and there are limited safety data of the impact of this violation. Neither patient was reported to have had infusional reactions. The patient who was non-compliant with Lugol's solution administration had an elevated TSH at baseline; no other TSH data were available. The second non-compliant patient, 012-035-007, had dosimetric and therapeutic dose infusional reactions, but had normal TSH values post-treatment.

| Patient ID | NHL grade | CGY* | Study day | Violation type | Violation description |
|------------|-----------|------|-----------|----------------|-----------------------|
|------------|-----------|------|-----------|----------------|-----------------------|

| <b>No measurable tumor sites</b>                                |   |    |     |           |   |
|---|---|----|-----|-----------|---|
| 012-035-005   | T | 0  | na  | Entry     | No tumor measuring 2x2 cm or > at baseline  |
| 012-037-001   | L | 65 | -10 | Entry     | No tumor measuring 2x2 cm or > at baseline  |
| <b>Failure to obtain radiologic studies at appropriate time</b> |   |    |     |           |   |
| 012-035-011   | L | 75 | -38 | Entry     | Chest, abdomen and pelvis CT scans not done within 28 days of enrollment; performed day 29      |
| 012-036-001   | L | 75 | -34 | Entry     | Head/neck and chest CT scans were not done within 28 days of enrollment; performed day 29       |
| 012-036-002   | L | 75 | -17 | Entry     | Chest CT scan was not done at baseline; no report chest x-ray baseline, weeks 7,13,25           |
| 012-036-006   | I | 75 | -2  | Entry     | Chest, abdomen and pelvis CT scans were not done at baseline; first entry of chest x-ray week 7 |
| <b>Violations of eligibility or timing of data collection</b>   |   |    |     |           |   |
| 012-037-005   | T | 75 | 15  | Entry     | Therapeutic dose not within 6-14 days of dosimetric dose due to hypercalcemia                   |
| 012-037-006   | I | 65 | 15  | Entry     | Therapeutic dose not received within 6-14 days of dosimetric dose                               |
| 012-037-015   | L | 75 | 0   | Entry     | Dosimetric dose received more than 10 days after enrollment                                     |
| 012-035-015   | T | 75 | -14 | Entry     | Pregnancy test done greater than 7 days prior to enrollment                                     |
| 012-035-003   | T | 65 | 0   | Entry     | Dosimetric dose date is > 10 days after enrollment date   |
| 012-037-004   | I | 75 | -23 | Entry     | Hematology done > 14 days prior to enrollment   |
| 012-037-002   | T | 75 | -6  | Entry     | Patient had a prior bone marrow transplant 1993   |
| 012-037-002   | T | 75 | -6  | Entry     | Initial diagnosis of diffuse large cell lymphoma from lymph node bx on 5/17/91                  |
| 012-037-004   | I | 75 | -6  | Entry     | History of prostate carcinoma in 10/94  |
| 012-035-008   | L | 75 | -6  | Entry     | Patient received 4 weeks of electron beam therapy within 4 weeks of enrollment                  |
| 012-035-005   | T | 0  |     | Entry     | Progression within previously irradiated field (Patient did not receive drug)                   |
| 012-036-001   | L | 75 | -34 | Entry     | Unilateral BM biopsy showed tumor involvement 25%; bilateral biopsy not done                    |
| 012-036-008   | L | 75 | -14 | Entry     | ANC 1490 at baseline  |
| <b>Informed consent</b>   |   |    |     |           |   |
| 012-037-001   | L | 65 | -2  | Entry     | Enrolled prior to signing consent (signed consent prior to receiving study drug)                |
| 012-037-003   | T | 75 | -6  | Entry     | Enrolled prior to signing consent (signed consent prior to receiving study drug)                |
| <b>Nuclide violations</b>                                       |   |    |     |           |   |
| 012-037-005   | T | 75 | 21  | Treatment | Iodide noncompliance, all meds stopped when patient intubated and sent to ICU                   |
| 012-035-007   | T | 75 | 16  | Treatment | Patient missed 3 days of SSKI secondary to GI upset   |
| 012-035-012   | L | 75 | 28  | Treatment | Therapeutic dose not within 6-14 days of dosimetric dose due to delay at Nordion supplier       |
| 012-036-007   | L | 75 | 14  | Treatment | Difference between prescribed and actual mCi dose > 10%   |
| 012-036-  | L | 75 | 0   | Treatment | Time started for Day 0, Day 2 and Day 6 background counts                                       |

|             |   |    |    |           |  |
|-------------|---|----|----|-----------|--|
| 010         |   |    |    |           | (dosimetry) unknown  |
| <b>HAMA</b> |   |    |    |           |  |
| 012-036-001 | L | 75 | 12 | Treatment | HAMA not done at Day 5                                       |
| 012-036-005 | T | 75 | 12 | Treatment | HAMA positive at Day 5 but therapeutic dose still delivered  |
| 012-037-003 | T | 75 | 12 | Treatment | HAMA positive at Day 5, but therapeutic dose still delivered |

### Study Population

The subjects enrolled in this study had similar baseline entry characteristics to those enrolled in study RIT-II-004 in terms of proportion with transformed disease, distribution of stages of disease, proportion with bulky disease, and prior treatment history, with the sole exception that all patients must have progressed following treatment with rituximab.

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Baseline Entry Characteristics for Study Population in Study CP 97-012

| Baseline entry characteristic                 | ITT population<br>n=43 |
|---|------------------------|
| Age (years)                                   |                        |
| Median(range)                                 | 56 (35-78)             |
| Q1; Q3  | 49; 65                 |
| Gender  |                        |
| Males (%)                                     | 29 (67%)               |
| Race  |                        |
| Caucasian (%)                                 | 35 (81%)               |
| Histologic diagnosis at entry                 |                        |
| W/o transformation                            |                        |
| Low grade                                     | 27 (63%)               |
| Intermediate grade                            | 3 (7%)                 |
| High grade                                    | 0                      |
| With transformation                           |                        |
| Low grade                                     | 1(2%)                  |
| Intermediate grade                            | 12 (28%)               |
| High grade                                    | 0                      |
| Stage of disease                              |                        |
| I   | 1 (2%)                 |
| II  | 7 (16%)                |
| III   | 9 (21%)                |
| IV  | 26 (61%)               |
| Missing                                       | 0                      |
| IPI category                                  |                        |
| 0   | 2 (5%)                 |
| 1   | 12 (28%)               |
| 2   | 15 (35%)               |
| 3   | 5 (12%)                |
| 4   | 4 (9%)                 |
| 5   | 1 (2%)                 |
| Missing                                       | 4 (9%)                 |
| Max. tumor diameter                           |                        |
| < 5 cm  | 24 (56%)               |
| ≥ 5, ≤10 cm                                   | 14 (33%)               |
| > 10 cm                                       | 5 (12%)                |
| # Prior chemo regimens                        |                        |
| Median (range)                                | 4 (1-11)               |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 3, 5                   |
| # Prior RT regimens                           |                        |
| Median (range)                                | 0 (0-4)                |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 0, 1                   |
| No Prior BMT                                  | 42 (98%)               |
| Time from diagnosis to entry (yrs)            |                        |
| Median i(range)                               | 4.2 (1.0, 14.2)        |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 2.7, 7.0               |

Efficacy Analyses

No primary efficacy endpoint was identified in the protocol. The analytic plan stated that analyses would be conducted in the intent-to-treat population, which was not further defined. The analytic plan also stated that additional analyses of response rates in patients who completed protocol-specified therapy would also be conducted. In addition, the proposed indicated population to be supported by this study differs from that eligible for the study. For these reasons, all pre-specified analyses were assessed in three populations:

- An intent-to-treat (ITT) population that includes all of the patients registered in the study (n=43). In the ITT analyses, patients who did not receive the tositumomab therapeutic regimen are treated as patients with no response and a response duration of 0 days.
- The “treated” population that includes all patients who received all or part of the tositumomab treatment regimen (n=40);
- The “proposed indication” population that includes patients with rituximab refractory, follicular NHL without major eligibility violations (n=30) The “indicated” population excludes 13 subjects listed below (some subjects are overlapping):
  - 3 subjects who did not receive the tositumomab therapeutic regimen (patients 012-035-005, 012-036-011 & 012-037-013)
  - 5 subjects with prior responses to rituximab that were durable for  $\geq 6$  months, i.e., were not rituximab-refractory (patients 012-035-001, 012-036-012, 012-037-002, 012-037-007 & 012-037-009)
  - 2 patients who lacked baseline radiographic studies (patients 012-036-002 & 012-036-006),
  - 2 patients without measurable 2 x 2 cm lesions (patients 012-035-005 & 012-037-001)
  - 1 patient who had a treatment within 4 weeks prior to enrollment (012-035-008).
  - 2 patients who did not have follicular histology (012-035-008 and 012-036-002)
  - 2 patients with follicular histology with transformation (012-037-002 and 012-035-015)

### Pre-specified Efficacy Analyses

The pre-specified study endpoints were response rate, complete response rate, response duration, time to progression, time to treatment failure, and survival. Time to treatment failure was removed as an endpoint in the fourth and final amendment to the protocol. Analyses of time to progression, time to treatment failure, and survival were not provided in FDA’s analyses, because these data cannot be interpreted in a study that does not contain an internal control population.

## Response Rates and Duration of Response for the Study CP-97-012

|   | ITT Investigator or (n=43)                  | ITT MIRROR (n=43)                            | Treated Investigator or (n=40)              | Treated MIRROR (n=40)                        | Indicated Invest. assess (n=30)             | Indicated MIRROR (n=30)                          |
|---|---|--|---|--|---|--|
| Overall response rate<br>(Number of responders)<br>95% CI   | 60% (26)<br>44%, 75%                        | 63% (27)<br>47%, 77%                         | 65% (26)<br>48%, 79%                        | 68% (27)<br>51%, 81%                         | 60% (18)<br>41%, 77%                        | 63% (19)<br>44%, 80%                             |
| Median Duration<br>(Years)<br>(K-M Curves)<br>95% CI on Median<br>IQ Range in Years<br>Range in Years | 1.9<br>0.9, ---<br>0.7, ---<br>0.3,<br>2.9+ | 1.3<br>0.8, ---<br>0.8, ---<br>0.1+,<br>2.9+ | 1.0<br>0.9, ---<br>0.7, ---<br>0.3,<br>2.9+ | 1.3<br>0.8, ---<br>0.8, ---<br>0.1+,<br>2.9+ | ---<br>1.3, ...<br>1.3, ---<br>0.3,<br>2.9+ | 2.1 yrs<br>0.9, ---<br>0.9, ---<br>0.3+,<br>2.9+ |
| CR (%)<br>95% CI  | 14% (6)<br>5%, 28%                          | 26% (11)<br>14%,<br>41%                      | 15% (6)<br>6%, 30%                          | 28% (11)<br>15%, 44%                         | 17% (5)<br>6%, 35%                          | 23% (7)<br>10%, 42%                              |
| CCR (%)<br>95% CI   | 19% (8)<br>8%, 33%                          | 5% (2)<br>1%, 16%                            | 20% (8)<br>9%, 36%                          | 5% (2)<br>1%, 17%                            | 20% (6)<br>8%, 39%                          | 3% (1)<br>0%, 17%                                |
| PR (%)<br>95% CI  | 28% (12)<br>15%, 44%                        | 33% (14)<br>19%,<br>49%                      | 30% (12)<br>17%, 47%                        | 35% (14)<br>21%, 52%                         | 23% (7)<br>10%,<br>42%                      | 37% (11)<br>20%, 56%                             |

--- indicates not reached  
+ indicates censored

The protocol was amended four times; the last amendment, which stated that efficacy analyses would be conducted according to MIRROR panel assessment, was activated more than one year after the last patient was enrolled. Therefore, it is appropriate to present both the investigator-assessed response rates and that derived from MIRROR panel review. The FDA assessed for concordance between the investigator-assessment and the MIRROR Panel assessment of response (CR + CCR + PR) and non-response (SD + PD). There were no significant differences ( $p = 1.0$ , McNemar's test) with only one discrepancy in determination of objective response. However, among the categories of response, the MIRROR panel identified a higher proportion of patients with CR as compared to the investigators; the latter identified a higher proportion of patients with CCR. In analyses where CR and CCR rates are pooled, this difference would not change the analysis.

### Other protocol-specified analyses

- In amendment 1, the analytic plan was revised; stating that analyses of response would be "stratified by response to prior Rituxan." The protocol does not provide additional details on the proposed stratification. For purposes of this analysis, the response rates are analyzed according to patients who responded to rituximab and

those who failed to respond to the most recent rituximab regimen. Since rituximab has a long serum half-life and can be detected in the serum 6-9 months after receiving a single 4 weekly course, patients in whom the response to rituximab was less than 6 months should be classified as refractory and analyzed with those who fail to achieve a response. As can be seen in the next table, the response rates to the tositumomab therapeutic regimen does not appear to differ qualitatively in patients who failed to respond to rituximab as compared to those who were responsive, although the duration of response is shorter in the rituximab non-responsive patients.

**Response rate to I 131 tositumomab in subsets of the study population based on prior response to rituximab.**

| Prior response to most recent rituximab regimen | Response to the tositumomab therapeutic regimen | Median Duration of response to the tositumomab therapeutic regimen |
|---|---|--|
| Rituximab-responsive (CR, CCR, or PR)           | 11/18 (61%)                                     | 2.1 years  |
| Rituximab non-responsive (PD OR SD)             | 16/25 (64%)                                     | 1.3 years  |

There were 4 patients enrolled who achieved a CR, CCR or PR to the most recent rituximab course that was durable for  $\geq 6$  months. The results in these patients whose disease was not refractory to rituximab are summarized as follows:

| Patient ID           | Rituximab Response | Duration of Response- Rituximab in Years | Tositumomab Therapeutic Regimen Response | Duration of Response- Tositumomab in Years |
|----------------------|--------------------|--|--|--|
| 012-036-001 41F L75B | PR                 | 0.5                                      | PR                                       | 0.8  |
| 012-036-012 50F L75B | CR                 | 0.6                                      | CR                                       | 1.9+                                       |
| 012-037-002 57M T75B | PR                 | 1.2                                      | CR                                       | 1.2  |
| 012-037-007 58F T75B | CR                 | 1  | PR                                       | 0.1+                                       |
| 012-037-009 52M L75B | PR                 | 0.6                                      | CR                                       | 0.8  |

- In amendment 4, the analytic plan in the protocol was modified to an analysis of comparison of the duration of response to the tositumomab therapeutic regimen and to the most recent rituximab regimen

Using the same algorithm as applied in study RIT-II-004, the following table provides a summary of the results for the comparison of response durations for the tositumomab therapeutic regimen and prior rituximab :

| Response                         | Frequency | % of 43 |
|----------------------------------|-----------|---------|
| Equivalent response duration     | 11        | 26 %    |
| Longer duration with tositumomab | 25        | 58 %    |
| Longer duration with Rituximab   | 7         | 16 %    |

The sign-rank test was used in FDA's analysis because it takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is a statistical change. The proportion of patients for whom the tositumomab therapeutic regimen provided more durable responses was significantly larger (sign-rank test)

The analysis of proportions was performed as follows:

- Let  $p_1$  = proportion of responses with equivalent duration to the tositumomab therapeutic regimen and to rituximab
- $p_2$  = proportion of responses with longer duration to the tositumomab therapeutic regimen
- $p_3$  = proportion of responses with longer duration to rituximab

Of interest is a test of the null hypothesis  $H_0 : p_2 = p_3$  conditioned on equivalent response, i.e., ignoring equivalent response, and  $n$  becomes 32, and test is  $H_0 : p_2 = p_3 = 0.5$  versus  $H_1 : p_2 \neq p_3$ .

$p$ -value for testing this  $H_0$  was significantly different (two sided, Fisher's exact) in favor of the tositumomab therapeutic regimen

| ITT population (n=43) |          |                         |         |       |
|-----------------------|----------|-------------------------|---------|-------|
|                       |          | Response to Tositumomab |         |       |
|                       |          | Response                | No Resp | Total |
| Response to Rituximab | Response | 11                      | 7       | 18    |
|                       | No Resp  | 16                      | 9       | 25    |
|                       | Total    | 27                      | 16      | 43    |

p-value (McNemar) = 0.0719

## SAFETY ASSESSMENT

The most frequent adverse events were hematologic toxicities. The incidence of grade 3-4 toxicities were 43%, 25%, and 10% for neutropenia, thrombocytopenia, and anemia, respectively. The most frequent non-hematologic toxicities were asthenia (35%), fever (30%), infection (28%), increased cough (23%), nausea (20%), pain (15%), pneumonia and dyspnea (13% each), vomiting (13%), rash (13%), vomiting (13%), arthralgia (10%) and myalgias (10%). The major organ systems affected were gastrointestinal (43% of patients) and respiratory (40% of patients). Other than the infectious events, most of the non-hematologic toxicity was mild to moderate in severity (NCI CTC grade 1-2). This study is notable for the relatively high rate of infections. A separate summary is provided for the hematologic toxicity, infectious complications, and infusional reactions.

**Infusion related AE .** The study required pre-medication with acetaminophen and an antihistamine 30 minutes prior to the dosimetric and the therapeutic infusions. Infusion-related AEs were reported in 10% (4/40) of the dosimetric infusions and 20% (8/40) of the therapeutic infusions. The symptom complex of infusion-related AEs includes nausea, chills and fever, pruritus and vomiting; 85% of these were NCI CTC grade 1 or 2. One patient (012-0360001) experienced grade 3 arthralgia, nausea, hypovolemia and vomiting during the therapeutic infusion on day 14. This reaction lasted 5 days and was not described as serious.

**Infections:** Infection-specific data case report forms were used during the first 12 weeks following the therapeutic dose. Infections were observed in 55% (22/40) of the patients; 22% of the infections were pneumonia (6 patients) and 7% were sepsis (2 patients). Almost all patients, 24/27, received antibiotics. The six cases of pneumonia are outlined below; two of the cases were in the same patient.

### Cases of pneumonia

| Patient ID  | NHL grade | AE grade | Serious AE | Study day | Duration (days) | Therapeutic measures                     |
|-------------|-----------|----------|------------|-----------|-----------------|--|
| 012-036-010 | L         | 2        | No         | 82        | 8               | Prescription drug(s)                     |
| 012-035-008 | L         | 3        | No         | 8         | 9               | Prescription drug(s)                     |
| 012-037-005 | T         | 3        | Yes        | 21        | 15              | Prescription drug(s) & hospitalization   |
| 012-037-006 | I         | 3        | Yes        | 5         | 8               | Prescription drug(s) and hospitalization |
| 012-037-    | I         | 3        | No         | 41        | Na              | Prescription drug(s)                     |

|             |   |   |    |    |    |                      |
|-------------|---|---|----|----|----|----------------------|
| 006         |   |   |    |    |    |                      |
| 012-037-007 | T | 3 | No | 71 | 21 | Prescription drug(s) |

L =low grade NHL ; T =transformed low grade NHL; I is intermediate grade NHL; Na = not available

### Per-Patient Incidence and Duration of Severe Hematologic Toxicity Study CP 97-012

| Hematologic toxicity       |                   |
|----------------------------|-------------------|
| Grade 3-4 neutropenia      | 43%               |
| Median duration (95% CI)   | 30 days (18, 43)  |
| Grade 3-4 thrombocytopenia | 25%               |
| Median duration (days)     | 32 days (15, 51)  |
| Grade 3-4 anemia           | 10%               |
| Median Duration (days)     | 36 days (16, ---) |

**Deaths during first 90 study days:** Three subjects died during the first 90 study days. Summary précis are given below. One of the patients who died (patient 012-035-008) withdrew from the study shortly after an agent related AE (tumor lysis syndrome). See subject précis in last section of this report.

- 012-035-008: Tumor lysis syndrome, hypoxia, hypercalcemia, death on study day 51.
- 012-036-005: Death on study day 66
- 012-037-005: Death on study day 35 due to aspiration pneumonia

**Serious adverse events:** There were 18 serious adverse events (SAE) reported for 8 patients (20% of the study population). Six of the 8 patients who experienced SAE were enrolled at one study site. Two patients who suffered SAE died prior to study day 90.

