

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125011/S024

Trade Name: Bexxar

Generic Name: Tositumomab and Iodine I 131 Tositumomab

Sponsor: Corixa Corporation

Approval Date: December 22, 2004

Indications: Treatment of relapsed or refractory, low grade, follicular or transformed CD20 positive non-Hodgkin's lymphoma who have not received Rituximab.

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RESEARCH**

APPLICATION NUMBER:
125011/S024

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| Pharmacology Review(s) | |
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| Clinical Pharmacology | X |
| Administrative/Correspondence Document(s) | X |

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RESEARCH**

APPLICATION NUMBER:

125011/S024

APPROVAL LETTER

Food and Drug Administration
Rockville, MD 20852**DEC 22 2004**

Our STN: BL 125011/24

Corixa Corporation
Attention: Monica S. Krieger, Ph.D.
Vice President, Regulatory Affairs
1900 9th Avenue, Suite 1100
Seattle, WA 98101

Dear Dr. Krieger:

Your request to supplement your biologics license application for Tositumomab and Iodine I 131 Tositumomab to expand the indication to include patients with relapsed or refractory, low grade, follicular or transformed CD20 positive non-Hodgkin's lymphoma who have not received Rituximab has been approved.

As requested in your letter of July 1, 2004, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe the clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival or improvement in disease-related symptoms. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Tositumomab and Iodine I 131 Tositumomab (BEXXAR[®]), or are not conducted with due diligence, the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval, to expand the indication to include patients with relapsed or refractory, low grade, follicular or transformed CD20 positive non-Hodgkin's lymphoma who have not received Rituximab, is contingent upon completion of a clinical study to verify the clinical benefit of the BEXXAR[®] therapeutic regimen. Identified as postmarketing commitment (PMC) #1 in the June 27, 2003, approval letter for your biologics license application under STN 125011/0 and as outlined in your July 1, 2004, supplement submitted under STN 125011/24, this PMC is subject to the reporting requirements of 21 CFR 601.70 and is as follows:

- To conduct an open-label efficacy trial of Rituximab versus the Bexxar 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 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, the study will be completed by September 3, 2007, and the final study report will be submitted by May 9, 2008.

For administrative purposes, all submissions related to this postmarketing study commitment should be clearly designated "Subpart E Postmarketing Study Commitments."

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125011. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 125011. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study commitment as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (<http://www.fda.gov/cder/pmc/default.htm>). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see <http://www.fda.gov/cber/gdlns/post040401.htm>) for further information.

As required by 21 CFR 601.45, please submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement

with a cover letter requesting advisory comment. Send two copies of the promotional materials to The Division of Drug Marketing, Advertising and Communications, HFD-42, Food and Drug Administration, 5600 Fishers Lane, Rockville MD 20852. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This information will be included in your biologics license application file.

Sincerely,

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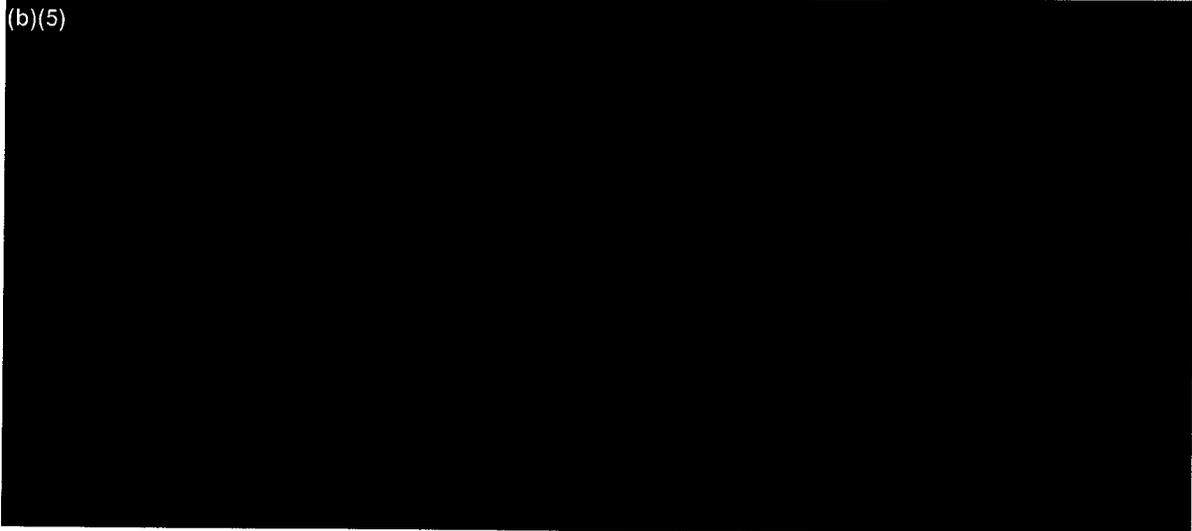
Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)

Summary Text: Clinical Supplmt. Efficacy - New/Expanded Indication;
Accelerated Approval

