## 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 labeled 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

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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 --- 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/$mm^3$ and a platelet count >100,000/$mm^3$ 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 x ULN) and hepatic function (defined as total bilirubin <1.5 x ULN and AST <5 x 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 than25%.
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/mm$^3$. Patients with platelet counts between 100,001 and 150,000/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- ----------

- 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/$mm^3$ platelets. ANC counts must be 1500 or greater before treatment is undertaken".

Amendment 2- ----------

- 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**.**
- 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- ----------

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

Amendment 4- ----------

- 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 --- 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- ----------
No significant changes

Amendment 6- ----------

- 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.

- Mark Kaminski, M.D.- Principal Investigator, University of Michigan
- Richard Wahl, M.D. – Principal Investigator, University of Michigan
- Susan Knox, M.D.- Principal Investigator, Stanford University

#### 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 ---------- first dose ---------- | | | | | |
| **Disease staging** | | | | | | | | | | |
| 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) | | | | | |
| **Incorrect timing or absence radiologic studies** | | | | | | | | | | |
| 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/---/00, 4 days after randomization | | | | | |
| 002-030-015 | T | B | -2 | ENTRY | Baseline radiologic tests for CAP were obtained 51 days prior to enrollment | | | | | |
| **Other eligibility or timing violations** | | | | | | | | | | |
| 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/mm3, 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/---/00 prior to HAMA results | | | | | |
| **Treatment violations** | | | | | | | | | | |
| 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 | ---------- | ---------- | 0 |
| Amendment 1 | ---------- | ---------- | 5 |
| Amendment 2 | ---------- | ---------- | 15 |
| Amendment 3 | ---------- | ---------- | 20 |
| Amendment 4 | ---------- | ---------- | 41 |
| Amendment 5 | ---------- | ---------- | 73 |
| Amendment 6 | ---------- | ---------- | 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.

## Baseline Entry Characteristics: Study RIT-II-002 (N = 78)

| Baseline Entry Variable | Arm A N= 42 | Arm B N= 36 | Arm B patients Cross-over 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 |
| 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%) |
| $\geq$ 5, $\leq$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) |
| $25^{th}$, $75^{th}$ quartiles | 1, 3 | 1, 3 | 1, 3 |
| # Prior radiation therapy regimens | | | |
| Median (range) | 0 (0-4) | 0 (0-5) | 0 (0-5) |
| $25^{th}$, $75^{th}$ 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) |
| $25^{th}$, $75^{th}$ 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.