#### Serious Adverse Events

| Patient     | Study day of SAE | Description SAE                      |
|-------------|------------------|--------------------------------------|
| 012-035-002 | 767              | Myelodysplasia                       |
|             | 804              | AML                                  |
| 012-035-008 | 8                | Hypoxia and tumor lysis syndrome     |
|             | 16               | Hypercalcemia                        |
| 012-037-003 | 48               | Hypercalcemia & acute renal failure  |
| 012-037-004 | 4                | Severe leg pain                      |
|             | 32               | Severe leg pain                      |
| 012-037-005 | 7                | Hypercalcemia & respiratory distress |

|             |    |  |
|-------------|----|--|
|             | 9  | Hypotension  |
|             | 19 | Staphylococcus septicemia, dyspnea, pleural effusion |
|             | 21 | Cardiac arrhythmias, respiratory distress, pneumonia |
|             | 25 | Right arm deep venous thrombus                       |
| 012-037-006 | 5  | Pneumonia  |
|             | 7  | Fever  |
| 012-037-011 | 7  | Anemia   |
|             | 14 | Anemia   |
|             | 20 | Anemia   |
| 012-037-012 | 88 | Abdominal cramps                                     |

## NARRATIVE DESCRIPTION OF PATIENT DEATHS DURING FIRST 90 STUDY DAYS

Patient 012-035-008: A 48 year old male was initially diagnosed with small cell lymphocytic lymphoma with plasmacytoid changes in June 1967. Four courses of chemotherapy included chlorambucil, cyclophosphamide and prednisone, rituximab and cyclophosphamide and fludarabine. At time of entry, the patient had increasing abdominal, inguinal and mediastinal adenopathy, subcutaneous nodules and fatigue, and an LDH of 608 IU/L. The day after the therapeutic dose the patient was diagnosed as having a tumor lysis syndrome manifested by respiratory distress, serum uric acid of 10.6 mg/dL, LDH of 4176. The syndrome was considered probably related to study agent. Hospitalization with aggressive hydration and allopurinol followed. A chest film showed lobe consolidation and pleural effusion. After recovery and discharge from the hospital, the patient was evaluated as having progressive disease and was withdrawn from the study on day 15; he started 3 days later on a chemotherapy regimen and died study day 51.

Patient 012-036-005: A 77 year old male was diagnosed with follicular, small cleaved cell NHL on 10/1992 and received CHOP, CNOP, carmustine and etoposide, fludarabine, interferon, cyclophosphamide, cladrubine, and teniposide and rituximab therapies in addition to three courses of radiotherapy to the lower spine. Patient entered study 12/1998. The 7 week assessment disclosed progressive NHL in the chest, abdomen and pelvis by CT; there were new lesions by physical examination. Subject withdrew on study day 49 and died on day 66.

Patient 012-037-005: A 63 year old male was initially diagnosed with follicular, small cleaved lymphoma in October 1998 and treated with courses of MACOP-B, MINE, ESHAP, alpha interferon, EPOCH, methotrexate and cytarabine, ESHAP, liposomal vincristine, rituximab, liposomal atragen, cyclophosphamide and etoposide, and vinblastine, dacarbazine plus 2 courses radiotherapy. When he presented for the therapeutic dose he was disoriented and lethargic; serum calcium was 12.5. A right scapular mass and worsening pleural effusion was related to lymphoma. After improvement the patient was given the therapeutic dose on 4/9/98 and 4 days later noted shortness of breath. During hospitalization blood cultures were positive for Staphylococcus and antibiotics were started. Venous thrombosis of the right arm developed. He died on day 35 of respiratory failure due to aspiration pneumonia.

### Narrative Description of Serious Adverse Events

Patient 012-035-002 : A 63 year old male was diagnosed with follicular, mixed small cleaved cell NHL in May 1996. He received courses of fludarabine, cyclophosphamide and rituximab plus one course of radiotherapy. After a partial response the patient withdrew for progressive disease and received additional therapy (not named). September 2000 he reported dyspnea, fatigue. A complete blood count showed low platelets. Myelodysplastic disease was diagnosed following a bone marrow.

Patient 012-035-008: Précis under deaths

Patient 012-037-003: A 66 year old male was diagnosed with follicular, small cleaved cell NHL in 5/1997 and received courses of CHOP, ProMACE-CytoBOM, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine and methotrexate and rituximab. Transformation to diffuse large cell lymphoma was observed. He entered study on 12/1998 and was hospitalized study day 48 because of hypercalcemia and acute renal failure. Calcium was 17 mg/dL. A CT scan showed increased adenopathy. Treatment with furosemide and hydration was started. The patient withdrew from study for progressive disease on the second hospital day and started on fludarabine and dexamethosone. Hydronephrosis of left kidney was observed and considered secondary to lymphadenopathy.

Patient 012-037-004: A 78 year old male was diagnosed with follicular, large cell lymphoma in 2/92 and received CHOP, prednisone, rituximab and cyclophosphamide. Medical history included prostate carcinoma in 1994. Entered study 1/99. Hospitalized on \_\_\_\_\_ for nerve block treatment of severe leg pain. He was further treated for the leg pain on \_\_\_\_\_ with laminectomy.

b(6)

Patient 012-037-006: Enrolled on March 24, 1999, received dosimetric dose on April 1, 1999. Patient was hospitalized with fever and RLL consolidation (sputum revealed gram positive cocci and rods) on / \_\_\_\_\_. The therapeutic dose of 131-I-tositumomab was given on / \_\_\_\_\_ (study day 15).

b(6)

Patient 012-037-006: A 64 year old female was diagnosed with follicular, large cell lymphoma in 2/1996 and received CHOP, interferon, mitoxantrone and prednisone, rituximab, FND and MINE. Entered study in 3/1999. Prior history of asthma and chronic bronchitis. Hospitalized for chest congestion study day 5 and treated for pneumonia [R lower lobe consolidation] with antibiotics. The patient improved with antibiotic therapy, blood cultures were negative and she was discharged on / \_\_\_\_\_.

b(6)

Patient 012-037-011: Patient was enrolled on July 7, 1999 with baseline hemoglobin of 6.3 gm/dL, hematocrit of 19.5%, and platelet count of 143,000 cells/ $\mu$ l. He received the dosimetric dose on July 15 and was returned for the therapeutic dose on July 22, 1999. However the dose was withheld when it was noted he had a hemoglobin of 5.8 gm/dL. He then received 2 units of packed RBC.

Patient 012-037-005: see précis under deaths

Patient 012-037- 011: A 52 year old male was diagnosed with follicular, mixed, small-cleaved cell lymphoma in 7/1998 and received CHOP, rituximab, ESHAP. Prior history fatigue and colon polyps. Entered with baseline hemoglobin of 6.3 g/dL . Platelets were 143,000/mm<sup>3</sup>. Therapeutic dose postponed because of anemia. After red blood cell transfusions, the tositumomab therapeutic regimen was initiated. The therapeutic dose was administered on July 28, 1999. The patient subsequently received additional RBC transfusions on July 29 (2 units) and August 4, 1999 (2 units). Hematocrit was stable between 29-33% from August 11, 1999 through October 26, 1999, without additional transfusions.

Patient 012-037-012: A 36 year old female was diagnosed with follicular small cleaved cell lymphoma (<50% large cells) in June 1997. Prior treatments included CVP, alpha interferon, and rituximab. She was enrolled in this study on July 19, 1999, received the dosimetric infusion on July 29, 1999 and the therapeutic infusion on August 5, 1999 (91.9 mCi; 75 cGy TBI). The patient began complaining of abdominal cramping on study day 88 and was hospitalized on \_\_\_\_\_ for management of abdominal pain, nausea, vomiting and bleeding. Lymphomatous involvement of the small bowel was reported following endoscopy on Dec. 6, 1999. CT of the abdomen on January 26, 2000 revealed increased thickening of the bowel and the patient was withdrawn for progressive disease on Feb. 3, 2000. The patient began CHOP chemotherapy on Feb. 18, 2000.

b(6)

#### *Study RIT-II-004*

Title: Multicenter, Pivotal Phase 3 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.

Design: A multicenter, historically-controlled, single-arm trial in patients with chemotherapy-refractory low grade or follicular NHL, with or without transformation.

Study opened- November 22, 1996

Study closed to accrual - March 6, 1998

Data cut-off- January 28, 2002

#### Study Sites

- Christie Hospital (UK)
- Cornell Medical Center
- Dana-Farber Cancer Institute
- Georgetown University
- Kaiser Permanente Medical Center
- Memorial Sloan-Kettering Cancer Center
- Rush-Presbyterian-St. Luke's Medical 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
- University of Washington

- Yale University School of Medicine

### Specific Aims and Objectives (original protocol)

1. To establish the response rate, response duration, time to progression, time to treatment failure and survival after treatment with iodine I-131 tositumomab Radioimmunotherapy (RIT) in patients with chemotherapy-refractory low-grade or transformed non-Hodgkin's lymphoma
2. To compare these endpoints to the patient's previous chemotherapy outcome
3. To assess the safety of iodine I-131 tositumomab RIT
4. To assess the quality of life of treated patients using the EORTC QLA-C30(+3) validated questionnaire.

### Eligibility criteria (original protocol)

#### Inclusion Criteria

1. Histologically confirmed diagnosis of CD20 positive low-grade or transformed low-grade non-Hodgkin's lymphoma.
2. Treatment with at least two cycles of a qualifying chemotherapy regimen (6 weeks of single agent therapy) (see below), with failure to achieve an objective response, or relapse/progression within 6 months after completion of the last qualifying chemotherapy (LQC) regimen. Patients must have objective evidence of relapse or failure to respond.
3. Karnofsky Performance Status  $\geq$  60%; anticipated survival of 3 months.
4. Absolute granulocyte count  $>$  1500/mm<sup>3</sup> and a platelet count  $>$  100,000/mm<sup>3</sup>.
5. Adequate renal (creatinine  $<$ 2.0 mg/dL) and hepatic function (bilirubin  $<$ 2.0 mg/dL).
6. Bidimensionally measurable disease or evaluable disease.
7. Copies of original medical notes and radiographic studies documenting the chemotherapy drugs, number of courses and dates of their LQC, response to the LQC and, for responders, the date of disease progression.

#### EXCLUSION CRITERIA

1. An average of  $>$ 25% of the intratrabecular marrow space involved with lymphoma.
2. Prior hematopoietic stem cell transplant.
3. Active obstructive hydronephrosis.
4. Pregnant or nursing females.
5. Disease progression within one year, arising in a field previously irradiated with  $>$ 3500 cGy.
6. Concurrent treatment with any other anti-cancer drugs or biologics.

#### Qualifying chemotherapy regimens

##### Original protocol

- Low grade NHL: CVP, COP-Bleo, CP, cytoxan, chlorambucil, fludarabine

- Intermediate grade NHL: C-MOPP, BACOP, CHOP, CHOP-Bleo, ProMACE-MOPP, CHOP-Bleo + alpha interferon, COMLA, MINE, ESHAP, DHAP, EPOCH, CEPP, ProMACE-CytoBOM, ICE, COP-BLAM, CNOP, FND, MACOP-B, m-BACOD  
Added in amendment 1 (Dec. 23, 1996)
- Intermediate grade NHL: VAPEC-B, IM-VP16  
Added in amendment 2 (July 9, 1997)
- CF, cladribine

#### Monitoring Plan (Original Protocol)

1. Baseline (Within 2 weeks of Enrollment)  
History and Physical with Karnofsky Status; Lab – CBC, Serum Chemistry (Creatinine, Total Bilirubin, Na K, Cl, Bun, LDH, Urinalysis Thyroid functions, HAMA); Tumor Staging consisting of Bone Marrow within 42 days of entry; CT and other radiographs as needed of the chest, abdomen, pelvis within 28 days of entry
2. Days 0; Day 2, 3, or 4; and Day 7  
Whole body biodistribution, Whole body dosimetry, and calculation of therapeutic dose
3. Treatment phase  
CBC weekly for weeks 3-9, 13 & 25; Serum Chemistry weeks 3, 7, 13 & 25; tumor restaging (physical examination, radiologic studies, and bone marrow biopsy [if positive at baseline]) weeks 7, 13, and 25; HAMA weeks 7 & 25
4. Follow-up (Every 13 weeks up to 2 years or until discontinuation)  
History and Physical with Karnofsky Status; CBC, Serum Chemistry, HAMA; Tumor restaging studies including radiologic evaluations and bone marrow biopsy
5. Long-term follow-up: Disease status and vital status every 6 months

#### Treatment Plan

The treatment consisted of two intravenous infusions; an initial dosimetric infusion followed in 7 to 14 days by a therapeutic infusion.

- The first day of the dosimetric phase was designated as study day 0. The dosimetric infusion contained 450 mg of tositumomab infused over 70 minutes (includes a 10 minute flush) immediately followed by 5 mCi (35 mg) of iodine I-131 tositumomab iodine infused over 30 minutes (includes a 10 minute flush).
- Seven to 14 days later the therapeutic dose consisting of 450 mg of tositumomab was infused over 70 minutes (includes a 10 minute flush) immediately followed by the patient –specific mCi activity (35 mg) of iodine I-131 tositumomab calculated to deliver a total body dose of 75 cGy and infused over thirty minutes. The calculation of the patient specific dose was base on the information obtained from the dosimetric infusion and is detailed in the protocol.
- The therapeutic dose was calculated to deliver 75 cGy TBD in patients with platelet counts  $\geq 150,000/\text{cu mm}$ . Patients with platelet counts between 100,001 and 150,000/cu mm were administered a therapeutic dose calculated to deliver 65 cGy TBD. Obese patients were dosed based upon 137% of their lean body mass.

#### Dose Modifications

- Obesity

Excessively obese patients (defined as patients weighing more than 137% of the calculated lean body mass) the calculations to determine the iodine I-131 tositumomab activity will be performed using an upper limit of mass (maximum effective mass) based upon height and gender (Table for determination of max effective mass included as Appendix 2 to the protocol).

- Baseline Thrombocytopenia  
The administered dose for patients with platelet counts between 100,001 and 150,000/cu mm will be adjusted to deliver an estimated activity of 65cGy TBD. An additional adjustment for obesity may be performed, if indicated.
- Toxicity
  - The infusion rate was to be decreased by 50% for fever of 38.5-38.9°C, mild to moderate rigors, mild to moderate mucosal congestion/edema, or 30-49% drop in systolic blood pressure
  - The infusion was to be stopped until resolution of toxicity and then resumed at 25-50% of the original infusion rate for fever >39°C, severe rigors, severe mucosal congestion/edema, or 50% decrease in systolic blood pressure.
- Patients who have not received at least 3 doses of SSKI, 3 doses of Lugol's solution, or 130 mg of potassium iodide at least 24 hours prior to the dosimetric dose, may not receive the dosimetric dose
- Patients who are seropositive for HAMA at day 5 may not receive the therapeutic infusion.

#### Concomitant Medications

- All patients were required to receive either Lugol's solution or potassium iodide tablets, beginning 24 hours before the dosimetric dose and continuing until 14 days after the last infusion of radiolabeled antibody.
- Thirty minutes prior to both the dosimetric dose and the therapeutic dose, all patients were premedicated with acetaminophen 650 mg p.o. and diphenhydramine 50 mg p.o.

#### Analytic Plan (Original Protocol)

##### Primary and Secondary Endpoints

The primary efficacy endpoint for this study will be the Overall Response Rate and duration established on this study.

Secondary efficacy endpoint analyses for this study will be survival, time-to-progression, time-to-treatment failure established on this study. Quality of life and safety analyses will also be included as secondary endpoint analyses. In addition, the response rate, response duration, time to progression and time to treatment failure will be compared with the patient's last qualifying chemotherapy regimen.

### **Statistical Considerations**

The proposed sample size of 60 patients was selected to enable response rates to be estimated with a maximum standard error of 0.065. The protocol stated that any patient who is enrolled but does not complete both the trace and therapeutic dose of Anti-B1, will be replaced so that a total of 60 radioimmunotherapy treated patients will be enrolled. Projected completion of accrual was September 1997.

### **Establishing of Response Rate, Best Response Rate and Duration Measures**

Estimates of the rates of response, complete response and overall response (complete, clinical complete and partial), will be estimated from the study response rates. All acquired data will be analyzed by intention-to-treat. Point estimates and two-sided 95% confidence intervals will be calculated. One-sided 95% confidence intervals for minimum response rates will also be calculated. Mean and median duration response, time-to-progression, time-to-treatment failure, and survival will be calculated. If the study evaluation is performed before all data have reached their respective endpoints, right censored data for duration estimates will be treated as independent censoring and Kaplan-Meier survival estimates will be employed. Time-to-progression analyses will treat patients' withdrawals and interventions for reasons other than progression or death as independent censoring. Subgroup analyses by number of previous therapies, time from diagnosis, histology, and previous response will be performed.

### **Efficacy Analyses: Patients As Their Own Control**

Although the eligibility criteria restrict the study to patients who completed their previous qualify chemotherapy regimen so that the appropriate comparison is based on patients who complete treatment, all acquired data will be analyzed by intention-to-treat methods. Two-sided paired-sample tests of equivalency of the response rates following RIT with the last previous qualifying chemotherapy response will be performed at the 5% level. Paired t-test and non-parametric Wilcoxon signed rank tests comparing the duration of response, time-to-progression, and time-to-treatment failure will be performed. If right-censoring is present, pair-matched censored survival tests will be performed. No stratification is present in the study as the patients as their own control performs this function. Subgroup analyses by number of previous therapies, time from diagnosis, histology, and previous response will be performed.

### **Revised, Final Analytic Plan**

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

The original sample size of 60 patients is adequate to detect a difference of 25% in the proportion of patients experiencing a longer duration of response (greater than 30 days) when treated with iodine I 131 tositumomab therapy compared to the proportion of patients experiencing a longer duration of response (greater than 30 days) to the LQC.

There are two dichotomous treatment outcomes that are assessed in this analysis

- Durations equivalent- defined as  $\leq 30$  days difference in response durations to Iodine I-131 tositumomab and to prior chemotherapy for an individual patients
- Durations non-equivalent- defined as  $> 30$  days difference in the durations of response to Iodine I-131 tositumomab and to prior chemotherapy.

Only the non-equivalent cases contribute to the test statistic in this approach. The null hypothesis is that the durations of response are the following the most recent chemotherapy regimen and following Iodine-131 Anti-B1 Antibody therapy.

### Statistical Test Method - McNemar's test

The assumptions used in this trial were that the expected proportion of patients responding to therapy decreases with each successive therapy. Under this assumption, it is expected that the proportion of patients responding to Iodine-131 Anti-B1 Antibody would be smaller than the proportion of patients who responded to the most recent,

**Table M**  
**Outcomes for McNemar's Test**

|                  |             | Prior Chemotherapy |          |
|------------------|-------------|--------------------|----------|
|                  |             | No Response        | Response |
| Iodine-131       | No Response | A                  | B        |
| Anti-B1 Antibody | Response    | C                  | D        |

test,  
ided

The McNemar's test is a test of the equality of the probability of each of these two groups. The response rate on the comparative chemotherapy is equal to that on Iodine-131 Anti-B1 Antibody if the number of patients in Group B equals the number of patients in Group C. McNemar's test statistic equals the proportion of patients in Group C of the patients in Group B or Group C. Under the null hypothesis, this equals 0.5.

*Efficacy analyses were to be conducted on a modified intent-to-treat basis, i.e., the analyses of efficacy include all patients who received any portion of the study drug including only the dosimetric dose.*

### MIRROR PANEL

*The MIRROR Panel was composed of two radiologists and two oncologists. All were board certified in their respective disciplines. The panel reviewed both patient radiographs and patient medical notes, while masked to the investigators' assessments of response. Efficacy endpoints include response rate, complete response rate, duration of response and time to progression based on the MIRROR Panel independent review assessment. The independent review process was coordinated by an independent CRO. The representative from the CRO facilitated the review process and ensured appropriate masking of the data and completion of the CRFs.*

## Amendments to the protocol and dates of amendment

### Amendment 1- December 23, 1996

- Expanded aims and objectives of the study defined the primary endpoint (overall response rate) and expanded the secondary endpoints to include 3 types of response rates (Best Response [regardless of durability], Response, and Prolonged Response), duration of unmaintained response, TTP, TTF, and survival. The results for each of these endpoints following Iodine I-131 tositumomab would be compared to that observed following the LQC, except for survival.
- Inclusion criteria modified to permit CD20 expression using any commercial antibody similar to the L26 or anti-B1 antibody; to allow for a limited exposure to treatment between the LQC and study entry, if the patient progressed on or after the intervening therapy and was enrolled within 6 months of completion of the LQC; added LDH <500 IU/mL; required that all patients have measurable disease; required patients with intervening chemotherapy to provide radiographic studies documenting baseline, best response, and

### Amendment 2 - June 4, 1997

- Aims and Objectives section revised to add the following "To compare the response rates, duration of responses, and time to treatment failure after 131-Iodine anti-B1 antibody RIT" to the patients previous qualifying chemotherapy outcome."
- Endpoints revised to read as follows: "The primary efficacy endpoint of the study is the comparison of the number of patients having a longer duration of response on Iodine-131 Anti-B1 antibody therapy to the number of patients having a longer duration of response on their last qualifying chemotherapy regimen. Secondary efficacy endpoint analyses are to establish response rates, complete response rates, time-to-progression, time-to-treatment failure, and survival established on this study. The comparison of the response rate and the TTF following RIT with the response rate and the time to treatment failure following the last qualifying chemotherapy regimen are additional secondary endpoint analyses. Quality of life and safety analyses will also be included as secondary endpoint analyses. Survival will be analyzed following RIT only."
- Eligibility criteria modified to (1) delete requirement for testing tumor biopsy material for CD20 antigen expression, (2) require that patients must have failed to respond or progressed within 6 months of completion of any additional therapy (after last qualifying therapy but prior to study entry) (3) delete LDH <500 IU/mL and WBC >3500/mm<sup>3</sup>, (4) adds stated that "at least one lesion must be at least 2 cm diameter" to requirement that patients have bidimensionally measurable disease, (5) changes requirement for baseline radiographic study for evaluation of LQC and any interval, non-qualifying therapy, to be obtained with 10 weeks prior to initiation of that therapy [previously required within 6 weeks prior to therapy] and also requires that medical notes documenting the patient's course on the LQC must be available, (6) broadens exclusion criteria to exclude patients receiving approved or non-approved anti-cancer drugs or biologics (previously excluded only non-approved drugs) (7) deletes exclusion criterion for patients who have been exposed to non-human monoclonal or polyclonal antibodies [such patients may be enrolled in seronegative for HAMA]
- Correction in of antibody dose administered based on more accurate protein measurement
- Permits multiple use of Anti-B1 vials (i.e., to prepare doses for more than one patient from the same vial)
- Treatment plan modified to require use of an in-line filter for infusion of study drug
- Limits collection of information on concomitant medications to the first 12 weeks of study, unless medication used to treat a drug-related adverse experience
- Revision of patient monitoring schema: (1) Expands follow-up for patients with disease progression. Patients who progress or have been followed without progression for 2 years will be evaluated every 6 months by physical exam and staging studies, evidence of toxicity (particularly pulmonary toxicity) and "thyroid function will be determined periodically"; (2) Adds  $\beta$ 2 microglobulin to baseline and on-study evaluations; (3) Blood sampling for

- pharmacokinetic analyses to be performed at one study site (Univ. of Nebraska); (4) States that HAMA assessment may be performed at study sites rather than by a central lab.
- Modifies duration of assessment for serious adverse events from first 12 weeks on study to 12 weeks or administration of alternative therapy for lymphoma, whichever occurs first
  - Extensive changes to statistical analysis section, including brief description of the procedures for review of medical records and radiographs to assess response and response duration to LQC and to Iodine I-131 tositumomab.
  - Common Toxicity Criteria added as supplemental grading scale
  - Modifies criteria for LQC to state that patients must receive at least 2 cycles of combination chemotherapy or 6 weeks of single agent therapy of the LQC, allows addition of agents to single agent and combination regimens or deletion of a drug (that drug or drug in that class) from a combination regimen if patient is known to be intolerant of, or have disease that is refractory to, the drug.

Amendment 3 -July 9, 1997

- Change title from "Phase II/III" to "Phase III"
- Radiolabeled anti-B1 (dosimetric and therapeutic doses) shipped as patient-specific doses from MDS Nordion, Inc to the study site.
- Definition of measurable disease modified in section of Response criteria to state "measurable lesions are defined as any lesion >2 cm in both perpendicular diameters at baseline."
- Addition of cladribine to LQC regimens

Amendment 4 -July 21, 1997

- Inclusion criteria modified with regard to documentation of response to last qualifying regimen. Written documentation must be provided from the referring physician (i.e., copies of original medical notes and radiographic reports) specifying the agents in the LQC, the number of course administered, the start and stop dates of LQC, the response to LQC, the date of response to LQC if applicable, and the date that stable or progressive disease. The same written documentation must be provided for any intervening non-qualifying therapy. Written documentation to be submitted to Coulter with the eligibility checklist and prior to enrollment, the documentation will undergo independent review to ensure that it is adequate. In addition, all radiographic studies for assessment of disease status at baseline, at best response (if applicable), and at progressive disease must be supplied to \_\_\_\_\_ for the LQC and any intervening non-qualifying chemotherapy regimen before the patient is enrolled. Evaluations that constitute evidence of disease progression after the last chemotherapy may also be used as the baseline for this study. **b(4)**
- Revision in definition of TTF; treatment failure to include "the decision to seek additional therapy" as an event, in addition to treatment withdrawal, study removal, [disease] progression, alternative therapy for patient's lymphoma, or death.

Amendment 5 -October 27, 1997

- Revised study endpoints to specify that (1) the primary efficacy endpoint will be based on response and response duration as assessed by the independent review panel; (2) all efficacy analyses will be performed using both Investigator-assessed and masked, independent review panel-assessed data.
- Modifies study population to state that any patient who is "determined to be HAMA-positive at baseline according to the validated, centralized HAMA assay will be replaced so that a total of 60 HAMA-negative patients who have received radioimmunotherapy will be enrolled."
- Modifies eligibility criteria to (1) permit baseline neutrophil and platelet counts to be obtained within 14 days (from 7 days) of study entry; (2) require that patients with low-grade NHL that has undergone transformation to a higher grade histology must have been treated with a prior therapy for intermediate-grade lymphoma. Re-biopsy to rule out transformation and to confirm low grade histology will be required only for those patients who have not received appropriate therapy for intermediate-grade lymphoma.

- Monitoring plan specifies thyroid function tests (total T3, free T4, and TSH) and timing of assessment (baseline, week 25, and at follow-up)
- Deletes determination of “best” response rates and comparisons of “best” response rates between Iodine I-131 tositumomab and LQC.
- Interim analysis plan expanded to state that analysis will include data on chemotherapy refractory status and on LQC as assessed by the independent review panel, percent of patients with non-equivalent durations of response following the LQC and Iodine I-131 tositumomab. The percent of patients contributing to the primary endpoint analysis will be calculated. The sample size will be adjusted if the percent suggests that primary endpoints analysis is underpowered.
- Objectives for independent-review panel specified. They are to obtain an independent confirmation of investigator-assessed response to therapy (LQC and Iodine I-131 tositumomab) and to verify the investigator’s assessment of each patient’s chemotherapy refractory status.

Amendment 6 -January 8, 1998

- Eligibility criteria modified to (1) to state that patients must *objective* evidence of disease progression or failure to respond; (2) requirement for baseline creatinine changed from <2.0 mg/dL to <1.5 times the upper limit of normal (ULN), requirement for baseline bilirubin changed from <2.0 mg/dL to <1.5 x ULN, and new requirement for AST and ALT < 5 times ULN added.
- Addition of CRO for data management responsibilities of independent review panel activities

Amendment 7 – April 24, 1998

- Modifies endpoints and analytic plan to state that the Independent review panel only reviews the fully assess the comparison of duration of response (primary study endpoint). All efficacy analyses will be performed using the investigator assess and *when appropriate*, the masked, independent review panel-assessed data.
- Study population modified at FDA’s request to include all patients who received at least a portion of the dosimetric dose in the primary efficacy analysis. Patients who are HAMA-seropositive will not be replaced and these patients will be included in the efficacy analysis.
- Revision of criteria for “removal from study”. Patients with adverse experiences that “require discontinuation of therapy” will not be removed from study.
- Definition of response revised from CR, CCR or PR confirmed by two separate response evaluations at least 4 weeks apart to “best response evaluation (ordered by CR, CCR, PR, SD, then PD) and does not require subsequent confirmation. Adds definition of “confirmed response” that requires CR, CCR or PR be confirmed by two separate response evaluations at least 4 weeks apart
- Modification of definition of “intent-to-treat” population, adding the phrase “including all patients who received at least a portion of the dosimetric dose”
- Appendix titled “Independent Review of Efficacy Data” deleted and replaced with “the Prior contents of the appendix have been superseded by the “Charter for the Independent Review of Efficacy and Chemotherapy-refractory Status in Study RIT-II-004”.

Amendment 8 – February 27, 2001

- Administrative changes reflecting acquisition of Coulter Pharmaceuticals by Corixa Corp.
- Modification to plan for long-term follow-up (LTFU)- plan now requires TSH and HAMA testing every 12 months.
- Modification to informed consent document describing risks of hypothyroidism as a delayed toxicity and of the additional testing requirements for LTFU.

Amendment to the Statistical analysis plan, not identified as a protocol amendment in the BLA  
Jan. 22, 2000

- The independent review of data was expanded from the assessment of the primary endpoint to include the assessments of secondary endpoints in study RIT-II-004 ("Expanded MIRROR Panel").

## STUDY RESULTS

### Patient Disposition

Sixty-one patients were enrolled at 8 centers.

- One patient (004-015-002) was not administered any study drug. The patient was enrolled on Feb. 25, 1997 and withdrew consent. The date of last follow-up for this patient is April 29, 1997.
- 60 patients received the dosimetric dose
  - One patient (004-018-001) received the dosimetric dose; the patient was withdrawn from study for encephalopathy on study day 13 prior to receiving the therapeutic dose.
  - One patient (004-015-005) received the dosimetric dose but experienced an infusion-related adverse experience on the day of the therapeutic dose infusion. The event occurred during administration of the unlabeled tositumomab, resulting in termination of treatment prior to administration of the radiolabeled portion of the therapeutic dose.
- 58 patients received both the dosimetric dose and the therapeutic dose.

### Study RIT-II-004: Enrollment by Protocol Amendment

| Submission              | Submission Date | Cumulative Number of Subjects Enrolled |
|-------------------------|-----------------|--|
| Original Protocol       | 10/09/1996      | 4                                      |
| Amendment 1             | 12/23/1996      | 21                                     |
| Amendment 2             | 06/05/1997      | 22                                     |
| Amendment 3             | 07/09/1997      | 26                                     |
| Amendment 4             | 07/23/1997      | 53                                     |
| Amendment 5             | 10/28/1997      | 58                                     |
| Amendment 6             | 01/09/1998      | 61                                     |
| Amendment 7             | 05/07/1998      | 61                                     |
| Amendment 8             | 05/15/2001      | 61                                     |
| <b>Total Enrollment</b> |                 | <b>61</b>                              |

### Conduct of the Study

*FDA's review of the case report forms for study RIT-II-004 noted the following unreported protocol violations of eligibility criteria for Subject No: 004-014-001, 004-018-001 and 004-020-007. These violations were discovered in the course of the review of case report forms.*

The subject was enrolled on December 9, 1996. The subject received fludarabine from June 3 through August 2, 1996. CT scan evaluations obtained prior to fludarabine were interpreted by the MIRROR as an SPPD of 66.66 cm<sup>2</sup>. CT scans following fludarabine on Aug 21, 1996 were read with an SPPD of 43.16 cm<sup>2</sup>. Baseline enrollment CT scans on study entry, December 9, 1996, were read with an SPPD of 22.00 cm<sup>2</sup>, documenting a decrease in the SPPD of 67%. Thus the subject had a PR to fludarabine at study entry, in violation of the eligibility criteria.

004-018-001: This 39 yo female experienced rapidly progressive disease through prior therapy. Prior treatment included cytarabine 1 gm/m<sup>2</sup> and etoposide 100 mg/m<sup>2</sup> IV on days 1-5, administered on October 13, (cycle 1) and November 10 (14?), 1996 (cycle 2). The second cycle was complicated by catheter-related sepsis (Staph aureus) treated with catheter removal. CBC, creatinine and liver functions were normal during that admission. The patient was re-admitted for the dosimetric dose on November 20, 1996 (study day -2) with increasing pleural effusions. Following administration of the dosimetric dose on ~~November 20, 1996~~ (day 0), she underwent thoracentesis and chest tube placement. On study day 6, the patient was noted to have hyperbilirubinemia and increased LFTs. On ~~November 26, 1996~~ (study day 10), she was admitted for the therapeutic dose with a history of increasing lethargy and 2-3 day history of confusion described as "trouble finding the right words". Examination reports extensive expressive and receptive dysphasia with slight impairment of memory. The patient was mildly thrombocytopenic (77,000) with worsening LFTs, notably LDH of 11, 640 IU/ml. A diagnosis of hepatic encephalopathy was made on study day 12, with progressive hepatic deterioration and death on study day 14.

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004-020-007: 45 yo male with diagnosis of NHL in Dec. 1994 and multiple chemotherapeutic regimens prior to study entry, received therapeutic dose of 82 mCi (75 cGy TBD) on Jan 2, 1998. Baseline CBC (12/12/97) revealed ANC 5.6, hemoglobin 12 gm/dL, and platelets 116,000. The patient responded to treatment (apparent CR) but suffered persistent thrombocytopenia through 1998 and 1999 with development of leukopenia in 1999 and a diagnosis of **MDS** in September 1999. The patient suffered subdural hematoma in June 2000 (secondary to thrombocytopenia) and died with progressive hemorrhage and hemoptysis on ~~June 2000~~ ).

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*Subjects for whom protocol violations were identified by the sponsor, are summarized in the following table.*

| Patent ID  | NHL subtype | Dose (cGy) | Study day | Violation type | Description  |
|--|-------------|------------|-----------|----------------|--|
| <b>Violation of Eligibility Criteria</b>   |             |            |           |                |  |
| 004-013-004 66F T75C   | T           | 75         | 0         | ENTRY          | WBC = 2.9, current protocol required >3.5 but was being amended                |
| 004-016-002 80M T65C   | T           | 65         | -1        | ENTRY          | WBC = 3.5, current protocol required >3.5 but was being amended                |
| 004-016-009 68M T75L   | T           | 75         | -8        | ENTRY          | Bone marrow involvement based on unilateral biopsy (20-25%)                    |
| 004-013-017 65M T65L   | T           | 65         | 0         | ENTRY          | Patient received oral prednisone 13 days prior to study entry                  |
| 004-020-002 50M T75C   | T           | 75         | 0         | ENTRY          | CT scans 29 days prior to enrollment (protocol requires 28 days)               |
| <b>Violations of Informed Consent</b>  |             |            |           |                |  |
| 004-014-006 48M L75L   | L           | 75         | -2        | ENTRY          | Verbal informed consent given, not signed until after enrollment (9/4/97)      |
| 004-018-001 39F T00C   | T           | 0          | -1        | ENTRY          | Informed consent not approved by ethics committee when signed                  |
| <b>Violation of Eligible NHL Histology</b>   |             |            |           |                |  |
| 004-021-001 51M I75C   | I           | 75         | 0         | ENTRY          | Mantle cell, pathology re-read   |
| <b>Violation of Thyroid Protection Protocol</b>                                      |             |            |           |                |  |
| 004-013-003 43M T65C   | T           | 65         | 0         | TREATMENT      | SSKI started on same day as dosimetric dose                                    |
| 004-013-004 66F T75C   | T           | 75         | 0         | TREATMENT      | Pt was started on SSKI plus potassium perchlorate rather than protocol regimen |
| 004-013-005 63M T75L   | T           | 75         | 0         | TREATMENT      | SSKI started on same day as dosimetric dose                                    |
| 004-013-006 38F L75L   | L           | 75         | 0         | TREATMENT      | SSKI started on same day as dosimetric dose                                    |
| 004-013-007 55M L75L   | L           | 75         | 0         | TREATMENT      | SSKI started on same day as dosimetric dose                                    |
| 004-013-009 61M L75L   | L           | 75         | 0         | TREATMENT      | SSKI started on same day as dosimetric dose                                    |
| 004-013-012 66F L75L   | L           | 75         | 0         | TREATMENT      | SSKI started on same day as dosimetric dose                                    |
| 004-020-008 71M L65L   | L           | 65         | 0         | TREATMENT      | Lugols solution dosed at 5 gtts tid, protocol requires 20 gtts/day             |
| <b>Violation of Timing for Dose Assessment or Administration of Therapeutic Dose</b> |             |            |           |                |  |
| 004-021-002 51M L65L   | L           | 65         | 15        | TREATMENT      | Therapeutic dose given 15 days after dosimetric dose                           |

ENT

|                      |   |    |   |           |   |
|----------------------|---|----|---|-----------|---|
| 004-029-003 39M L75L | L | 75 | 1 | TREATMENT | Second total body count performed on day 1 and third on day 5 |
|----------------------|---|----|---|-----------|---|

**Violation of Therapeutic Dose Administration**

|                      |   |      |    |               |  |
|----------------------|---|------|----|---------------|--|
| 004-020-005 66M L88L | L | 87.8 | 8  | TREATM<br>ENT | Calculated dose 104 mCi, actual dose 125 mCi |
| 004-020-006 60M L75L | L | 75   | 8  | TREATMENT     | Enrolled at 65 cGy, treated at 75 cGy        |
| 004-020-007 45M L75L | L | 75   | 14 | TREATMENT     | Enrolled at 65 cGy, treated at 75 cGy        |

**Financial Disclosure**

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

The following investigators disclosed one or more of the above types of financial arrangements meeting:

- 
- 
- 
- 



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FDA Assessment of Potential Conflicts- There was no evidence that the data from these sites were significantly different from other study sites or altered the results of the study.

**Bioresearch Monitoring Inspection Results**

*Inspections of five clinical sites were performed in support of BLA 99-0813 for Protocol RIT-II-004 entitled "Multicenter, Pivotal Phase III Study of Iodine-131 Anti-B1 Antibody (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grade Histologies." In addition one of the sites (University of Nebraska) was also inspected for Protocol RIT-II-001, entitled "Multicenter, Phase II Dosimetry/Validation Study of 131Iodine-AntiB1(murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grades" after the sponsor reported that data was missing. The inspections were conducted in accordance with CPGM 7348.811, the Inspection Program for Clinical Investigators.*

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

| Site                     | Investigator     | Form 483 | Classification |
|--------------------------|------------------|----------|----------------|
| Kaiser - Vallejo         | Dr. Fehrenbacher | No       | VAI            |
| Stanford University      | Dr. Knox         | Yes      | VAI            |
| University of Michigan   | Dr. Kaminski     | Yes      | VAI            |
| University of Washington | Dr. Press        | Yes      | VAI            |
| University of Nebraska   | Dr. Vose         | Yes      | VAI            |

### Inspectional Summary Statement

The results of bioresearch monitoring inspections indicate that the deviations are not substantive, with the exceptions noted (verification of dose delivered), and that the submitted data can be considered reliable and accurate.

### Study Population:

*The study population consists of low grade and follicular NHL; approximately 1/3 of the patients have disease, which has transformed to a higher histologic subtype. The population has been heavily pretreated with chemotherapy (median number of prior regimens –4) but not radiotherapy. None of the patients have undergone dose-intensive chemotherapy with prior stem cell support. The majority had advance disease (stage III and IV) and 11% have bulky lesions. The characteristics of the population at study entry are summarized in the following table.*

Baseline Characteristics for Patient Population in Study RIT-II-004

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| Baseline Characteristic                       | ITT population<br>n=61 |
|---|------------------------|
| Age (years)                                   |                        |
| Median(range)                                 | 59 (38-82)             |
| Q1; Q3  | 52; 68                 |
| Gender  |                        |
| Males (%)                                     | 38 (62%)               |
| Race  |                        |
| Caucasian (%)                                 | 59 (97%)               |
| Histologic diagnosis at entry                 |                        |
| W/o transformation                            |                        |
| Low grade                                     | 37 (61%)               |
| Intermediate grade                            | 1 (2%)                 |
| High grade                                    | 0                      |
| With transformation                           |                        |
| Low grade                                     | 0                      |
| Intermediate grade                            | 23 (37%)               |
| High grade                                    | 0                      |
| Stage of disease                              |                        |
| I   | 0                      |
| II  | 1(2%)                  |
| III   | 13 (21%)               |
| IV  | 47 (77%)               |
| Missing                                       | 0                      |
| IPI category                                  |                        |
| 0   | 0                      |
| 1   | 7 (12%)                |
| 2   | 22 (36%)               |
| 3   | 22 (36%)               |
| 4   | 7 (12%)                |
| 5   | 1 (2%)                 |
| Missing                                       | 2 (3%)                 |
| Max. tumor diameter                           |                        |
| < 5 cm  | 25 (41%)               |
| ≥ 5, ≤10 cm                                   | 29 (48%)               |
| > 10 cm                                       | 7 (11%)                |
| # Prior chemo regimens                        |                        |
| Median (range)                                | 4 (2-13)               |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 3, 5                   |
| # Prior RT regimens                           |                        |
| Median (range)                                | 0 (0-7)                |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 0, 1                   |
| No Prior BMT                                  | 61 (100%)              |
| Time from diagnosis to entry<br>(mos)         |                        |
| Median (range)                                | 4.4 (0.8, 27.8)        |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 2.6, 7.2               |

Primary Efficacy Outcome:

The response to treatment and response duration for the most recent qualifying chemotherapy regimen and for Iodine I-131 tositumomab was determined by the Expanded MIRROR panel for 60 patients; data were not reviewed for the patient who withdrew from study and received neither the dosimetric nor therapeutic dose. There were 7 patients who responded to the LQC for an ORR of 12% and a CR/CCR of 2%. There were 28 subjects who responded to Iodine I-131 tositumomab for an ORR of 47% and a CR/CCR of 20%. The response determinations by the MIRROR panel are summarized in the table below.

| Treatment Response by Expanded MIRROR Panel (Effoutm dataset)<br>According to Treatment for Patients enrolled in RIT-II-004 |                              |                          |
|---|------------------------------|--------------------------|
| Response Category   | Last Qualifying Chemotherapy | IODINE I-131 TOSITUMOMAB |
| Complete Response,  | 1                            | 8                        |
| Complete Clinical Response  | 0                            | 4                        |
| Partial Response  | 6                            | 16                       |
| Stable Disease  | 5                            | 4                        |
| Progressive disease   | 48                           | 28                       |
| Total Patients  | 60                           | 60                       |

There were 28 patients whose disease did not respond to either therapy or for whom the duration of response to either therapy was roughly equivalent (< 30 days difference in the duration of response to either treatment). This group was classified as "Duration Equivalent".

|                    | Response to Iodine I-131 tositumomab | No Response to Iodine I-131 tositumomab |    |
|--------------------|--------------------------------------|---|----|
| Responded to LQC   | 3                                    | 4                                       | 7  |
| No Response to LQC | 25                                   | <b>28</b>                               | 53 |
|                    | 28                                   | 32                                      |    |

The remaining 32 patients achieved an objective tumor response (CR, CCR, or PR) following Iodine I-131 tositumomab, the last qualifying chemotherapy regimen, with a difference in the durations of response to Iodine I-131 tositumomab and to the last qualifying chemotherapy regimen of more than 30 days. Among these 32 patients, 27 patients experienced a longer duration of response to Iodine I-131 tositumomab (difference in the durations  $\geq 30$  days) as compared to the duration of response to last qualifying chemotherapy regimen. This group of 27 consisted of 25 patients who failed to respond to the LQC but did respond to Iodine I-131 tositumomab and 2 patients who responded to both the LQC and to Iodine I-131 tositumomab but had a longer duration of

response to Iodine I-131 tositumomab than to LQC (difference in response durations  $\geq$  30 days).

|                    | Response to Iodine I-131 tositumomab | No Response to Iodine I-131 tositumomab |    |
|--------------------|--------------------------------------|---|----|
| Responded to LQC   | (2 + 1)                              | 4                                       | 7  |
| No Response to LQC | 25                                   | 28                                      | 53 |
|                    | (27 + 1)                             | 32                                      |    |

The remaining 5 patients experienced a longer duration of response to the last qualifying chemotherapy regimen (difference in the durations  $\geq$ 30 days) as compared to the duration of response to Iodine I-131 tositumomab. This group was comprised of 4 patients who responded to the LQC but not to Iodine I-131 tositumomab and one patient who responded to both the LQC and Iodine I-131 tositumomab, in whom the duration of response to LQC was longer than to Iodine I-131 tositumomab.

|                    | Response to Iodine I-131 tositumomab | No Response to Iodine I-131 tositumomab |           |
|--------------------|--------------------------------------|---|-----------|
| Responded to LQC   | (2 + 1)                              | 4                                       | 7 (2 + 5) |
| No Response to LQC | 25                                   | 28                                      | 53        |
|                    | 28                                   | 32                                      |           |

Based on the Expanded MIRROR Panel assessment of response and response duration as described above, the following proportions were generated for use in the primary efficacy analysis:

28/60 (47%) patients had an equivalent duration of response

32/60 (53%) patients had a non-equivalent duration of response

- 27/32 (84%) patients had a longer duration of response to Iodine I-131 tositumomab
- 5/32 (16%) patients had a longer duration of response to the last qualifying chemotherapy regimen

## Primary Efficacy Analysis

The primary efficacy endpoint of the study was the comparison, as assessed by the Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel, of the number of patients having a longer duration of response (i.e., more than 30 days) on their last qualifying chemotherapy regimen to the number of patients having a longer duration of response on IODINE I-131 TOSITUMOMAB™.