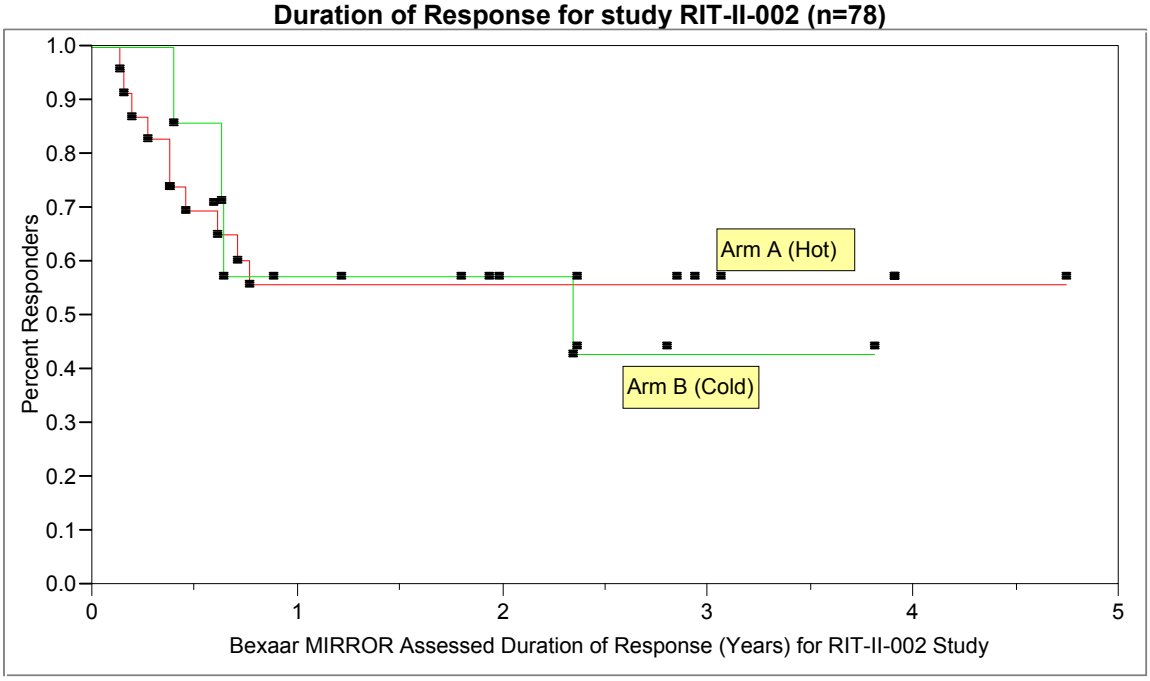
## Efficacy Outcomes

### MIRROR Panel–Assessed Outcomes: Study RIT-II-002

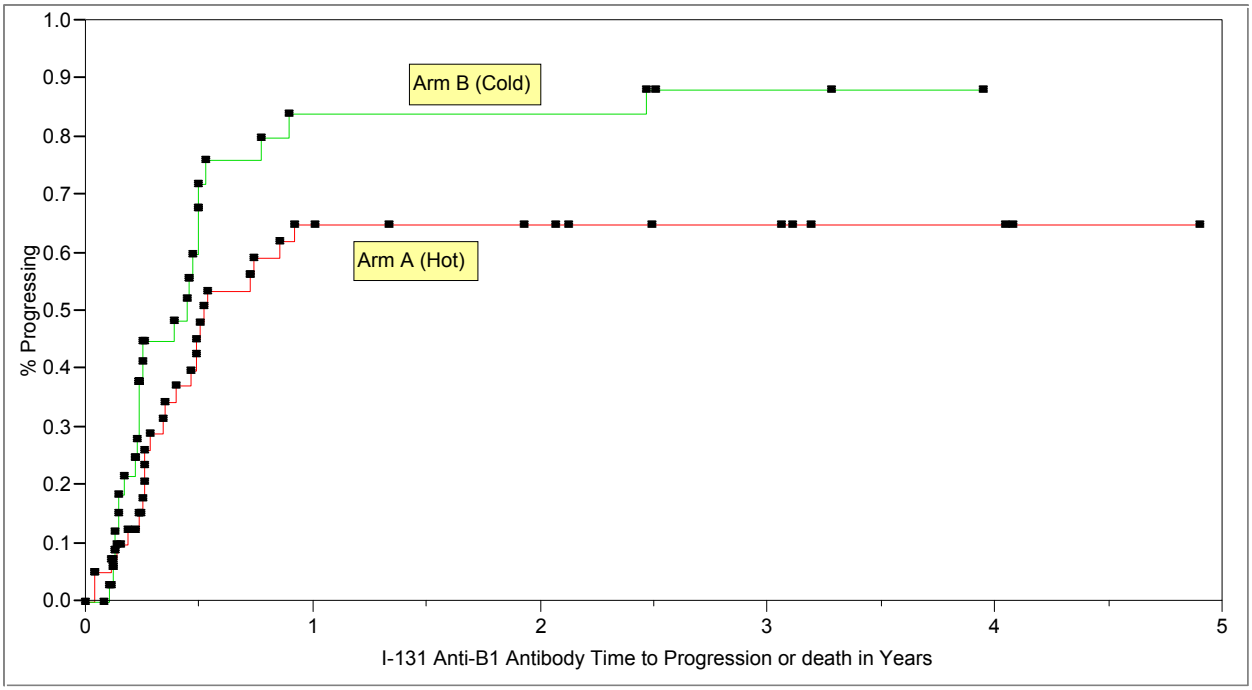
| Efficacy Endpoint | Arm A (N = 42) | Arm B (N = 36) | P-value |
|---|---|---|---|
| **Primary endpoint** | | | |
| **Complete response** | **14/42 (33%)** | **3/36 (8%)** | **0.01** |
| **Secondary endpoints** | | | |
| **Overall Response** | **23/42 (55%)** | **7/36 (19%)** | **0.001** |
| **Median 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**