FDA followed the protocol defined primary endpoint and compared the duration of response on I-131 Antibody therapy to prior chemotherapy. The duration of response is linked with the response. If there is no response (SD, PD) on both (Bexaar & Prior Chemo) then these patients were classified as equivalent regardless of how long their Stable Disease (in favor of either Iodine I-131 tositumomab or prior Chemo) was or if they had a response (CR, CCR or PR), but the difference in the duration of response between Bexaar and prior Chemo was less than 30 days. There were 28 patients in this group. The remaining 32 patients had a CR or CCR or PR on either therapy and the difference in the duration of response was more than 30 days. There were 27 patients from these 32 whose the duration of response was longer than 30 days on Iodine I-131 tositumomab as compared to Prior Chemo, and 5 from these 32 whose duration of response was longer than 30 days on prior chemo as compared to Bexaar.

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

| Response                                      | Frequency | % of 60 |
|---|-----------|---------|
| Equivalent duration                           | 28        | 47 %    |
| Longer response with Iodine I-131 tositumomab | 27        | 45 %    |
| Longer response with Chemo                    | 5         | 8 %     |

The sign-rank test takes all data into account, equivalent as well as non- equivalent cases, and tests the hypothesis that overall there is a statistically change. Then two proportions can be compared.

**p < 0.0001 using sign-rank test in favor of Bexaar.**

### Analysis of Proportions

Let  $p_1$  = proportions of equivalent responses

$p_2$  = proportions of responses favoring Iodine I-131 tositumomab

$p_3$  = proportions of responses favoring prior chemotherapy

Of interest is to test the null hypothesis  $H_0 : p_2 = p_3$  conditioned on equivalent response, i.e., ignoring equivalent response, and n becomes 32, and test is  $H_0 : p_2 = p_3 = 0.5$  versus  $H_1 : p_2 \neq p_3$ . The p-value for testing this  $H_0$  is < 0.0001 (Exact Binomial test) **in favor of Bexaar**

**Note: FDA's analysis differs slightly from the analysis of the primary efficacy endpoint as performed by the sponsor.**

While, FDA and the sponsor used different approaches to assess the primary endpoint, the results of both tests were similar; both demonstrating a highly significant increase in

the durations of response after Iodine I-131 tositumomab. The sponsor applied the one-sided exact McNemar's test for comparing the number of patients with longer response on Iodine I-131 tositumomab compared to the number of patients with longer response on chemotherapy. This test only accounts for patients with nonequivalent durations of response. FDA applied the Wilcoxon signed rank test using all response duration data. As the Wilcoxon signed rank test includes the magnitude of the duration of response, it is more powerful in this study (as the higher response rate after Iodine I-131 tositumomab is also associated with a longer duration of response). The sponsor approach accounts for the paired censored data. As the censored values were almost exclusively with the longest durations of response, the censoring effect is minimal. Thus, while the statistical approaches used by FDA and the sponsor differed, the conclusions were similar.

## Secondary Efficacy Outcomes

1. Comparison of other efficacy outcomes between Iodine I-131 tositumomab and LQC: The protocol identified several secondary endpoints, including comparisons between efficacy outcomes following Iodine I-131 tositumomab as compared to the most recent qualifying chemotherapy regimen. These outcomes included comparisons of overall response rates, complete response rates, durations of overall response and of complete responses. For each of these analyses, the differences were in favor of Iodine I-131 tositumomab and were significantly different.

MIRROR Panel-Assessed Secondary Efficacy Endpoint Data:  
Study RIT-II-004 (N = 60)

| Secondary Efficacy Endpoints  | Last Qualifying<br>Chemotherapy<br>(N = 60) | Iodine I 131<br>tositumomab<br>(N = 60) |
|---|---|---|
| Overall Response Rate   | 7/60 (12%)                                  | 28/60 (47%)                             |
| Median (95% CI) duration of<br>response for responders<br>(months)          | 4.1<br>(3.0–5.4)                            | 11.7<br>(6.9–NR)                        |
| Complete response Rate  | 1/60 (2%)                                   | 12/60 (20%)                             |
| Median (95% CI) duration of<br>response for complete<br>responders (months) | 4.8   | NR<br>(12.5–NR)                         |

## Exploratory Analyses

1. Subset analyses of the primary efficacy analysis in patients whose disease has undergone transformation and in patients whose disease has not undergone transformation to a higher histologic subtype of NHL.

Subset analyses were done comparing Last Qualifying Chemotherapy Response – Original & Expanded MIRROR Assessed to Iodine I-131 tositumomab Confirmed Response – expanded MIRROR Assessed to evaluate if the original and expanded MIRROR assessment made any difference to the efficacy of the primary endpoint for each of the following two subset populations.

- (1) Patients with low grade non-Hodgkin’s lymphoma (NHL) that has not undergone transformation (36 patients) – Not Transformed
- (2) Patients with intermediate grade, follicular NHL that has not undergone transformation (1 patient)
- (3) Patients with low grade non-Hodgkin’s lymphoma (NHL) that has undergone transformation (23 patients) – Transformed

Last Qualifying Chemotherapy Response Versus Iodine I-131 tositumomab Confirmed Response – expanded MIRROR Assessed

Using previously defined algorithm, the following table provides a summary of the results of the subset analysis for the primary endpoint (the patient with an intermediate grade histologic subtype of NHL was not classified as not transformed, this patient was a non-responder):

| Response                                      | Low Grade/follicular |         | Transformed |         |
|---|----------------------|---------|-------------|---------|
|   | Frequency            | % of 37 | Frequency   | % of 23 |
| Equivalent response duration                  | 11                   | 30 %    | 17          | 74 %    |
| Longer duration with Iodine I-131 tositumomab | 22                   | 59 %    | 5           | 22 %    |
| Longer duration with Chemo                    | 4                    | 11 %    | 1           | 4 %     |
| p-value (sign-rank test)                      | <0.0001              |         | 0.0625      |         |

**Conclusions:** There is a significant difference in favor of Iodine I-131 tositumomab for patients with low grade, untransformed NHL ( $p < 0.0001$ ), but not significantly different in patients with NHL with transformation, ( $p=0.0625$ , trend in favor of Iodine I-131 tositumomab). Iodine I-131 tositumomab activity is different in two sub-populations. The patients with NHL without transformation (all but one with low grade histologic subtype) benefit significantly more from Iodine I-131 tositumomab than transformed patients ( $p=0.0071$ , Fisher’s exact test).

2. Assessment of response to Iodine I-131 tositumomab in patient subsets (patients with and without evidence of histologic transformation to a more aggressive (higher grade) histologic subtype).

At the initiation of the study, the sponsor was urged to limit the patient population to a more homogeneous group. Specifically, the sponsor was asked to exclude subjects with evidence of histologic transformation since FDA felt this was a biologically different disease than low grade and follicular lymphoma. The sponsor declined, stating that evidence of histologic transformation was a prognostic factor but only one of many in this chemotherapy refractory population. As a result of these discussions, the protocol was to include a plan for analysis of the study results in patient subsets, i.e., those with and those without evidence of histologic transformation. As can be seen in the table below, the likelihood of achieving a response was much lower in the transformed subset.

| Response Category | Response Rate in Subset without Transformation | Response Rates in Subset with Transformation<br>N =23 |
|-------------------|--|---|
| CR                | 14% (5/37)                                     | 13%(3/23)   |
| CCR               | 11% (4/37)                                     | 0 (0/23)  |
| PR                | 38% (14/37)                                    | 8% (2/23)   |
| ORR               | 62% (23/37)                                    | 21% (5/23)  |
| SD                | 8% (3/37)                                      | 4% (1/23)   |
| PD                | 30% (11/37)                                    | 74% (17/23)   |

3. Analyses of response according to I-131 dose administered  
The dose of 131-Iodine administered was derived for each subject. This exploratory analyses were conducted to assess for relationships between response to Iodine I-131 tositumomab treatment and the total dose of 131-I administered or the dose adjusted for body mass or surface area administered. The results are presented in the table below.

| Confirmed Response according to Dose of Iodine-131 |              |            |         |
|--|--------------|------------|---------|
| Dose Basis   | Non Response | Response   | Total   |
| Dose (mCi)   |              |            |         |
| Median   | 77.9         | 97.7       | 90.2    |
| Range  | (0-173.4)    | (47.2-212) | (0-212) |
| Dose (mCi/m <sup>2</sup> )                         |              |            |         |
| Median   | 43.9         | 49.7       | 46.4    |
| Range  | (0-83.8)     | (33-100)   | (0-100) |
| Dose (mCi/kg)                                      |              |            |         |
| Median   | 1.1          | 1.2        | 1.2     |
| Range  | (0-2)        | (0.9-2.4)  | (0-2.4) |

4. During the course of the study, the source of the tositumomab antibody was changed from ~~\_\_\_\_\_~~ to Coulter. The antibodies from the different manufacturing sites were biochemically comparable and yielded a similar pharmacokinetic profile. A comparison of the response rates by antibody-source showed a slightly higher but not significantly different response rate for the ~~\_\_\_\_\_~~-manufactured antibody product than for the Coulter-manufactured product.

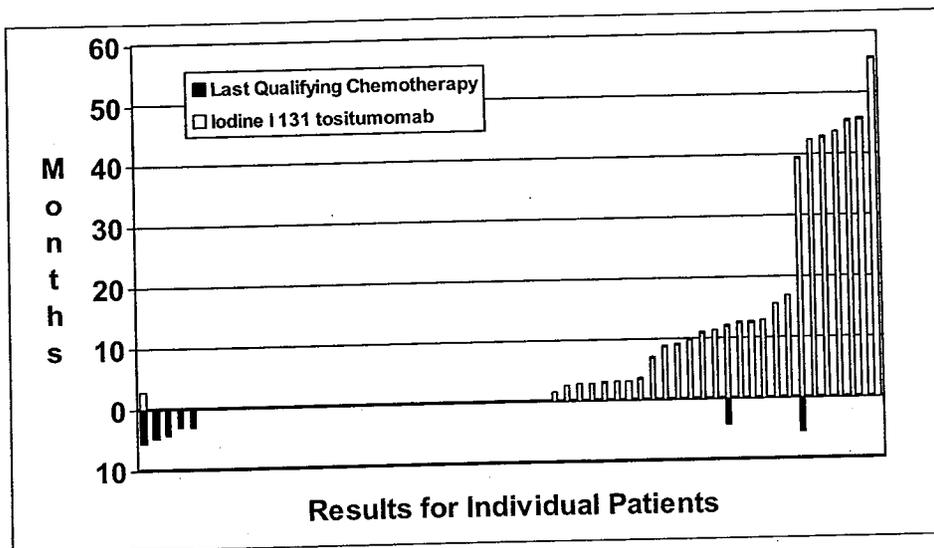
**b(4)**

| I-131-B1 Therapy Response Assessment by Antibody Manufacturer |   |                                  |
|---|---|----------------------------------|
| Antibody Manufacturer   | Overall Response Rate<br>(No. responders/total) | Total number of patients treated |
| Coulter-manufactured antibody                                 | 35% (7/20)                                      | 20                               |
| — manufactured antibody                                       | 52% (21/40)                                     | 40                               |
| <b>Total</b>  | <b>46% (28/60)</b>                              | <b>60</b>                        |

b(4)

The following figure illustrates the relative comparison of the duration of response for each patient following treatment with their LQC and following treatment with iodine I 131 tositumomab. On the left side of the figure are data from 5 patients with a longer duration of response for the LQC; in the center there are data from 29 patients with less than 30 days difference in the duration of response; and on the right side of the figure are data from 26 patients with a longer duration of response after iodine I 131 tositumomab.

FIGURE: PAIRED COMPARISON OF DURATION OF RESPONSE



### Safety Assessment

The most common and the most severe adverse events were hematologic toxicities. The following are the most common non-hematologic toxicities: asthenia (57%), fever (38%), nausea (37%), increased cough (30%), pain (25%), anorexia (25%), vomiting (22%), diarrhea (22%), abdominal pain (20%), chills (18%), infection (17%), and dyspnea (15%). The non-hematologic toxicities were predominantly mild to moderate in severity.

The hematologic toxicities were predominantly severe (grade 3 or 4 according to the NCI CTC) and prolonged in nature. The profile of the hematologic toxicity is summarized in the following table.

### Per-Patient Incidence of Grade 3-4 Hematologic Toxicity

| Hematologic Toxicity  | Efficacy studies<br>n=229                              |
|---|--|
| <b>Neutropenia</b><br>% Documented Grade 3-4 toxicity<br>Median days to nadir (95% CI)<br>25 <sup>th</sup> and 75 <sup>th</sup> percentiles for days to nadir<br>Median duration of documented Grade 3-4 toxicity<br>25 <sup>th</sup> and 75 <sup>th</sup> percentiles for duration of toxicity (days)      | 59%<br>42 (41, 45)<br>39 ; 47<br>30 (22, 43)<br>21; 49 |
| <b>Thrombocytopenia</b><br>% Documented Grade 3-4 toxicity<br>Median days to nadir (95% CI)<br>25 <sup>th</sup> and 75 <sup>th</sup> percentiles for days to nadir<br>Median duration of documented Grade 3-4 toxicity<br>25 <sup>th</sup> and 75 <sup>th</sup> percentiles for duration of toxicity (days) | 48%<br>34 (32, 35)<br>28; 40<br>29 (23, 40)<br>22; 43  |
| <b>Anemia</b><br>% Documented Grade 3-4 toxicity<br>Median days to nadir (95% CI)<br>25 <sup>th</sup> and 75 <sup>th</sup> percentiles for days to nadir<br>Median duration of documented Grade 3-4 toxicity<br>25 <sup>th</sup> and 75 <sup>th</sup> percentiles for duration of toxicity (days)           | 19%<br>48 (42, 55)<br>39; 60<br>22 (6, 36)<br>16; 36   |

#### Serious Adverse Events (SAE)

There were 23 SAE reported in 17 (28%) patients. An additional 4 patients (7% of the study population) developed MDS. A summary of these events are provided below

- 004-013-001- 69 yo male who presented with dyspnea, right-sided pleuritic chest pain, dry cough and fatigue on study day 68. The patient was not febrile and ANC was 1.7. A VQ scan was indeterminate. The patient was treated with antibiotics and coumadin (for presumptive diagnoses of **pneumonia** and/or **pulmonary embolism**)
- 004-013-002- 62 yo female hospitalized on study day 75 with productive cough and wheezing. The patient was afebrile and ANC was normal. The patient was treated for **exacerbation of COPD** and **bronchitis**, with symptomatic improvement.
- 004-013-005- 63 yo male developed rapidly progressive disease, particularly a cervical mass with compression of local structures. The patient was removed from study on day 20. On study day 30, he was admitted with fever, non-productive cough, anemia and thrombocytopenia (ANC was grade 0). The presumptive diagnosis was **aspiration pneumonia**. The patient also required platelet and RBC transfusions. He did not respond to antibiotic therapy with persistent fevers and progressive disease. He died on study day 43.

- 004-015-005- 59 yo male who admitted for his therapeutic infusion on study day 8. The infusion was interrupted three times severe Infusional toxicity within 5 minutes of the initiation of infusion on each attempt. The infusion reactions consisted of severe rigors, tachycardia to 133 pbm, and on the last attempt, temperature of 39.4 in conjunction with severe rigors. The patient was observed overnight and remained afebrile. A pre-infusion HAMA was negative; a post-infusion attempt HAMA was not obtained. Although not identified as an SAE, this would appear to represent a significant **allergic reaction** requiring in-patient observation. The patient never received the radiolabeled portion of the therapeutic dose. The patient was subsequently hospitalized on study day 20 for **pneumonia**. The patient was hospitalized on study day 91 for a second episode of **pneumonia** and anemia requiring 5 units pRBCs (discharged with hemoglobin on 8.5 gmn/dL). The patient had evidence of persistent anemia and received additional pRBC transfusions and a course of epoietin therapy (study days 111-181). The patient had several subsequent admissions for bronchitis and pneumonia prior to removal from study on day 168 for disease progression.
- 004-013-010: 53 yo male developed shaking chills and fever to 39.1 C the evening of the dosimetric dose infusion. The fever and chills resolved. The patient was admitted for the therapeutic dose and again experience fever and shaking chills that evening. The patient was subsequently diagnosed with **catheter-related sepsis** on study day 16 after continued fevers and development of tenderness at the port-a-cath site. The patient was admitted for catheter removal on study day 23 and was noted to be hypoxic. A diagnosis of **P. carinii pneumonia** was made and he was treated with antibiotics including high dose Bactrim. On study day 42, the patient developed pancytopenia, requiring transfusions, filgrastim, and dose-reduction of Bactrim; cytopenias recovered by study day 62.
- 004-013-013: 55 yo female who was diagnosed with superior vena cava syndrome secondary to thrombosis (attributed to catheter) on study day 28
- 004-013-017: 62 yo male admitted on study day 21 for **abdominal distention, constipation, and left sided chest pain**. The etiology of these complaints remains unclear. The patient was also admitted on study day 47 for **anemia** requiring transfusions (intermittently until patient left study on day 60) and on study day 56 for thoracentesis. The patient was withdrawn from study on day 57 for progression disease.
- 004-014-002: 58 yo female admitted on study day 13 and 22 for **severe pain, pitting edema of the extremities due to disease progression**. The patient **died** of progressive disease on day 41.
- 004-014-007: 58 yo female who was removed from study on day 24 for disease progression and **died** on study day 79
- 004-015-003: 59 yo male was hospitalized for therapeutic dose administered on study day 9 and developed new onset **atrial flutter** on study day 12. Patient under successful conversion to normal sinus rhythm on study day
- 004-015-006: 71 yo female fell on study day 77 and **fractured her right hip**. Post-operative course complicated by persistent fevers and confusion. Patient was discharged from study on day 110 due to the intervening medical complications and died at home on study day 136.
- 004-106-001: 62 yo male with normal platelet count of 160,000, ANC 2.5 and hemoglobin on study day 0. On the day of therapeutic infusion, platelet count was 140,000. Patient was dosed at 75mCi TBD based on day 0 CBC. The patient experience transient cytopenias days 34-42. On study day 131, patient was

admitted with **febrile neutropenia** and **pancytopenia**. Subsequent course complicated by H. simplex infection. The patient was treated with filgrastim and transfusion support. Recovery of counts was documented on study day 167.