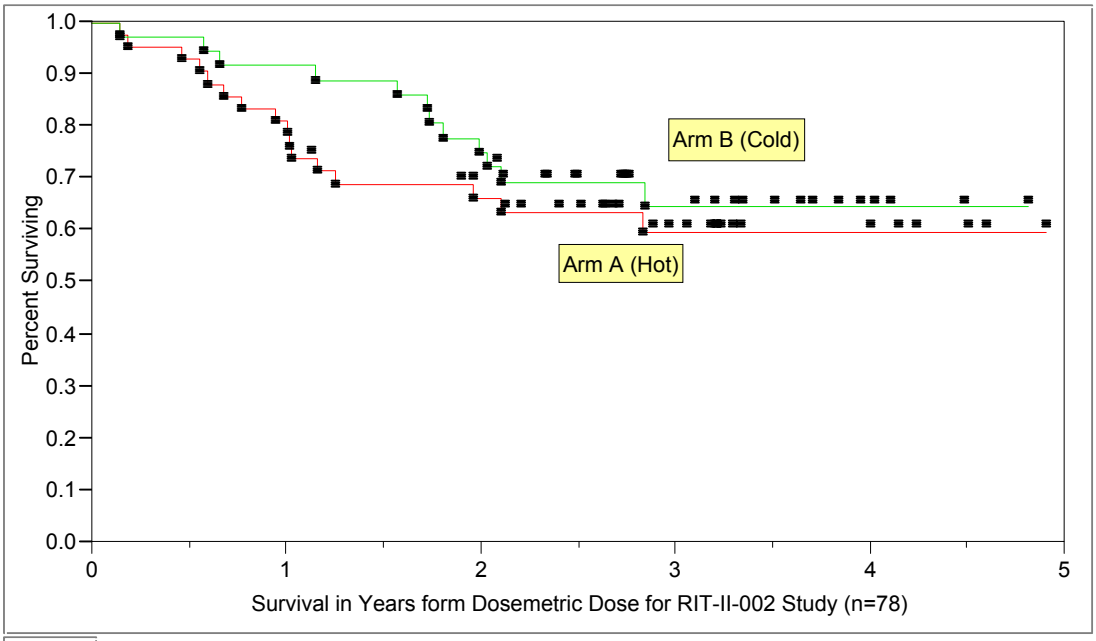
**Duration of Response for study RIT-II-002 (n=78)**




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


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
% Progressing
Arm B (Cold)
Arm A (Hot)
0
1
2
3
4
5
I-131 Anti-B1 Antibody Time to Progression or death in Years