- 004-016-003: 45 yo female with multiple chemotherapeutic regimens prior to entry, received 75cGy TBD in May 1997. The patient had an ongoing CR as of September 1999 with normal CBC, however cytogenetics were abnormal on bone marrow aspirate in Oct. 1999. Patient has had repeated abnormal cytogenetics with normal CBC as of August 2000. This patient has a diagnosis of evolving **MDS**.
- 004-016-004: 55 yo male admitted on study day 73 with **intractable nausea and vomiting, dehydration and renal failure**. The patient was removed from study on day 77. The etiology of the protracted vomiting was felt to be due to disease progression and the patient subsequently received additional chemotherapy.
- 004-016-007: 61 yo male with multiple prior chemotherapeutic regimens who received 75 cGy TBD in August 1997. The patient was platelet and RBC transfusions intermittently between September and December 1997. The patient had persistent thrombocytopenia (45,000-78,000) throughout 1998 and 1999. Although disease progression was documented in 1998, he received no additional treatment for NHL. A diagnosis of **MDS** was made in Jan. 2001.
- 004-016-008: 72 yo female presented with **worsening of pre-existing peripheral neuropathy** (burning leg pain bilaterally) on study day 20. Symptoms persisted and worsened despite outpatient medical management in a pain clinic. The patient was admitted on study day 74 with intractable pain from arthralgias, myalgias, and neuropathy. Management during hospitalization not well described; the patient was discharged on study day 81 on gabapentin with improvement in pain. Pain was persistent at study day 188.
- 004-016-011: 75 yo female with a history of prior SVT (on therapeutic anticoagulation) and a history of dyspnea on exertion on study day -1. The patient continued to have dyspnea, which progressed over time and was attributed to disease progression (including chest wall mass and recurrent pleural effusion) following treatment. The patient was hospitalized on study day 52 for **increasing dyspnea** attributed the chest wall mass causing restriction, and to a lesser degree, recurrent pleural. Although "cardiomegaly" is reported by sponsor, narrative summary states that LVEF was normal and heart was normal size. The patient was discharged to hospice and died on study day 61.
- 004-018-001: This 39 yo female experienced rapidly progressive disease through prior therapy. Prior treatment included cytarabine 1 gm/m<sup>2</sup> and etoposide 100 mg/m<sup>2</sup> IV on days 1-5, administered on October 13, (cycle 1) and November 10 (14?), 1996 (cycle 2). The second cycle was complicated by catheter-related sepsis (Staph aureus) treated with catheter removal. CBC, creatinine and liver functions were normal during that admission. The patient was re-admitted for the dosimetric dose on November 20, 1996 (study day -2) with increasing pleural effusions. Following administration of the dosimetric dose on [REDACTED] (day 0), she underwent thoracentesis and chest tube placement. On study day 6, the patient was noted to have hyperbilirubinemia and increased LFTs. On [REDACTED] (study day 10), she was admitted for the therapeutic dose with a history of increasing lethargy and 2-3 day history of confusion described as "trouble finding the right words". Examination reports extensive expressive and receptive dysphasia with slight impairment of memory. The patient was mildly thrombocytopenic (77,000) with worsening LFTs, notably LDH of 11, 640 IU/ml. A diagnosis of hepatic encephalopathy was made on study day 12, with progressive hepatic deterioration and death on study day 14.

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- 004-020-007: 45 yo male with diagnosis of NHL in Dec. 1994 and multiple chemotherapeutic regimens prior to study entry, received therapeutic dose of 82 mCi (75 cGy TBD) on Jan 2, 1998. Baseline CBC (12/12/97) revealed ANC 5.6, hemoglobin 12 gm/dL, and platelets 116,000. The patient responded to treatment (apparent CR) but suffered persistent thrombocytopenia through 1998 and 1999 with development of leukopenia in 1999 and a diagnosis of **MDS** in September 1999. The patient suffered subdural hematoma in June 2000 (secondary to thrombocytopenia) and died with progressive hemorrhage and hemoptysis on \_\_\_\_\_.
- 004-020-008: 62 yo male with a diagnosis of NHL in November 1995. He received multiple chemotherapeutic regimens prior to study entry in Jan. 7, 1998. The patient received the therapeutic dose of 96 mCi (65 cGy TBD) on Jan 16, 1998. Pretreatment CBC revealed ANC 1.8 hemoglobin 10.8 and platelet count of 104,000. The most recent prior chemotherapy regimen was CHOP/CNPP which was discontinued on Dec. 11, 1996. The patient achieved a PR to 131-iodine tositumomab but progressed on study day 392. Subsequent therapy included a single course (4 weekly doses) of Rituxan. The patient's CBC was reported to be "normal" in June 2000, but abnormal in November 2000. A diagnosis of **MDS** was made in Jan. 2001.
- 004-029-001: 72 yo male enrolled on \_\_\_\_\_ with a ANC of 2.8, hemoglobin of 16.0 gm/dL, and platelets 134, 000 (most recent chemotherapy completed August 1997). The patient received the dosimetric dose on \_\_\_\_\_ and a therapeutic dose of 66 mCi (65 cGy TBD) on \_\_\_\_\_. The patient was hospitalized for anuria on study day 85 due to **bilateral obstructive hydronephrosis**, treated with percutaneous nephrostomy. He simultaneously developed bilateral lower extremity edema; in the evaluation of this, a diagnosis of **bilateral DVT** was made. On study day 90, the patient underwent cystoscopy (reason not provided) and a diagnosis of lymphoma invading the bladder was made.

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## SUPPORTIVE PHASE 1 & PHASE 2 STUDIES

### Study RIT-II-002

Title: Randomized Study of Iodine I 131 Tositumomab vs. Anti-B1 Antibody Alone in Chemotherapy-Relapsed and Refractory Low-Grade or Transformed Low-Grade NHL.

#### Design

*Study RIT-II-002 was a randomized two-arm, open-label, multi-center study conducted in patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. The study was designed to determine the incremental benefit of the radioconjugate compared to the unlabeled antibody. The study compared the safety and efficacy of the radiolabeled antibody (Arm A) versus the unlabeled antibody (Arm B). A one-way cross-over at the time of disease progression was permitted for patients in the unlabeled arm (to receive iodine I-131 tositumomab).*

Protocol activated- March 18, 1996

Accrual was from September 18, 1996 to June 1, 2000

*Principal Investigators and Study Sites*

*John Leonard, M.D., New York Hosp.-Cornell Medical Center*

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Objectives (Final protocol)

Primary objective:

The comparison of the rates of complete response between the Iodine I-131 Anti-B1 antibody (iodine – I 131 tositumomab) and the unlabeled anti-B1 ("cold" tositumomab) arms.

Secondary objectives included comparisons between the Iodine I-131 Anti-B1 antibody and the unlabeled anti-B1 arms for:

- response rates (overall and complete),
- durations of response and complete response,
- comparison of times to progression; and
- safety and tolerance

Inclusion criteria (final protocol after the inclusion amendments 1-6)

1. Patients must have a histologically-confirmed initial diagnosis of low grade non-Hodgkin's B-cell lymphoma [according to International Working Formulation for Clinical Usage A, B, and C] or low-grade lymphoma that has transformed to intermediate- or high-grade histology. The following low-grade histologies are to be included: small lymphocytic (with or without plasmacytoid differentiation); follicular, small-cleaved; and follicular, or mixed small-cleaved and follicular large cell (<50% large cell component).
2. Patients must have evidence that their tumor tissue expresses the CD20 antigen. Immunoperoxidase stains of paraffin-embedded tissue showing positive reactivity with L26 antibody or immunoperoxidase stains of frozen tissue showing positive reactivity with Anti-B1 Antibody (Coulter Clone®) or similar commercially-available CD20 antibody (greater than 50% of tumor cells are positive) or evidence of CD20 positivity by flow cytometry (greater than 50% of tumor cells are positive) are acceptable evidence of CD20 positivity. Testing of tumor tissue from any time in the course of the patient's disease is acceptable.
3. Patients must have received at least one chemotherapy regimen that included an anthracycline, an anthracenedione, or an alkylating agent. Patients must have progressive disease [at least a 25% increase in tumor size at one or more site(s) of disease or new site(s) of disease] within 12 months of receiving their last chemotherapy regimen.
4. Patients must have a performance status of at least 60% on the Karnofsky Scale and an anticipated survival of at least 3 months.

5. Patients must have an absolute neutrophil count  $>1,500/\text{mm}^3$  and a platelet count  $>100,000/\text{mm}^3$  within 14 days of study entry. These blood counts must be sustained without support of hematopoietic cytokines or transfusion of blood products.
6. Patients must have adequate renal function (defined as serum creatinine  $<1.5 \times$  ULN) and hepatic function (defined as total bilirubin  $<1.5 \times$  ULN and AST  $<5 \times$  ULN) within 14 days of study entry
7. Patients must have evaluable, bi-dimensionally measurable disease. At least one lesion must be 2 x 2 cm by CT scan.
8. Patients must be at least 18 years of age.

#### **Exclusion Criteria (final protocol after the inclusion amendments 1-6)**

1. Patients with more than an average of 25% of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens as assessed microscopically within 42 days of study entry. Bilateral posterior iliac crest core biopsies are required if the percentage of intratrabecular space involved exceeds 10% on a unilateral biopsy. The mean of bilateral biopsies must no more than 25%.
2. Patients who have received cytotoxic chemotherapy, radiation therapy, immunosuppressants, or cytokine treatment within 4 weeks prior to study entry (6 weeks for nitrosourea compounds) or who exhibit persistent clinical evidence of toxicity. The use of steroids must be discontinued at least 1 week prior to study entry.
3. Patients who have undergone prior stem cell transplant.
4. Patients with active obstructive hydronephrosis.
5. Patients with evidence of active infection requiring intravenous antibiotics at the time of study entry.
6. Patients with New York Heart Association class III or IV heart disease or other serious illness that would preclude evaluation.
7. Patients with prior malignancy other than lymphoma, except for adequately-treated skin cancer, *in situ* cervical cancer, or other cancer for which patient has been disease-free for 5 years.
8. Patients with known HIV infection.
9. Patients with known brain or leptomeningeal metastases.
10. Patients who are pregnant or nursing. Patients of childbearing potential must undergo a pregnancy test within 7 days of study entry and antibody is not to be administered until a negative result is obtained. For those patients in Arm B, the pregnancy test must be repeated within 7 days of crossover. Males and females must agree to use effective contraception for 6 months following the therapeutic dose, as applicable.
11. Patients with previous allergic reactions to iodine. This does not include reactions to intravenous iodine-containing contrast materials.
12. Patients who were previously given monoclonal or polyclonal antibodies.
13. Patients who previously received radioimmunotherapy.
14. Patients with progressive disease within one year of irradiation arising in a field that has been previously irradiated with  $>3500$  cGy.
15. Patients with *de novo* intermediate- or high-grade lymphoma.
16. Patients who have received  $>3$  chemotherapy regimens (different or identical agents).

Randomization (Final protocol, after the inclusion of amendments 1-6)

Randomization was performed at an external site. There were no stratification criteria specified and no details regarding the randomization procedure in the protocol other than that the randomization would allocate patients equally (1:1) to the two study arms.

Treatment Plan (Final protocol, after the inclusion of amendments 1-6):

#### Arm A

The treatment program consisted of two intravenous infusions; an initial dosimetric infusion followed in 7 to 14 days by a therapeutic infusion.

- The first day of the dosimetric phase was designated as study day 0. The dosimetric [tracer dose] infusion contained 450 mg of Anti-B1 antibody infused over 70 minutes (includes a 10 minute flush) immediately followed by 5 mCi (35 mg) of Iodine -131 Anti-B1 Antibody infused over 30 minutes (includes a 10 minute flush).
- Seven to 14 days later, the therapeutic dose consisting of 450 mg of Anti-B1 antibody was infused over 70 minutes (includes a 10 minute flush) immediately followed by the patient -specific milliCurie activity (35 mg) of Iodine-131 Anti-B1 Antibody calculated to deliver a total body dose of 75 cGy and infused over thirty minutes. The calculation of the patient specific dose was base on the information obtained from the dosimetric infusion and is detailed in the protocol.
- The therapeutic dose was calculated to deliver 75 cGy TBD in patients with platelet counts  $\geq 150,000/\text{mm}^3$ . Patients with platelet counts between 100,001 and  $150,000/\text{mm}^3$  were administered a therapeutic dose calculated to deliver 65 cGy TBD. Obese patients were dosed based upon 137% of their lean body mass.
- Starting 24 hours before the dosimetric dose and continuing for 14 days after the last infusion of radiolabeled antibody, either Lugol's solution or potassium iodide tablets were given to all patients.
- Thirty minutes prior to both the dosimetric dose and the therapeutic dose, patients were pre-medicated with acetaminophen 650 mg p.o. and diphenhydramine 50 mg p.o.
- Patients were tested for HAMA at day 5 and HAMA+ subjects were not given the therapeutic infusion.

#### Arm B

- The first day of the dosimetric phase was designated as study day 0. The dosimetric [tracer dose] infusion contained 450 mg of Anti-B1 antibody infused over 70 minutes (includes a 10 minute flush) immediately followed by 35 mg unlabeled anti-B1 antibody.
- A second dosimetric infusion was administered between study days 7-14, consisting of 450 mg unlabeled anti-B1 IV over 60 minutes followed by 35 mg of unlabeled anti-B1 antibody

Concomitant medications:

- Thirty minutes prior to both the dosimetric dose and the therapeutic dose, patients were pre-medicated with acetaminophen 650 mg p.o. and diphenhydramine 50 mg p.o.

Dose modifications

- Patients with conversion to HAMA+ could not receive the therapeutic infusion.
- Dose adjustments of radiolabeled antibody for obesity and for thrombocytopenia were as described in study report for RIT-II-004

### *Monitoring Plan*

*(Final study protocol, after the inclusion of amendments 1-6):*

Tumor response was assessed at baseline, at 6 weeks, 3 months and then at 3-month intervals until 2 years. AE, SAE and morbidity/mortality data were collected at each contact. Hematologic data were obtained at baseline, and weeks 3 through 13 unless more frequent counts were indicated. After grade 0 toxicity has been observed on 2 or more occasions the protocol stated that weekly hematology testing could be discontinued. After week 13, the follow up phase began with collection of hematology & serum chemistry test samples, TSH levels, physical and history and HAMA every 13 weeks until year two or death or the patient is withdrawn from study for disease progression or concomitant therapy. The final HAMA measurement was at week 26. Withdrawn patients were entered into long term follow up [LTFU] which collected information on disease and vital status, history of thyroid medication, history regarding myelodysplastic disease or other malignancy and any subsequent therapy for NHL. In amendment 1 samples for HAMA and TSH were added to LTFU requirements.

### Original analytic plan

A sample size of 28 patients was selected based on a comparison of CR rates between Arms A and B. The sample size was stated to be sufficient to detect a clinically important difference in CR rates with a one-sided test at the 0.05 level. Comparisons of complete response duration, overall response rates, overall response durations, and time to progression between study arms were planned, however the timing and statistical methods to be employed were not provided. In addition, CR rates, ORR, response durations and TTP would be compared in the subset of patients enrolled in Arm B who progressed and crossed over to anti-B1 radioimmunotherapy following progression. Formal hypotheses to be tested and the timing of the analyses were not stated. Comparisons of response rates would be performed using a Fisher's exact test and time to event comparisons (response durations, TTP, TTF) were to be performed using the log-rank test. Comparisons of  $\geq$  grade 3 adverse events would be performed using Fisher's exact test. Comparison of the changes in laboratory values from baseline would be compared using the log-rank test.

### Final Analytic Plan

*(Final study protocol, after the inclusion of amendments 1-6):*

The primary endpoint was the comparison (using Fischer's Exact Test) of the complete response rates between the two treatment arms (A and B), as determined by the assessment of an independent review of films and medical information (MIRROR Panel). A single interim analysis was performed by the Data Safety Monitoring Board (DSMB), who applied the Lan-DeMets implementation of O'Brien-Fleming boundary for correction for the interim look; based on this interim analysis, the final analysis level of significance was adjusted to 0.049.

The secondary endpoints included comparison of overall response rate, the duration of response, time to progression and time to death. Based on results from RIT-I-000 and RIT-II-001, a 30% CR rate was estimated for treatment arm patients (Arm A) and a 5% rate for Arm B patients exposed to the "cold" antibody. Using a 2 sided alpha of 5%, it was calculated that equal randomization of 78 patients would result in 80% power to demonstrate a difference in CR rate. The primary analysis was a comparison of the

complete response rate between arms of the intent-to-treat population with calculation of 2 sided 95% confidence intervals. P values would be calculated without adjustments except for any interim analyses. Secondary analyses would be performed for crossover patients for response rate and duration of response (McNemar's test). Mean and median durations of response, time to treatment failure and survival will also be calculated.

Based on amendment 6 to the protocol, the analyses of study endpoints were based upon the determination of responses and response durations derived from an assessment of the CRFs and clinical data by an independent reviewer (MIRROR) panel. The MIRROR panel was composed of two teams of radiologists and oncologists who reviewed the CTs and determined the response assignment and duration of response. MIRROR panel radiographs were masked as to information on treatment arm of the patient and to investigators' assessment of response.

## AMENDMENTS TO THE STUDY (BY DATE OF ACTIVATION)

### *Amendment 1- August 14, 1996*

- Section 2, -Definition of chemo-refractory patients changed from, "low grade NHL who have progressed within one year after completing last chemotherapy regimen", to add "failed to respond following relapse".
- Section 5.1.3 under definition of progressive disease the phrase, "failed to respond to combination chemotherapy following relapse" was added.
- Under patient selection Section 5.1 the description of CD20+ antigen testing was preceded by the phrase, "Prior to treatment, CD20 expression will be tested on tumor biopsy material" .....
- To Section 6.2 which describes experimental program for arm A the phrase was added, "Dose will be adjusted for obese patients (as per appendix F) and for those with between 100,000 and 150,000/mm<sup>3</sup> platelets. ANC counts must be 1500 or greater before treatment is undertaken".

### *Amendment 2- May 27, 1997*

- Primary endpoint changed from comparison, between arms, of rates of complete response [CR] and the durations of CR to only rates of complete response. Duration of response became a secondary endpoint.
- Inclusion criteria changed from, "histologically confirmed diagnosis of low grade NHL according to IWF Formulation..." to "histologically confirmed initial diagnosis of low grade NHL according to IWF Formulation".
- Inclusion criteria three and four were rewritten to read: "Patients must have received at least one chemotherapy regimen that included an anthracycline, an anthracenedione, or an alkylating agent. Patients must have progressive disease (at least 25% increase in tumor size at one or more sites of disease or new sites of disease) within 12 months of receiving their last chemotherapy regimen. Patients who have received > 3 chemotherapy regimens are excluded".
- Recalculation of extinction coefficient for anti-B1. It is now —
- Crossover patients must fulfill the same initial inclusion and exclusion criteria and be crossed over within 3 months of progression.
- All SAE within the 12 weeks after study entry must be reported. After 12 weeks only SAE probably or possibly related to study agent are to be tracked.
- Sample size increased from 28 to 78.
- Study converted from single center to multi-center study.

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- The analytic plan was extensively revised.
- Addition of 2 new response categories (Best Response and Prolonged Response) with retention of the original definition of Response (requiring a duration of response of at least 4 weeks),
- Addition of a DSMB permitted to perform at least one and possibly two interim analyses.
- Analyses in “patients completing therapy” in addition to analyses in the ITT population.
- Inclusion of Cox model in the analyses of secondary endpoints

*Amendment 3- July 9, 1997*

- Measurable lesions for evaluating tumor response are defined as any lesion  $\geq 2$  cm in both perpendicular diameters at baseline.

*Amendment 4- June 8, 1998*

- Endpoints section 1.2 changed to read: Secondary endpoint analyses will include comparisons of the response rates, durations of response and complete response, time to progression, time to treatment failure and safety and tolerance between the Iodine-131 anti-B1 antibody and the unlabeled anti-B1 antibody arms.
- Maximum number to be enrolled at any one site is 26 to ensure adequate patient numbers at each site.
- Confirmed response requires that CR, CCR or PR be confirmed by two separate response evaluations at least 4 weeks apart.
- The term, “prolonged response”, which was described as a response confirmed by evaluations spanning at least 12 weeks, was removed from protocol.
- Time of treatment failure definition changed from start of treatment to date of enrollment – to first occurrence of treatment withdrawal, study removal, progression, alternative therapy or death.

*Amendment 5- May 18, 1999.*

*No significant changes*

*Amendment 6- August 17, 2001*

- Time to treatment failure removed from abstract, MIRROR Panel assessments, statistical techniques, and endpoints sections
- Long term follow up added TSH and HAMA monitoring. Final HAMA on week 26 removed.
- MIRROR panel assessment added to determine primary endpoint ( Section 9.9). Statistical section 10.7 expanded to include analyses adjusting for prognostic factors (Cox model).

## RESULTS

## Conduct of the Study

### Bioresearch Monitoring

FDA did not conduct audits of this study at clinical sites.