**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 ≥ 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

| Body System<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 |
| **Body as a Whole** | | | | **Metabolic system** | | | |
| Abdominal pain | 17 | 8 | 16 | Edema | 5 | 6 | 0 |
| | 40 | 36 | 42 | Peripheral edema | 7 | 8 | 11 |
| Asthenia | 12 | 8 | 11 | Weight loss | 5 | 0 | 16 |
| Back pain | 10 | 11 | 0 | Dehydration | 0 | 6 | 0 |
| Chest pain | 24 | 19 | 16 | **Musculoskeletal** | | | |
| Chills | 0 | 8 | 5 | Arthalgia | 19 | 19 | 5 |
| Face edema | 33 | 22 | 16 | Myalgia | 17 | 17 | 0 |
| Fever | 14 | 19 | 21 | **Nervous system** | | | |
| Headache | 5 | 17 | 16 | Anxiety | 5 | 3 | 5 |
| Infection | 10 | 6 | 0 | Dizziness | 7 | 8 | 0 |
| Injection site pain | 10 | 3 | 0 | Insominia | 10 | 8 | 5 |
| Malaise | 10 | | 16 | Depresson | 0 | 6 | 0 |
| Neck pain | 10 | 10 | 21 | Parasthesia | 2 | 6 | 5 |
| Pain | 21 | 3 | 0 | Somnolence | | | |
| Pelvic pain | 7 | 6 | 0 | **Respiratory system** | | | |
| Sepsis | | | | Cough increased | 17 | 8 | 32 |
| **Cardiovascular** | 7 | 0 | 0 | Dyspnea | 14 | 3 | 16 |
| Palpitation | 14 | 11 | 0 | Pharyngitis | 19 | 11 | 16 |
| Vasodilatation | 0 | 8 | 0 | Rhinitis | 10 | 14 | 16 |
| Syncope | | | | Bronchitis | 2 | 8 | 5 |
| **Digestive system** | 14 | 8 | 0 | Epistaxis | 5 | 0 | 0 |
| Anorexia | 7 | 6 | 0 | Lung disorder | 5 | 0 | 0 |
| Constipation | 17 | 11 | 5 | Pleural effusion | 2 | 8 | 5 |
| Diarrhea | 10 | 6 | 11 | **Skin & appendages** | | | |
| Dyspepsia | 5 | 0 | 0 | Pruritus | 5 | 14 | 11 |
| Dysphagia | 5 | 3 | 5 | Rash | 31 | 14 | 16 |
| Flatulence | 48 | 17 | 11 | Sweating | 14 | 8 | 11 |
| Nausea | 7 | 6 | 0 | | | | |
| Vomiting | | | | | | | |

**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 ----------.

| Grade 3-4 hematologic toxicity in patients receiving I-131 tositumomab | | |
|---|---|---|
| **Toxicity Measure** | **Arm A N=42** | **Arm X N=19** |
| **Neutropenia** | | |
| % 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) |
| **Thrombocytopenia** | | |
| % 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) |
| **Anemia** | | |
| % 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 bleeing 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 n=42** | | | **Arm B N=36** | | | **Arm X n=19** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **%** | | | **%** | | | **%** | | |
| | **3&4** | **3** | **4** | **3&4** | **3** | **4** | **3&4** | **3** | **4** |
| **Hematologic toxicity** | | | | | | | | | |
| **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 cholecytitis; 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 ≥ 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-B1antibody (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 ----------. 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 hematopoeitic stem cell transplantion. 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 hematopoeitic stem cell transplantion. 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 ----------] and 2 amendments to Phase B [----------]

# 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.

- Mark Kaminski, M.D.- Principal Investigator, University of Michigan
- Richard Wahl, M.D. – Principal Investigator, University of Michigan

## 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 ≥ 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.

**Enrollment into Phase A by Cohort**
**Patients without Prior Bone Marrow Transplantation**

| Total Body Dose Cohort (cGy) | Anti-B1 Antibody Predose (mg) | # of evaluable Patients/total at dose level | Number of Patients with Dose-Limiting Toxicity | Patient ID |
|---|---|---|---|---|
| 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 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) |
| $25^{th}$, $75^{th}$ quartiles | 2, 5 |
| # Prior radiation therapy regimens | |
| Median (range) | 0 (0-4) |
| $25^{th}$, $75^{th}$ quartiles | 0, 1 |
| No Prior BMT | 45 (76%) |
| Time from diagnosis. to entry (mos) | |
| Median (range) | 3.8 (0.5-17.8) |
| $25^{th}$, $75^{th}$ quartiles | 2.5, 7.2 |

## Efficacy Analyses

The study enrolled a heterogenous group of patients and was not intended to provide more than anectodotal 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 n=6 | 25 cGy n=3 | 35 cGy n=4 | 45 cGy n=9 | 55 cGy n=8 | 65 cGy n=6 | 75 cGy n=20 | 85 cGy n=3 | All 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/$m^2$, 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 TBD (cGy) | ANC | Platelets | Hemoglobin |
|---|---|---|---|
| **25–55** | | | |
| N | 13 | 13 | 13 |
| Mean Nadir | 2000 cells/$mm^3$ | 134,000 cells/$mm^3$ | 11.5 g/dL |
| SD of Nadir | 1000 cells/$mm^3$ | 41,000 cells/$mm^3$ | 1.4 g/dL |
| Grade III[a] (%) | 1 (8%) | 0 (0%) | 0 (0%) |
| Grade IV[a] (%) | 1 (8%) | 0 (0%) | 0 (0%) |
| **65–75** | | | |
| N | 24 | 24 | 24 |
| Mean nadir | 1300 cells/$mm^3$ | 76,000 cells/$mm^3$ | 10.7 g/dL |
| SD of nadir | 1200 cells/$mm^3$ | 49,000 cells/$mm^3$ | 1.9 g/dL |
| Grade III[a] (%) | 8 (33%) | 4 (17%) | 1 (4%) |
| Grade IV[a] (%) | 4 (17%) | 4 (17%) | 1 (4%) |
| **85** | | | |
| N | 3 | 3 | 3 |
| Mean nadir | 900 cells/$mm^3$ | 78,000 cells/$mm^3$ | 8.8 g/dL |
| SD of nadir | 1300 cells/$mm^3$ | 115,000 cells/$mm^3$ | 2.9 g/dL |
| Grade III[a] (%) | 0 (0%) | 0 (0%) | 2 (67%) |
| Grade IV[a] (%) | 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 ---, 1992. On October ---, 1992, the patient developed diaphoresis, tachypnea and **pulmonary infiltrates**. On October ---, 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 ---, Nov ---, and Dec ---, 1992) and one therapeutic dose [45 cGy TBD] on Dec. ---, 1992. The patient subsequently received external beam RT (time unspecified). She was diagnosed with **MDS** in August 1995 and died in ----------.

- 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 ---, 1993; infusion was reported to be uncomplicated. On June ---, 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. Cystosopy was performed on Oct. --, 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 therapuetic 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 carcinima of the rectum** in March 1996, treated with APR. Patient diagnosed with **MDS** in Feb. 1998 and died August 1998.
- 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 May 1997.
- 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

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 February 1997 (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).

**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-OO2 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.

- Mark Kaminski, M.D.- Principal Investigator, University of Michigan
- Richard Wahl, M.D. – Principal Investigator, University of Michigan
- Susan Knox, M.D.- Principal Investigator, Stanford University
- David Colcher, Ph. D.- Investigator, University of Nebraska

## 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 (23–74)** |
| **Time from diagnosis to study entry (months) (range)** | **41 (8–264)** |
| **Median number of prior chemotherapy regimens (range)** | **4 (1–8)** |
| **Grade** | |
| **Low grade** | **33/47 (70%)** |
| **Transformed low grade** | **14/47 (30%)** |
| **Bone marrow involvement** | **24/47 (51%)** |
| **Bulky disease (>500 g)** | **17/47 (44%)** |
| **Elevated LDH** | **18/47 (38%)** |
| **Response to last chemotherapy[a]** | |
| **Response (PR + CCR + CR)** | **24/47 (51%)** |
| **Complete response (CCR + CR)** | **8/47 (17%)** |

[a] **Unconfirmed response rates.**

### 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.

| **Toxicity Measure** | **N=47** |
|---|---|
| **Neutropenia** | |
| % Documented Grade 3-4 toxicity | 62% |
| **Thrombocytopenia** | |
| % Documented Grade 3-4 toxicity | 57% |
| **Anemia** | |
| % 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 docuemnted 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