### Disclosure: Financial Interests and Arrangements of clinical Investigators

The following are investigators disclosing (Form FDA 3455) any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

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### Patient disposition

A total of 78 subjects were enrolled. One subject was removed from study due to reactivation of hepatitis prior to receipt of the therapeutic dose. Of the 78, 42 were randomized to receive Iodine I 131 tositumomab (Arm A) and 36 to received unlabelled tositumomab (Arm B). At the time of the study report, 31 patients had withdrawn from Arm A (29 for disease progression) and 33 had withdrawn from Arm B (32 for disease progression). No patient dropped out due to adverse events.

Patients randomized to unlabeled antibody (Arm B) who experienced disease progression within 3 months of treatment with unlabeled antibody were permitted to receive I 131 tositumomab (the tositumomab therapeutic regimen) in a cross-over arm (denoted Arm X). Among the 36 patients randomized to arm B, there were 32 who experienced progressive disease. Nineteen of the 32 withdrawn subjects were crossed over to Arm X. The remaining 13 were not crossed over for a variety of reasons; the major reason was development of a human anti-murine antibody (HAMA) immune response after exposure to cold anti-B1 antibody. Three patients randomized to Arm B had not experienced disease progression and one patient withdrew from the study.

Reasons cited for 13 patients with progressive disease who did not cross over were:

- ✓ seropositivity for HAMA ( n=8)
- ✓ sought alternative therapy (n=3)
- ✓ death ( n=1)
- ✓ presence of minimal progressive disease ( n=1).

### Protocol Violations:

Thirty-one violations were reported in 29 patients. Patient 200-030-004 [arm B] and 200-030-904\*[arm X] were reported to have had protocol violations both during participation in Arm B and after being crossed over to arm X. Two protocol violations were reported for Patient 002-034-009. Eligibility or treatment/dosing reasons are listed below. Serious

eligibility violations were encountered for 002-011-002 (question of disease progression at baseline), possibly for 002-030-004 and 002-030-015 (question of appropriate studies for disease staging) and patient 002-034-007 (progressive disease not shown until 18 months after last chemotherapy). The number of discrepancies in therapeutic dose and incorrect SSKI dosing were substantial.

| TABLE 002-1   |       |     |      | VIOLATIONS |  |
|---|-------|-----|------|------------|--|
| Patient   | Grade | Arm | Day  | Type       | Violation  |
| 002-011-002   | L     | B   | -215 | ENTRY      | Did not have progression on CT, enrolled 11/16/96 first dose 6/18/97             |
| <b>Disease staging</b>                                |       |     |      |            |  |
| 002-011-007   | L     | B   | -37  | ENTRY      | Disease staging done 37 days prior to dosimetric dose (protocol requires 28)     |
| 002-023-001   | L     | A   | -38  | ENTRY      | Disease staging done 38 days prior to dosimetric dose (protocol requires 28)     |
| <b>Incorrect timing or absence radiologic studies</b> |       |     |      |            |  |
| 002-030-004   | L     | B   | 0    | ENTRY      | Neck CT at baseline performed 1 day after dosimetric dose                        |
| 002-034-018   | L     | B   | -3   | ENTRY      | Head/neck and chest CT scans obtained 1/10/00, 4 days after randomization        |
| 002-030-015   | T     | B   | -2   | ENTRY      | Baseline radiologic tests for CAP were obtained 51 days prior to enrollment      |
| <b>Other eligibility or timing violations</b>         |       |     |      |            |  |
| 002-034-007   | L     | B   | -3   | ENTRY      | Progression shown 18 months post last chemotherapy (protocol requires <12)       |
| 002-011-009   | T     | A   | -8   | ENTRY      | Bone marrow biopsy 43 days before enrollment (protocol requires 42)              |
| 002-011-020   | L     | A   | -3   | ENTRY      | Bone marrow biopsy 46 days before enrollment (protocol requires 42)              |
| 002-030-001   | L     | B   | 0    | ENTRY      | Pregnancy test not done at baseline  |
| 002-030-011   | L     | A   | -5   | ENTRY      | Patient is CD20 positive at entry but >50% positive cells not quantified         |
| 002-030-013   | T     | B   | 0    | ENTRY      | Karnofsky performance status not done at baseline                                |
| 002-030-017   | L     | B   | -6   | ENTRY      | Baseline bone marrow biopsy not assessable- poor quality of specimen             |
| 002-030-020   | L     | A   | -37  | ENTRY      | CBC/chemistry for study entry obtained 35 days prior to enrollment               |
| 002-030-023   | L     | A   | -40  | ENTRY      | Baseline bone marrow biopsy result 20% involvement by unilateral biopsy          |
| 002-030-904   | L     | X   | -5   | ENTRY      | Crossover to arm A 10 months following disease progression                       |
| 002-034-015   | L     | A   | -7   | ENTRY      | Baseline platelet count 99,000 cells/mm <sup>3</sup> , protocol requires 100,000 |
| 002-034-016   | L     | A   | -7   | ENTRY      | History of prostate cancer >4 years ago, PSA level is low normal                 |
| 002-034-913   | L     | X   | 13   | ENTRY      | Received therapeutic dose on 2/10/00 prior to HAMA results                       |
| <b>Treatment violations</b>                           |       |     |      |            |  |
| 002-011-003   | L     | A   | 0    | TREATMENT  | SSKI started same day as dosimetric dose   |
| 002-011-005   | L     | A   | 5    | TREATMENT  | 2nd gamma camera scan done day 5 instead of Day 2,3, or 4 per protocol           |
| 002-025-003   | L     | A   | 0    | TREATMENT  | Patient not treated until 20 days after randomization                            |
| 002-026-004   | T     | A   | 0    | TREATMENT  | Patient not treated until 20 days after randomization                            |
| 002-026-005   | T     | A   | 0    | TREATMENT  | SSKI started same day as dosimetric dose   |
| 002-030-009   | T     | A   | 0    | TREATMENT  | SSKI started same day as dosimetric dose   |
| 002-030-012   | L     | A   | 0    | TREATMENT  | Patient not treated until 27 days after randomization                            |
| 002-030-925   | L     | X   | 21   | TREATMENT  | 2nd dosimetric dose given due to manufacturing delay in therapeutic dose         |
| 002-033-001   | L     | A   | 15   | TREATMENT  | 15 days between dosimetric and therapeutic doses                                 |
| 002-034-009   | L     | A   | 7    | TREATMENT  | Site did not resolve dose calculation discrepancy                                |
| 002-034-009   | L     | A   | 9    | TREATMENT  | SSKI stopped on day 9 due to mouth sores   |
| 002-034-011   | L     | A   | 7    | TREATMENT  | Site did not resolve dose calculation discrepancy                                |

**Study Population**

A total of 78 patients with previously treated low-grade or transformed low-grade NHL were enrolled in this multi-center study. The median follow up was 24.9 months (range: 1.9–52.0 months).

**Protocol RIT-II-002 Enrollment by Protocol Amendment**

|                   | Amendment date  | Effective date  | Cumulative enrollment |
|-------------------|-----------------|-----------------|-----------------------|
| Original protocol | March 19, 1996  | April 11, 1996  | 0                     |
| Amendment 1       | August 14, 1996 | August 29, 1996 | 5                     |
| Amendment 2       | May 27, 1997    | June 4, 1997    | 15                    |
| Amendment 3       | July 9, 1997    | July 11, 1997   | 20                    |
| Amendment 4       | June 6, 1998    | June 9, 1998    | 41                    |
| Amendment 5       | May 18, 1999    | June 3, 1999    | 73                    |
| Amendment 6       | August 17, 1999 | August 24, 1999 | 78                    |
|                   |                 |                 | 78                    |

*The baseline entry characteristics for the study population by treatment arm and for the patients who cross-over in Arm B are presented in the table below.*

**APPEARS THIS WAY  
ON ORIGINAL**

BASELINE ENTRY CHARACTERISTICS: STUDY RIT-II-002 (N = 78)

| Baseline Entry Variable                       | Arm A<br>N= 42 | Arm B<br>N= 36 | Arm B patients<br>Cross-over<br>n=19 |
|---|----------------|----------------|--------------------------------------|
| Age (years)                                   |                |                |                                      |
| Median (range)                                | 56 (28-75)     | 55 (32-85)     | 59 (37-81)                           |
| Q1; Q3  | 50, 67         | 46, 65         | 53, 70                               |
| Gender  |                |                |                                      |
| Males (%)                                     | 23 (50%)       | 18 (50%)       | 11 (58%)                             |
| Race  |                |                |                                      |
| Caucasian (%)                                 | 39 (93%)       | 33 (92%)       | 18 (95%)                             |
| Histologic diagnosis at entry                 |                |                |                                      |
| Without transformation                        |                |                |                                      |
| Low grade                                     | 36 (86%)       | 28 (78%)       | 17 (89%)                             |
| Intermediate grade                            | 0              | 0              | 0                                    |
| High grade                                    | 0              | 0              | 0                                    |
| With transformation                           |                |                |                                      |
| Low grade                                     | 3(7%)          | 2 (5%)         | 1 (5%)                               |
| Intermediate grade                            | 3 (7%)         | 6 (17%)        | 1(5%)                                |
| High grade                                    | 0              | 0              | 0                                    |
| Stage of disease                              |                |                |                                      |
| I   | 0              | 1 (3%)         | 0                                    |
| II  | 5 (12%)        | 3 (8%)         | 3 (16%)                              |
| III   | 10 (24%)       | 9 (25%)        | 7 (37%)                              |
| IV  | 27 (64%)       | 23 (64%)       | 9 (47%)                              |
| Missing                                       | 0              | 0              | 0                                    |
| IPI category                                  |                |                |                                      |
| 0   | 0              | 0              | 0                                    |
| 1   | 11 (26%)       | 9 (25%)        | 3 (11%)                              |
| 2   | 17 (40%)       | 18 (50%)       | 5 (26%)                              |
| 3   | 8 (19%)        | 7 (19%)        | 4 (21%)                              |
| 4   | 4 (10%)        | 1 (3%)         | 2 (11%)                              |
| 5   | 0              | 0              | 0                                    |
| Missing                                       | 0              | 0              | 0                                    |
| Max. tumor diameter                           |                |                |                                      |
| < 5 cm  | 20 (48%)       | 24 (67%)       | 9 (47%)                              |
| ≥ 5, ≤10 cm                                   | 18 (43%)       | 11 (31%)       | 9 (48%)                              |
| > 10 cm                                       | 4 (9%)         | 1 (3%)         | 1 (5%)                               |
| # Prior chemotherapy regimens                 |                |                |                                      |
| Median (range)                                | 2 (1-4)        | 2 (1-5)        | 2 (1-4)                              |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 1, 3           | 1, 3           | 1, 3                                 |
| # Prior radiation therapy regimens            |                |                |                                      |
| Median (range)                                | 0 (0-4)        | 0 (0-5)        | 0 (0-5)                              |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 0,0            | 0,0            | 0,0                                  |
| No Prior BMT                                  | 42 (100%)      | 36 (100%)      | 19 (100%)                            |
| Time from diagnosis to entry (yrs)            |                |                |                                      |
| Median (range)                                | 2.6 (0.5-15.4) | 2.4 (0.6-19.7) | 2.6 (1.7 -20.2)                      |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 1.6, 3.7       | 1.9, 3.7       | 2.3, 4.6                             |

Efficacy Results

There was a significantly higher complete response rate in patient randomized to Arm A as compared to Arm B as well as a significantly increased overall response rate in Arm A. The duration of response however, not significantly different in the two arms; 10 of the 23 responding patients have relapsed in Arm A and 4 of the 7 responding patients have relapsed in Arm B. There was also no difference in overall survival between the two study arms. The median survival has not been reached in either study arm, with 16 of 42 patients dead in Arm A and 12 of 36 patients dead in Arm B. However, there was a significant difference in time to death or progression between the study arms (p=0.031). The survival curves for duration of response, time to progression or death, and time to death are displayed below.

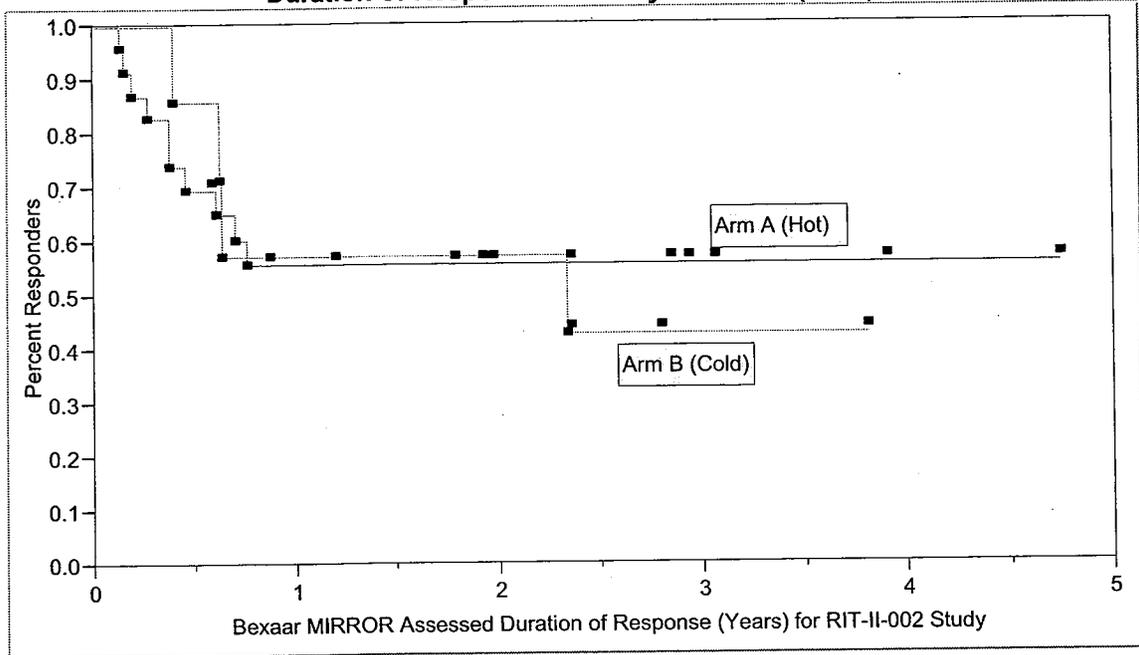
### Efficacy Outcomes

#### MIRROR PANEL-ASSESSED OUTCOMES: STUDY RIT-II-002

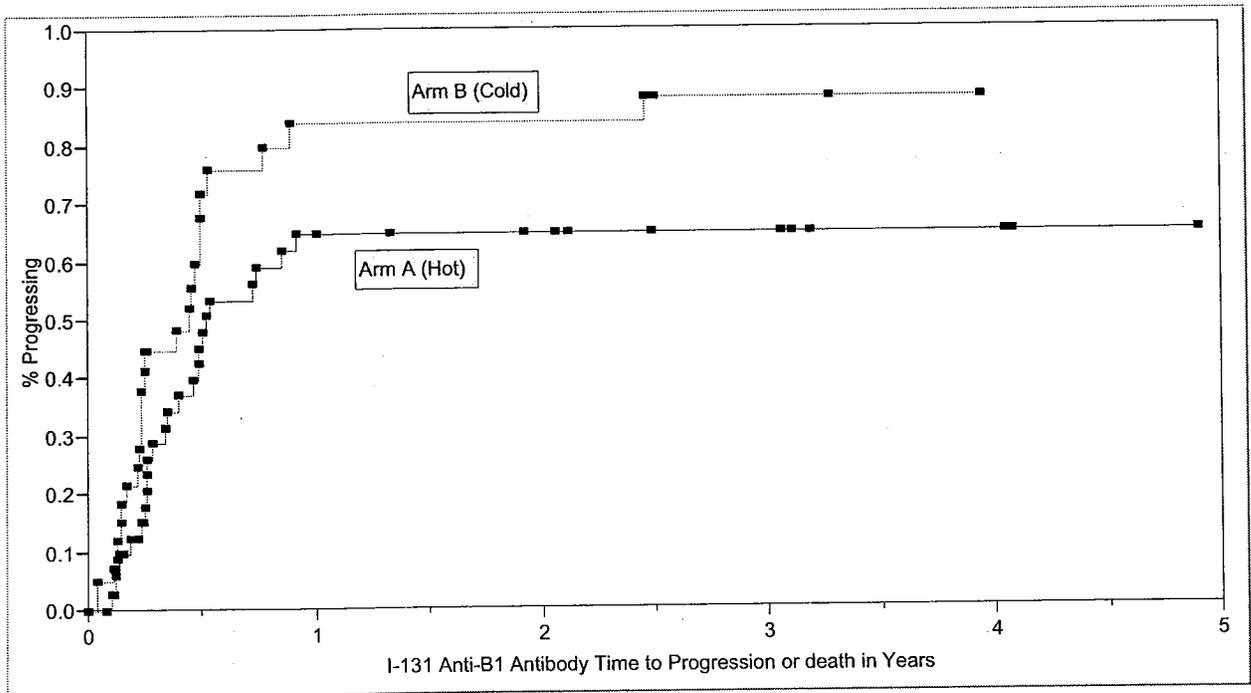
| Efficacy Endpoint                                   | Arm A<br>(N = 42) | Arm B<br>(N = 36) | P-value |
|---|-------------------|-------------------|---------|
| <b>Primary endpoint</b>                             |                   |                   |         |
| Complete response                                   | 14/42 (33%)       | 3/36 (8%)         | 0.01    |
| <b>Secondary endpoints</b>                          |                   |                   |         |
| Overall Response                                    | 23/42 (55%)       | 7/36 (19%)        | 0.001   |
| Median duration (yrs) of response (95% CI)          | NR (0.5–NR)       | 2.3 (0.4, NR)     | 0.9     |
| Median duration (mos) of complete response (95% CI) | NR (NR, NR)       | NR (28, NR)       | 0.4     |
| Median time to progression or death (yrs) (95% CI)  | 0.52 (0.35, NR)   | 0.45 (0.24, 0.5)  | 0.031   |

Fisher's exact test for response rates  
 Log-rank test for duration measures  
 NR = Not reached  
 CI = 95% confidence interval

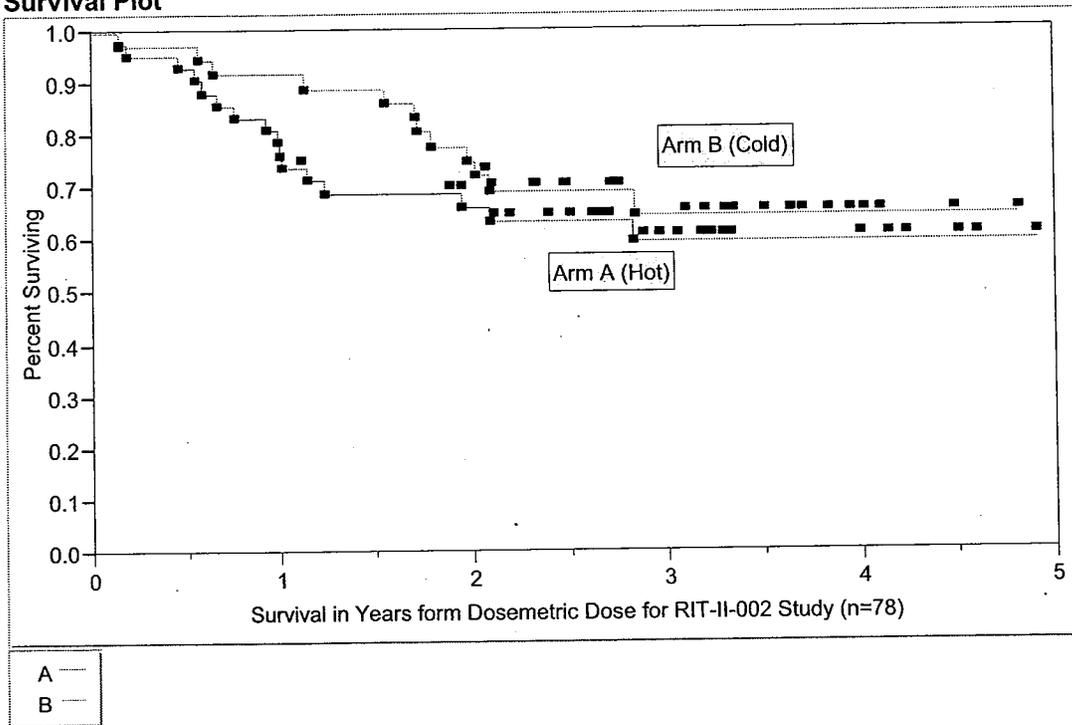
**Duration of Response for study RIT-II-002 (n=78)**



**Time to Progression or death in Years Hot (Arm A, n=42) vs Cold (Arm B, n=36) -- Study RIT-II-002**



**Product-Limit Survival Fit  
Survival Plot**



**Safety Assessment**

**Adverse events:** The most frequent adverse events were nausea, asthenia, fever, rash, chills and pain. Adverse events, both the incidence of all adverse events and of serious adverse events (26% vs. 11%), were higher in patients receiving I 131 tositumomab than in those who received the unlabeled antibody. Gastrointestinal adverse events, particularly nausea, were significantly more frequent in patients receiving radiolabeled antibody as compared to those receiving unlabeled antibody. NCI CTC grade 3-4 non-hematologic adverse events that were reported in >5% of patients included myeloproliferative disorder, chronic leukemia, and lymphoma like reaction and pneumonia. Adverse events reported in  $\geq 5\%$  of patients, regardless of relationship to study drug, are shown in the following table.

*Per-patient incidence of adverse events regardless of severity or relationship to study agent*

| <u>Body System</u><br>COSTART Preferred term | Arm A | Arm B % | Arm X % | Body system<br>COSTART Preferred term | Arm A % | Arm B % | Arm X % |
|--|-------|---------|---------|---------------------------------------|---------|---------|---------|
| N  | 42    | 36      | 19      |                                       | 42      | 36      | 19      |
| <b><u>Body as a Whole</u></b>                | 17    | 8       | 16      | <b><u>Metabolic system</u></b>        | 5       | 6       | 0       |
| Abdominal pain                               | 40    | 36      | 42      | Edema                                 | 7       | 8       | 11      |
| Asthenia                                     | 12    | 8       | 11      | Peripheral edema                      | 5       | 0       | 16      |
| Back pain                                    | 10    | 11      | 0       | Weight loss                           | 0       | 6       | 0       |
| Chest pain                                   | 24    | 19      | 16      | Dehydration                           | 19      | 19      | 5       |
| Chills                                       | 0     | 8       | 5       |                                       | 17      | 17      | 0       |
| Face edema                                   | 33    | 22      | 16      | <b><u>Musculoskeletal</u></b>         |         |         |         |
| Fever  | 14    | 19      | 21      | Arthralgia                            | 5       | 3       | 5       |
| Headache                                     | 5     | 17      | 16      | Myalgia                               | 7       | 8       | 0       |
| Infection                                    | 10    | 6       | 0       |                                       | 10      | 8       | 5       |
| Injection site pain                          | 10    | 3       | 0       | <b><u>Nervous system</u></b>          | 0       | 6       | 0       |
| Malaise                                      | 10    |         | 16      | Anxiety                               | 2       | 6       | 5       |
| Neck pain                                    | 10    | 10      | 21      | Dizziness                             |         |         |         |
| Pain   | 21    | 3       | 0       | Insomnia                              |         |         |         |
| Pelvic pain                                  | 7     | 6       | 0       | Depression                            | 17      | 8       | 32      |
| Sepsis                                       | 7     | 0       | 0       | Parasthesia                           | 14      | 3       | 16      |
|  | 14    | 11      | 0       | Somnolence                            | 19      | 11      | 16      |
| <b><u>Cardiovascular</u></b>                 | 0     | 8       | 0       |                                       | 10      | 14      | 16      |
| Palpitation                                  |       |         |         | <b><u>Respiratory system</u></b>      | 2       | 8       | 5       |
| Vasodilatation                               | 14    | 8       | 0       | Cough increased                       | 5       | 0       | 0       |
| Syncope                                      | 7     | 6       | 0       | Dyspnea                               | 5       | 0       | 0       |
| <b><u>Digestive system</u></b>               | 17    | 11      | 5       | Pharyngitis                           | 2       | 8       | 5       |
| Anorexia                                     | 10    | 6       | 11      | Rhinitis                              |         |         |         |
| Constipation                                 | 5     | 0       | 0       | Bronchitis                            | 5       | 14      | 11      |
| Diarrhea                                     | 5     | 3       | 5       | Epistaxis                             | 31      | 14      | 16      |
| Dyspepsia                                    | 48    | 17      | 11      | Lung disorder                         | 14      | 8       | 11      |
| Dysphagia                                    | 7     | 6       | 0       | Pleural effusion                      |         |         |         |
| Flatulence                                   |       |         |         |                                       |         |         |         |
| Nausea                                       |       |         |         | <b><u>Skin &amp; appendages</u></b>   |         |         |         |
| Vomiting                                     |       |         |         | Pruritus                              |         |         |         |
|  |       |         |         | Rash                                  |         |         |         |
|  |       |         |         | Sweating                              |         |         |         |

**Hematologic toxicity:**

The most frequent adverse event (all severity) and the most frequent severe adverse events were hematologic. In the 19 subjects in arm X there were 11 patients with documented hematologic toxicity and 3 with undocumented toxicity for a cumulative total of 14 (74%). Source was FDA analysis using CRTs submitted 9/7/01.

| <b>Grade 3-4 hematologic toxicity in patients receiving I-131 tositumomab</b> |                       |                       |
|---|-----------------------|-----------------------|
| <i>Toxicity Measure</i>   | <b>Arm A<br/>N=42</b> | <b>Arm X<br/>N=19</b> |
| <i>Neutropenia</i>  |                       |                       |
| % Documented Grade 3-4 toxicity   | 33%                   | 58%                   |
| Median days to nadir  | 47 (42, 49)           | 43 (39, 47)           |
| Median duration of documented Grade 3-4 toxicity                              | 21 (14, 36)           | 31 (15,49)            |
| <i>Thrombocytopenia</i>   |                       |                       |
| % Documented Grade 3-4 toxicity   | 33%                   | 47%                   |
| Median days to nadir (95% CI)   | 36 (29, 38)           | 35 (28,36)            |
| Median duration of documented Grade 3-4 toxicity                              | 29 (22, 54)           | 28 (16,90)            |
| <i>Anemia</i>   |                       |                       |
| % Documented Grade 3-4 toxicity   | 14%                   | 11%                   |
| Median days to nadir  | 48 (40, 51)           | 47 (36, 61)           |
| Median duration of documented Grade 3-4 toxicity                              | 18 (6, ---)           | 35 (10, ---)          |

**Hematologic toxicity in crossover population:** The table below compares documented hematologic toxicity in the three arms and shows a higher incidence of grade 3-4 toxicity in arm A as compared to B, as well as a higher incidence of hematologic grade 3-4 toxicity in arm X as compared to Arm A. Notable is the rate of grade 3-4 neutropenia (8%) with the unlabeled tositumomab, which exceeds that generally observed with other anti-CD20 antibodies. If this is a real finding, the mechanism is unclear. In addition, the incidence of severe cytopenias and of bleeding events in patients who were treated in Arm B and crossed over to treatment with iodine I 131 tositumomab in the 3-month interval permitted in this study is higher than observed in patients in Arm A (initial treatment with the iodine I 131 tositumomab therapeutic regimen. Again, given the small patient numbers it is unclear whether this finding is real or a chance event.

Recovery from hematologic toxicity was evaluated at week 13. There were 35 (of the 42 patients) actively followed in Arm A for hematologic toxicity at week 13. Two patients among the 35 had persistent hematologic toxicity (grade 3 and one grade 4 neutropenia). There were 2 patients, among the 22 being actively followed for toxicity at week 13 in Arm B, who had persistent toxicity (both had Grade 4 neutropenia).

**Percent subjects with grade 3-4 hematologic toxicity**

|                             | Arm A<br>n=42 |    |    | Arm B<br>N=36 |   |   | Arm X<br>n=19 |    |    |
|-----------------------------|---------------|----|----|---------------|---|---|---------------|----|----|
|                             | %             |    |    | %             |   |   | %             |    |    |
|                             | 3&4           | 3  | 4  | 3&4           | 3 | 4 | 3&4           | 3  | 4  |
| <b>Hematologic toxicity</b> |               |    |    |               |   |   |               |    |    |
| ANC < 1000 cells/mm         | 33            | 17 | 17 | 8             | 6 | 3 | 58            | 21 | 37 |
| Platelets < 20,000/ mm      | 33            | 21 | 12 | 0             | 0 | 0 | 47            | 21 | 26 |
| Hgb                         | 8             |    |    | 0             |   |   | 11            |    |    |
| Bleeding events             | 10            |    |    | 3             |   |   | 16            |    |    |

**HAMA:** HAMA was detected at week 7 (5 cases), week 13 (2 cases) and at 6 months in one case. As noted, 32 patients in Arm B with progressive disease had an option of a one-way cross-over to Arm X. Nineteen of the 32 patients crossed over to arm X (to receive iodine I 131 tositumomab therapy). The 13 patients with progressive disease who did not crossover included 8 who could not be crossed over because of positive HAMA tests.

**Serious adverse events:**

There were 15 patients in the randomized portion of the study who suffered one or more serious adverse events. The iodine I 131 tositumomab arm had an approximately 2-fold higher rate of SAE. A similarly high rate of SAE were observed in the patients who crossed over to iodine I 131 tositumomab after disease progression on Arm B.

- 26% (11/42) of patients randomized to iodine I 131 tositumomab (tositumomab therapeutic regimen) experienced one or more SAEs. Ten patients (24%) were hospitalized for the following adverse events: acute cholecystitis; abdominal pain; back pain; constipation; spinal cord compression; pleural effusion; bacteremia (2 patients); dyspnea; GI hemorrhage; small bowel obstruction; deep vein thrombosis. There was one patient with a serious adverse event who experience septicemia that did not require hospitalization.
- 11% (4/36) patients randomized to unlabelled tositumomab experienced at least one SAE. Four patients (11%) were hospitalized for the following adverse events: chest and abdominal pain; syncope /dehydration and hypothermia; retroperitoneal bleed; hydronephrosis; bacteremia; fungemia; febrile neutropenia.
- 37% (7/19) of patients who crossed over to receive I-131 tositumomab (crossed-over after progression) experienced one or more SAEs. Five patients (21%) were hospitalized for the following adverse events: ulcerated node; thrombocytopenia; basal cell carcinoma; bronchitis; abdominal bloating and dyspnea and edema. The patients with SAEs not requiring hospitalization experienced CML and gastric adenocarcinoma, respectively.

**Deaths:** There were 13 total deaths in RIT-II-002 of which 2 were prior to day 90, 3 by day 189, 4 by day 270, and 8 by one year. Arm A had 2 deaths (weeks 8 & 10) and 6 patients who withdrew (weeks 3, 6, 7, 9 and 11) during the first 90 study days.

Patients who died in first ninety days of study

| Patient ID # | Age in yrs | Sex | NHL grade* | Study arm | Study Day of death |
|--------------|------------|-----|------------|-----------|--------------------|
| 002-030-002  | 69         | F   | L          | A         | 54                 |
| 002-030-009  | 51         | M   | T          | A         | 69                 |
| 002-030-018  | 62         | F   | T          | B         | 53                 |

- L = low grade lymphoma without transformation and T = transformed low grade lymphoma

**Studies supporting dosing Strategy**

**STUDY RIT-I-000 Phase 1**

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

Background: This initial study of iodine I 131 tositumomab was a Phase 1/2, single-center, open-label, dose-escalation study. The study was conducted in two Phases. Phase A assessed the impact of a range of cold antibody loading doses on the biodistribution of I 131 tositumomab while simultaneously assessing the toxicity and maximum tolerated dose of I 131 labeled antibody in patients with low-grade, transformed low-grade, intermediate-grade, or high-grade NHL and no prior stem cell transplantation. Phase B assessed the maximum tolerated dose, the dose-limiting toxicity of I 131 labeled antibody in patients with potentially impaired marrow reserve (due to prior hematopoietic stem cell transplants), and the activity at the MTD in patients who had not undergone transplantation.

Study initiated April 24, 1990  
 Phase B initiated October 5, 1994  
 Closed on January 17, 1996  
 Date cut-off: Dec. 1, 2000

Study Sites:  
 University of Michigan Medical Center

Objectives:

1. To evaluate the activity (response) of a pan anti-B cell antibody, B1, that has been conjugated with I-131 in patients with refractory B cell lymphomas
2. To define the toxicity of B1 conjugated with I-131 in patients with refractory B cell lymphomas

3. To determine if B1 conjugated with I-131 can be used as a vehicle to deliver effective radiation to tumor sites and establish the biodistribution, dosimetric parameters, clearance, and tumor specificity
4. To assess the effect of total antibody protein dose on the biodistribution of radiolabeled B1
5. To assess degrees of localization and antigen saturation within tumors by immunohistochemical techniques
6. To assay for human anti-murine antibody (HAMA) production following administration of the murine antibody

#### Inclusion Criteria

1. Histologically documented non-Hodgkin's lymphoma, of low, intermediate or high grade by the IWF
2. Failed previous standard therapies
3. Lymphoma must be immunologically determined to be of the B cell lineage and reactive with the B1 antibody
4. Life expectancy > 3 months, KPS  $\geq$  60%
5. Serum creatinine < 2.0 mg/dL, bilirubin < 3.0 mg/dL
6. Free of acute and chronic infections and off antibiotics for at least one week
7. Must not have received cytotoxic chemotherapy, radiation therapy, and/or immunosuppressants within 4 weeks prior to entry
8. ANC > 1500, platelets > 100,000, and < 25% of cells in the marrow composed of tumor cells
9. Must not have received extensive prior external beam radiotherapy, such as total or subtotal lymphoid irradiation
10. Must have measurable or evaluable disease
11. Must have easily accessible sites of disease for biopsy prior to entry
12. Must be able to give informed consent

Monitoring Plan: CBCs weekly for 8 weeks (twice weekly CBCs for  $\geq$  grade 1 toxicity), serum chemistries at baseline, day 14, weeks 6 and 12. Tumor restaging studies at baseline and weeks 6 and 12.

#### Treatment Plan:

The study was modified numerous times over the course of the study.

Phase A: The general treatment plan for Phase A remained unchanged, however the dose cohorts were modified several times. All patients were to receive two or more dosimetric doses of anti-B1 antibody. The dosimetric doses were administered 7-14 days apart. The amount of unlabeled antibody was varied (generally increased) between the initial and subsequent dosimetric doses given to an individual patient so that an assessment of the impact of the amount of unlabeled antibody [administered within 30 minutes prior to the radiolabeled tracer dose] on the biodistribution could be assessed and compared within an individual patient. In addition, the dose of unlabeled antibody on the initial dosimetric dose was increased in successive groups of patients in a manner not prospectively defined in the protocol, although the analytic plan indicated that intra-patient comparisons in groups of 3 to 6 patients should be sufficient to identify within patient differences in biodistribution.

The dosimetric dose consisted of 35 mg of unlabeled anti-B1 antibody administered intravenously (IV) over one or more hours, following by an IV dose over 1-2 hours,

followed 30-60 minutes later with 1 mg of B1 antibody labeled with 5 mCi I 131 co-administered with additional unlabeled anti-B1 antibody (10-15 mg of antibody total) as an IV infusion over minutes to hours.

The amount of unlabeled antibody administered in the initial part of the dosimetric infusion varied over the course of the study. The unlabeled doses of antibody administered at the initial dosimetric infusion included 0 mg, 95 mg, 475 mg,

In addition, the therapeutic dose was increased in successive cohorts of 3-6 patients to determine the maximum tolerated therapeutic dose. Although modified several times, the treatment plan incorporated the scheme of starting at 25 cGy total body dose (TBD) and increasing by 10 cGy TBD in subsequent cohorts until the MTD was reached or exceeded. Gamma counts were measured daily for 7 days following the dosimetric dose. The gamma count data were then used to determine each patient's clearance of the drug (i.e., total body residence time: TBRT), which was utilized to determine the patient-specific activity (mCi) required to deliver a desired uniform TBD (cGy) of radiation.

Phase B was introduced by an amendment to the protocol in November 1994. During Phase B, there was exploration of the activity of treatment regimen at the MTD for 131-iodine labeled anti-B1 and the optimal dose of unlabeled antibody in the dosimetric/therapeutic in 12 patients with CD20 positive NHL who had not undergone a prior hematopoietic stem cell transplantation. In addition, during Phase B, the MTD of the therapeutic dose of 131-iodine labeled anti-B1 was determined in patients with CD20 expressing NHL with a history of prior hematopoietic stem cell transplantation. The treatment plan was not described for these patients, however a range of doses beginning at a dose of 45 cGy TBD and escalating/de-escalating in 10 cGy increments was administered in groups of patients (1-3).

#### Analytic Plan

The analytic plan was modified over time. The major objectives were to determine the optimal biologic dose of unlabeled antibody as a component of the dosimetric dose and the maximum tolerated dose (MTD) of the therapeutic dose. The definition of dose-limiting toxicity (DLT), upon which the MTD was based, was revised during the course of the study. The final protocol defined the MTD as the level below the dose level at which there was a one-third or greater incidence of DLT. DLT was defined as any non-hematologic Grade 3 or 4 dose-related toxicity, any Grade 3 hematologic toxicity of >2 weeks duration, or any Grade 4 hematologic toxicity of >1 week duration. The determination of the optimal biologic dose of unlabeled antibody was described in qualitative terms in the analytic plan.

#### Amendments to the study

*There were 3 amendments to Phase A [dated August 1990, May 21 1991, June 17, 1993, and February 1994] and 2 amendments to Phase B [November 1994 and October 1997]*

#### RESULTS:

##### Conduct of the study:

The results of this study were not audited by FDA at the clinical study sites

The sponsor reports 11 protocol violations among 9 patients; all were violations of the eligibility criteria.

**Disclosure: Financial Interests and Arrangements of clinical Investigators**

The following are investigators disclosing (Form FDA 3455) any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

- \_\_\_\_\_ **b(6)**
- \_\_\_\_\_

**Patient Enrollment and Disposition:**

A total of 59 patients were enrolled. The first 47 were enrolled in Phase A and 12 additional patients were enrolled in Phase B.

- 59 patients received  $\geq 1$  one dosimetric dose,
- 53 patients received a therapeutic dose; of these, 14 were re-treated

**Dropouts**

- **1 patients did not receive the therapeutic dose due to development of HAMA after dosimetric doses**
  - **4 patients did not receive the therapeutic dose due to rapidly progressive disease**
- **1 patients did not receive the therapeutic dose due to adverse event (disorientation for 10 hours post-administration)**

*Patient Disposition*

**In Phase A, patients were sequentially enrolled into treatment cohorts, which included a simultaneous intra-patient escalation of the dose of unlabeled tositumomab, administered as multiple dosimetric doses, and intra-patient dose escalation, in cohorts of three to six patients, of the total body dose of iodine I 131 tositumomab. The enrollment into the various cohorts are summarized in the table below.**

| <b>Enrollment into Phase A by Cohort</b>                  |                                      |   |   |                   |
|---|--------------------------------------|---|---|-------------------|
| <b>Patients without Prior Bone Marrow Transplantation</b> |                                      |   |   |                   |
| <b>Total Body Dose</b>                                    | <b>Anti-B1 Antibody Predose (mg)</b> | <b># of evaluable Patients/total at</b> | <b>Number of Patients with Dose-Limiting Toxicity</b> | <b>Patient ID</b> |
|   |                                      |   |   |                   |

| Cohort (cGy) |                 | dose level |   |  |
|--------------|-----------------|------------|---|--|
| 25           | 95, 0, 95       | 3/4        | 0 | (000-002-[001, 002,004])               |
| 35           | 0, 475, 95, 475 | 4/4        | 0 | 000-002-[005, 006, 007, 008]           |
| 45           | 95, 95, 475     | 3/5        | 0 | 000-002-[009, 010, 013]                |
| 55           | All 475         | 3/5        | 0 | 000-002-[014, 015, 016]                |
| 65           | All 475         | 3/4        | 0 | 000-002-[019, 020, 023]                |
| 75           | All 475         | 6/6        | 1 | 000-002-[024, 025, 026, 031, 032, 034] |
| 85           | All 475         | 3/3        | 2 | 000-002-[027, 028, 029]                |

*During Phase B, there were 15 additional patients without a history of prior bone marrow transplantation enrolled at a fixed dose of 75mCi TBD. There was a separate dose ranging assessment in patients with prior bone marrow transplantation. Dose cohorts and number of patients enrolled are summarized in the following table. This approach was not well described in the protocol and the enrollment did not appear to follow entry into sequential cohorts with dose escalation between cohorts. Rather, dose selection appeared to be somewhat random.*

Enrollment into Phase B by Cohort

**Patients with Prior Bone Marrow Transplantation**

| TBD cohort (cGy) | # patients enrolled |
|------------------|---------------------|
| 65               | 2                   |
| 55               | 5                   |
| 45               | 6                   |

**Study Population:**

The study population contained a mixture of patients with chemosensitive and chemotherapy-refractory disease. Of the 59 patients enrolled, 30 (51%) had responded to the most recent chemotherapeutic regimen. Of these 19 (33% of the overall study population) had achieved a complete or clinical complete response to the most recent treatment regimen.

### BASELINE ENTRY CHARACTERISTICS

| RIT-II-000                                    | Total enrollment<br>n=59 |
|---|--------------------------|
| Age (years)                                   |                          |
| Median (range)                                | 50 (23-75)               |
| Q1; Q3  | 41, 59                   |
| Gender  |                          |
| Males (%)                                     | 37 (63%)                 |
| Race  |                          |
| Caucasian (%)                                 | 54 (92%)                 |
| Histologic diagnosis at entry                 |                          |
| W/o transformation                            |                          |
| Low grade                                     | 28 (48%)                 |
| Intermediate grade                            | 15 (25%)                 |
| High grade                                    | 2 (3%)                   |
| With transformation                           |                          |
| Low grade                                     | 0                        |
| Intermediate grade                            | 12 (22%)                 |
| High grade                                    | 2 (3%)                   |
| Stage of disease                              |                          |
| I   | 3 (5%)                   |
| II  | 4 (7%)                   |
| III   | 13 (22%)                 |
| IV  | 39 (66%)                 |
| Missing                                       |                          |
| IPI category                                  |                          |
| 0   | 2 (3%)                   |
| 1   | 11 (19%)                 |
| 2   | 24 (41%)                 |
| 3   | 19 (32%)                 |
| 4   | 3 (5%)                   |
| 5   | 0                        |
| Missing                                       | 0                        |
| Max. tumor diameter                           |                          |
| < 5 cm  | 41 (70%)                 |
| ≥ 5, ≤10 cm                                   | 16 (27%)                 |
| > 10 cm                                       | 2 (3%)                   |
| # Prior chemotherapy regimens                 |                          |
| Median (range)                                | 3 (1-11)                 |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 2, 5                     |
| # Prior radiation therapy regimens            |                          |
| Median (range)                                | 0 (0-4)                  |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 0, 1                     |
| No Prior BMT                                  | 45 (76%)                 |
| Time from diagnosis.<br>to entry (mos)        |                          |
| Median (range)                                | 3.8 (0.5-17.8)           |
| 25 <sup>th</sup> , 75 <sup>th</sup> quartiles | 2.5, 7.2                 |

### Efficacy Analyses

The study enrolled a heterogenous group of patients and was not intended to provide more than anecdotal information on clinical activity. In addition, because of the patient heterogeneity and the small numbers of patients who received a particular TBD, it is

difficult to draw conclusions regarding the dose-response relationship. The data presented below are not an ITT analysis. For example, no patient was intended to receive “0 cGy” TBD- each of these patients was unable to receive study drug in a treatment cohort for various reasons, including toxicity with dosimetric infusion, development of HAMA, and/or disease progression. The dose selected by the sponsor for use in Phase 2 studies is based upon determination of the MTD and not necessarily the optimal biologic dose (OBD), which cannot be determined in a study of this size and with this degree of heterogeneity. The data presented in the table below are provided only for information.

### Response Rate Analysis for RIT-I-000 by Total Dose (cGy) received

| Response Variable | 0 cGy<br>n=6 | 25 cGy<br>n=3 | 35 cGy<br>n=4 | 45 cGy<br>n=9 | 55 cGy<br>n=8 | 65 cGy<br>n=6 | 75 cGy<br>n=20 | 85 cGy<br>n=3 | All<br>n=59 |
|-------------------|--------------|---------------|---------------|---------------|---------------|---------------|----------------|---------------|-------------|
| CR                |              |               | 1             |               |               | 1             | 2              | 1             | 5           |
| CCR               |              |               | 1             | 1             | 3             | 2             | 4              |               | 11          |
| PR                | 1            | 1             |               | 3             | 2             | 3             | 2              |               | 12          |
| % ORR             | 17%          | 33%           | 50%           | 44%           | 62%           | 100%          | 40%            | 33%           | 48%         |
| 95% CI            | (0.4, 64)    | (0.8, 91)     | (1, 99)       | (14, 79)      | (24, 91)      | (54,100)      | (19, 64)       | (0.8,91)      | (34, 61)    |

### Safety Analyses

Study RIT-I-000 was designed to determine the optimal unlabeled (cold) predose of Anti-B1 Antibody to maximize tumor targeting and the maximum tolerated non-myeloablative radiation dose level.

The sponsor anticipated that bone marrow toxicity would be dose limiting. The sponsor elected the dose escalation design based on whole body radiation-absorbed dose, on the assumption that the whole body radiation dose would be more closely related to levels of bone marrow toxicity as compared to an escalation based on mCi/kg, mCi/m<sup>2</sup>, or mCi.

Because the direct estimation of radiation dose to bone marrow is not feasible with unsealed source radiation therapy and marrow dosimetry from blood is not considered to be reliable in NHL subjects with normal B-cell populations as well as variable bone marrow involvement, the Total Body Dose (TBD) of radiation exposure was utilized as a surrogate for bone marrow dosimetry. Therefore, dose cohorts were escalated based on TBD and subjects were followed for dose-limiting toxicity (DLT) with expectations that the DLT would be related to declines in peripheral blood assessments, e.g. neutropenia, thrombocytopenia and anemia.

The MTD was set at one level below the dose level at which there was a one-third or greater incidence of DLT. The DLT was defined as any non-hematologic Grade 3 or 4 dose-related toxicity, a Grade 3 hematologic toxicity of >2 week’s duration, or a Grade 4 hematologic toxicity of >1 week duration.

The dose escalation was performed in subjects without prior bone marrow transplantation (BMT).

The maximum non-myeloablative TBD level was established in study RIT-I-000, based on 2 of 3 patients who had a DLT at 85 cGy TBD. Therefore, the MTD was established to be 75 cGy TBD for patients with no prior BMT

**Dose-Dependent Hematologic Toxicity for Study RIT-I-000:  
Patients without Prior Bone Marrow Transplant**

| Dose Cohort<br>TBD (cGy)   | ANC                        | Platelets                     | Hemoglobin |
|----------------------------|----------------------------|-------------------------------|------------|
| <b>25-55</b>               |                            |                               |            |
| N                          | 13                         | 13                            | 13         |
| Mean Nadir                 | 2000 cells/mm <sup>3</sup> | 134,000 cells/mm <sup>3</sup> | 11.5 g/dL  |
| SD of Nadir                | 1000 cells/mm <sup>3</sup> | 41,000 cells/mm <sup>3</sup>  | 1.4 g/dL   |
| Grade III <sup>a</sup> (%) | 1 (8%)                     | 0 (0%)                        | 0 (0%)     |
| Grade IV <sup>a</sup> (%)  | 1 (8%)                     | 0 (0%)                        | 0 (0%)     |
| <b>65-75</b>               |                            |                               |            |
| N                          | 24                         | 24                            | 24         |
| Mean nadir                 | 1300 cells/mm <sup>3</sup> | 76,000 cells/mm <sup>3</sup>  | 10.7 g/dL  |
| SD of nadir                | 1200 cells/mm <sup>3</sup> | 49,000 cells/mm <sup>3</sup>  | 1.9 g/dL   |
| Grade III <sup>a</sup> (%) | 8 (33%)                    | 4 (17%)                       | 1 (4%)     |
| Grade IV <sup>a</sup> (%)  | 4 (17%)                    | 4 (17%)                       | 1 (4%)     |
| <b>85</b>                  |                            |                               |            |
| N                          | 3                          | 3                             | 3          |
| Mean nadir                 | 900 cells/mm <sup>3</sup>  | 78,000 cells/mm <sup>3</sup>  | 8.8 g/dL   |
| SD of nadir                | 1300 cells/mm <sup>3</sup> | 115,000 cells/mm <sup>3</sup> | 2.9 g/dL   |
| Grade III <sup>a</sup> (%) | 0 (0%)                     | 0 (0%)                        | 2 (67%)    |
| Grade IV <sup>a</sup> (%)  | 2 (67%)                    | 2 (67%)                       | 0 (0%)     |

**Narrative summaries of Serious Adverse Events**

- Patient 000-002-004: 42 y/o male diagnosed with low grade NHL in Dec. 1987 and treated with multiple chemotherapeutic agents/regimens. Received 25 cGy TBD (58 mCi) of 131-Iodine tositumomab in March 1991 and retreated with 43 mCi 131-Iodine tositumomab in November 1992. The patient progressed and received additional chemotherapy and RT to the groin. Diagnosed with **MDS** in September 1998.
- Patient 000-002-011: Patient diagnosed with NHL in 1982. Enrolled progressive NHL and massive adenopathy. Patient received two dosimetric doses, the second on September 23, 1992. On October 3, 1992, the patient developed diaphoresis, tachypnea and **pulmonary infiltrates**. On October 7, 1992, the patient developed **acute renal failure** (oliguria and creatinine clearance of 16 mg/dL). The patient was withdrawn prior to the administration of the therapeutic dose and treated with oxygen, diuretics, and chemotherapy for progressive disease.
- Patient 000-002-013: 50 y/o female diagnosed with low grade NHL in 1978 and treated with a variety of chemotherapeutic agents and interferon therapy. She received three dosimetric doses (Nov 18, Nov 25, and Dec 9, 1992) and one therapeutic dose [45 cGy TBD] on Dec. 18, 1992. The patient subsequently received external beam RT (time unspecified). She was diagnosed with **MDS** in August 1995 and died in \_\_\_\_\_.

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- Patient 000-002-014: 66 y/o male diagnosed with low-grade NHL in 1978, treated with CVP, CHOP, and radiotherapy prior to study entry. The patient received three dosimetric infusions
- Patient 000-002-019- Myelodysplasia (see ISS, subsection on **MDS and AML** for details)
- Patient 000-002-021 / ~~\_\_\_\_\_~~: **Disorientation**. This subject was a 64 y/o old female at study entry, with initial diagnosis of NHL in 1992. Prior therapy included 6 cycles of CHOP from Sept 1992 through March 1993 with partial response. Patient received the dosimetric dose of tositumomab on June 16, 1993; infusion was reported to be uncomplicated. On June 23, 1993, the patient complained of disorienting dreams. The patient received the second dosimetric dose of tositumomab later that day. The infusion was complicated only by a mild increase in temperature to 37.5C. Ten hours after the infusion, the patient was disoriented. This was attributed to multiple medications (MS Contin, oxycodone, cyclobenzaprine, and amitriptyline). The patient was removed from study because of this intercurrent event, identified as a serious adverse event and in order to begin alternative therapy. There is insufficient information to assess resolution of this event. The patient subsequently began DHAP chemotherapy on June 29, 1993 and died on ~~\_\_\_\_\_~~, attributed to progressive lymphoma.
- Patient 000-002-031 ~~\_\_\_\_\_~~ - **Leukemia** This patient was identified as having - no description of this provided in the summary.
- Patient 000-002-044 ~~\_\_\_\_\_~~ - **Superficial bladder cancer**. The subject was a 48 year old male at study entry, with a diagnosis of low grade NHL in October 1981 and a diagnosis of low grade papillary transitional cell carcinoma of the bladder on October 19, 1995. Cystoscopy was performed on Oct. 19, 1995 (study day 253) reviewed papillary lesions. Patient underwent TURB October 20, 1995. Of note, a CT scan report of January 24, 1994 had noted a thick-walled bladder in a focal fashion in several areas, "etiology uncertain, bladder neoplasm cannot be excluded". In April 1996, new papillary lesions noted on cystoscopy. The patient underwent TURB and intravesical mitomycin C.
- Patient 000-002-046: 33 y/o female with transformed NHL at enrollment, developed pancytopenia, Coombs negative hemolytic anemia, and hospitalized for **febrile neutropenia** on study day 47. Patient remained culture negative, responded to antibiotics and discharged on study day 57. Received packed RBC x 4, but no platelets. Duration of pancytopenia approximately 20 days; anemia unresolved at day 77.
- Patient 000-002-050: 50 y/o female at entry, extensive prior history of chemotherapy, received 2 therapeutic doses of iodine I 131 tositumomab (114 mCi [75 cGy] and 84 mCi [75 cGy]) in June and Oct. 1995, respectively. Patient diagnosed with **squamous cell carcinoma of the rectum** in March 1996, treated with APR. Patient diagnosed with **MDS** in Feb. 1998 and died ~~\_\_\_\_\_~~.
- Patient 000-002-052: 57 y/o male diagnosed with follicular mixed NHL in 1982. He received 2 therapeutic doses of iodine I 131 tositumomab (106 mCi [65 cGy] and 70 mCi [65 cGy]) in August 1995 and April 1996 respectively. He was diagnosed with **superficial bladder cancer** in October 1996, treated with TURB. The patient died of progressive lymphoma in ~~\_\_\_\_\_~~.
- Patient 000-002-055: 66 y/o male diagnosed in 1982 with follicular mixed NHL, extensive pretreatment history. He received therapeutic dose of iodine I 131 tositumomab (90 mCi [75 cGy]) in Nov. 1995. Patient had a pretreatment bone marrow that was normocellular with 3% blasts and 31% monocytes in Oct. 1995. At

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the time of entry, the patient appears to have been ineligible based on modest cytopenias (ANC 1083, Hgb 9.5 gm/dL, platelets 73, 000) on study day -2 [study day 0 – ANC 1474, Hgb 10.0 gm/dL, platelets 75, 000]. The post-treatment course was complicated by development of **cellulitis** on study day 20, treated with oral antibiotics and was hospitalized for fever and new skin lesions that responded to antibiotic therapy on study day 61; subsequently diagnosed with Sweet's syndrome on biopsy. The patient received filgrastim post-iodine I 131 tositumomab and remained anemic and thrombocytopenic, through study day 68, with intermittent transfusions. The patient was diagnosed with **MDS** on study day 96, in Feb. 1996. He died on ~~study day 470~~ (study day 470 due to secondary leukemia, and infectious complications).

- Patient 000-002-056: 70 y/o female with a diagnosis of follicular, small cleaved NHL in January 1989. The patient had an extensive pretreatment history for NHL. She was also diagnosed with ductal carcinoma of the R breast, treated with lumpectomy (patient refused further therapy). She received one therapeutic infusion of iodine I 131 tositumomab (61 mCi [75 cGy]) in Dec. 1995. At the time of entry she had a slightly hypocellular marrow and mild thrombocytopenia (platelets 138,000). The patient achieved a CR and received no additional treatment for NHL on study. She development disease progression and was withdrawn from study in May 1997. The patient developed pancytopenia and was diagnosed with **MDS** in January 1999, although bone marrow biopsies in 1997 revealed a hypocellular marrow and abnormal cytogenetics (monosomy 8).

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### Study RIT-II-001

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

Design: Multicenter, single arm study to assess the reproducibility of the dosimetry methods developed in RIT-II-000.

Study initiated December 5, 1995

Study closed to enrollment November 20, 1996

Date cut-off December 1, 2000

### Study Sites

- 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
- University of Washington

### Objectives

The primary objective of this multi-center study was to demonstrate that each independent site could reproducibly and accurately 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. Dosimetry methods and calculations from each participating site were validated by a central dosimetry center at the University of Michigan.

#### Eligibility

Patients were eligible 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 was required to contain an anthracycline or anthracenedione. Progression after single-agent steroids was not sufficient for study entry. Patients who were treated with chemotherapy for low-grade lymphoma and subsequently transformed to a higher grade were eligible even if they had not received specific treatment for their transformed lymphoma.

#### Treatment Plan

As described in RIT-II-002 for Arm A.

#### Patient Monitoring

Monitoring was similar to the other studies with the exception that gamma camera images for calculation of dosimetry were obtained daily on study days 0-7.

#### Analysis plan:

*Descriptive statistics for assessment of toxicity, response rates and durations.*

### **STUDY RESULTS**

#### Bioresearch Monitoring Inspections

The University of Nebraska study site was inspected for Protocol RIT-II-001, entitled "Multicenter, Phase II Dosimetry/Validation Study of 131Iodine-AntiB1(murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grades" after the sponsor reported that data was missing. The inspections were conducted in accordance with CPGM 7348.811, the Inspection Program for Clinical Investigators. Specific questions concerning the studies were included.

#### Disclosure: Financial Interests and Arrangements of clinical Investigators

The following are investigators disclosing (Form FDA 3455) any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

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## Inspectional Summary Statement

*The results of bioresearch monitoring inspections indicate that the deviations are not substantive, with the exceptions noted (failure to calculate residual activity, eligibility entry violations), and that the submitted data can be considered reliable and accurate.*

## Patient Enrollment and Disposition

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: 0.2–58.3 months).

### Patient Entry Characteristics Study RIT-II-001 (n=47)

|  |               |
|--|---------------|
| Male/female  | 25/22         |
| Median age (years) (range)                           | 51<br>(23–74) |
| Time from diagnosis to study entry (months) (range)  | 41<br>(8–264) |
| Median number of prior chemotherapy regimens (range) | 4<br>(1–8)    |
| Grade  |               |
| Low grade  | 33/47 (70%)   |
| Transformed low grade                                | 14/47 (30%)   |
| Bone marrow involvement                              | 24/47 (51%)   |
| Bulky disease (>500 g)                               | 17/47 (44%)   |
| Elevated LDH   | 18/47 (38%)   |
| Response to last chemotherapy <sup>a</sup>           |               |
| Response (PR + CCR + CR)                             | 24/47 (51%)   |
| Complete response (CCR + CR)                         | 8/47 (17%)    |
| <sup>a</sup> Unconfirmed response rates.             |               |

## Dosimetry Endpoints

Assessment of all of the onsite calculations and the administered activity of iodine I 131 tositumomab (mCi) by the independent dosimetry center indicated that the calculations performed at the treating centers were within 10% of those calculated at the dosimetry center.

### Activity Results

The overall response rate was 49% (23/47). The complete response rate (CR + CCR) was 30% (14/47).

### Safety Results

Non-hematologic toxicities were qualitatively similar to that reported in other studies. Hematologic toxicities were somewhat more frequent than in the other studies.

| <i>Toxicity Measure</i>         | <b>N=47</b> |
|---------------------------------|-------------|
| <i>Neutropenia</i>              |             |
| % Documented Grade 3-4 toxicity | 62%         |
| <i>Thrombocytopenia</i>         |             |
| % Documented Grade 3-4 toxicity | 57%         |
| <i>Anemia</i>                   |             |
| % Documented Grade 3-4 toxicity | 21%         |

### Narrative descriptions of serious adverse events

- 001-003-002: 60 y/o female, diagnosed with follicular mixed NHL in 1988. She had an extensive pre-treatment history for NHL. The patient received one therapeutic dose of iodine I 131 tositumomab (76 mCi [75cGy]) in Feb. 1996. At study entry, bone marrow was normocellular without evidence of lymphoma. Baseline CBC revealed ANC 3300, Hgb 11.1 gm/dL, and platelet count of 107,000. The patient had a partial response with disease progression diagnosed in Nov. 1996, treated with local RT. During this treatment period, the patient was modestly pancytopenic (WBC 1900, Hgb 9.0 gm/dL, platelets 79,000). The patient was diagnosed with **MDS** in a bone marrow biopsy in Dec. 1996. The patient died of progressive NHL and pancytopenia (complications of MDS).
- 001-003-004: 46 y/o female with diagnosis of colon cancer in 1970 and a diagnosis of NHL in 1993. The patient received on therapeutic dose of iodine I 131 tositumomab (107 mCi [75 cGy]) in May 1996. At the time of study entry, the patient had extensive adenopathy in the chest, abdomen, and pelvis, and three hepatic lesions; the hepatic lesions were felt to represent lymphomatous involvement of the liver. Following iodine I 131 tositumomab, the patient developed RUQ pain and nausea. In addition, she was pancytopenia and transfused on several occasions between study days 34 and 62. She developed fevers and **sinusitis** during a period when her neutrophil counts were approximately 500/cu mm. The fevers responded to oral antibiotics although symptoms of sinusitis persisted. The patient had persistent intermittent low grade fevers without concurrent neutropenia and RUQ pain with increasing liver lesions. Upon admission for evaluation (study day 77), she was found to have **catheter-related bacteremia** (coag negative Staph and

Clostridium) that responded to antibiotics and removal of the catheter. On study day 103, the enlarging liver lesions were documented to be metastatic adenocarcinoma (**recurrent colon cancer**) and the patient was withdrawn from study.

- 001-004-006: 35 y/o female with original diagnosis of NHL in June 1995. Prior treatment, history was remarkable for bloody diarrhea during CHOP chemotherapy that responded to steroid therapy. She received one therapeutic dose of iodine I 131 tositumomab (60 mCi [75 mCi]) in August 1996. The patient developed bloody diarrhea on study day 32, in the setting of concurrent pancytopenia. She began steroids on study day 32 with improvement in bloody diarrhea (**exacerbation of ulcerative colitis**) but presented with fever and rigors, ANC 0, Hgb 8.7 gm.dL, and platelet count of 34,000 on study day 34 (**febrile neutropenia**). She responded to IV antibiotics and received filgrastim, epoetin, and was continued on steroids. Recovery of neutrophils documented by day 43 and recover from anemia and thrombocytopenia documented by study day 82.
- 001-005-001: 40 y/o female diagnosed with follicular small cleaved cell NHL in April 1992. The patient received one therapeutic dose of iodine I 131 tositumomab (177 mCi [75 cGy, unadjusted]) in Dec. 1995. The dose was not adjusted for obesity and low platelet counts of 131,000 and under the current proposed dosing regimen would have received 124 mCi 131-I. The patient developed **persistent thrombocytopenia** between study days 30-184 and persistent anemia when the patient left study for disease progression. The patient was pancytopenic requiring numerous platelet and RBC transfusions and filgrastim by study day 30 and remained thrombocytopenic and received numerous platelet transfusions

## 6.2 Other Trials

Not Applicable

## 6.3 Literature Review and Other Relevant Materials

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## **Appendix A:**

**The following FDA reviewers substantially contributed in performing the clinical review of Bexxar:**

**Kaushik Shastri  
Stephen Litwin  
George Mills  
Satish Misra  
Harvey Luksenburg  
Mary Andrich  
Susan Jerian  
Patricia Keegan**

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49 Page(s) Withheld

       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)