(b)(5)



cc: Attached label is sent to everyone

HFD-107/K. Shastri

HFD-107/M. Andrich

HFD-109/D. Slavin

HFD-107/A. Rajpal

HFD-711/M Rothmann

HFD-711/A. Chakravarty

HFD-711/S. Misra

HFD-711/K. Koti

HFD-430/R. Pratt

HFD-328/J. Li

HFD-106/K. Weiss

HFD-106/G. Jones

HFD-123 /Keith Webber

HFM-110/RIMS/R. Eastep

HFD-020/John Jenkins

HFD-005/Mike Jones

HFD-400/ODS M. Dempsey

HFD-006/Exec sec P. Guinn

HFD-013/FOI D. Taub

HFD-013/FOI H. Brubaker

HFD-240/OTCOM/ B. Poole

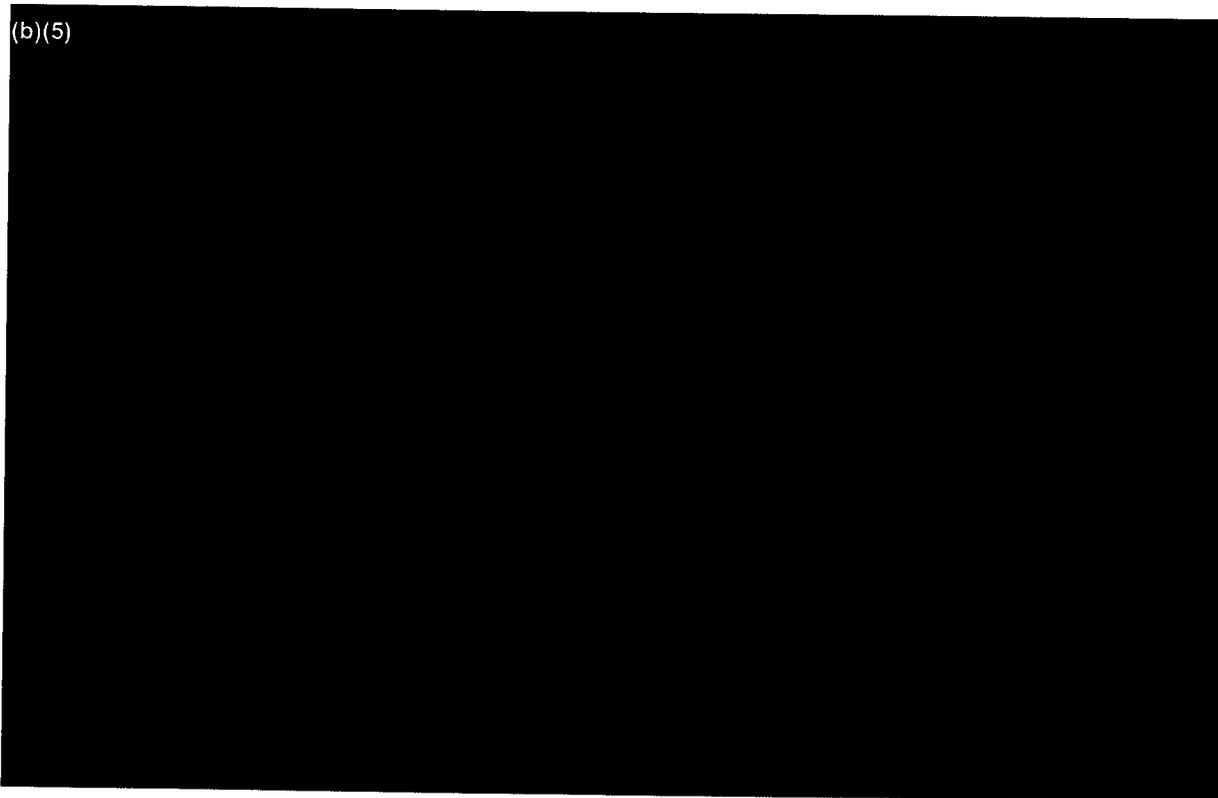
HFI-20/Press/ L. Gelb

HFI-20/Press/ J. Brodsky

HFD-230/OTCOM/CDER WebMaster
HFD-001/B. Duvall-Miller (if PMC commitments)
HFD-42/DDMAC/M. Kiester
HFD-410/ODS/DSRCS/ Karen Young
HFD-950/OCTAP/T. Crescenzi
HFD-960/OCTAP/G. Carmouze
HFD-320/DMPQ/ J. Famulare
HFD-322/PCB/ E. Rivera-Martinez
HFM-555/DMA/ S. Kozłowski
HFM-535/DTP/ A. Rosenberg
HFM-570/DTBOP/ P. Keegan
HFM-570/DTBIMP/ M. Walton
HFD-328/TFRB Blue File/Mike Smedley
HFD-430/ODS/DDRE (hard copy)
HFD-410/CDER Medwatch Safety Labeling (hard copy)
DRMP BLA file (hard copy)

History: Slavin: 12-1-04; Slavin 12.20.04; Slavin 12-21-04

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APPLICATION NUMBER:

125011/S024

LABELING

DEC 22 2004

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Rx Only

BEXXAR®

P/N 400009-B

**Tositumomab and
Iodine I 131 Tositumomab**7
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27**WARNINGS**

Hypersensitivity Reactions, including Anaphylaxis: Serious hypersensitivity reactions, including some with fatal outcome, have been reported with the Bexxar therapeutic regimen. Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Patients who develop severe hypersensitivity reactions should have infusions of the BEXXAR therapeutic regimen discontinued and receive medical attention (see **WARNINGS**).

Prolonged and Severe Cytopenias: The majority of patients who received the BEXXAR therapeutic regimen experienced severe thrombocytopenia and neutropenia. The BEXXAR therapeutic regimen should not be administered to patients with >25% lymphoma marrow involvement and/or impaired bone marrow reserve (see **WARNINGS** and **ADVERSE REACTIONS**).

Pregnancy Category X: The BEXXAR therapeutic regimen can cause fetal harm when administered to a pregnant woman.

Special requirements: The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides. The BEXXAR therapeutic regimen should be administered only by physicians who are in the process of being or have been certified by Corixa Corporation in dose calculation and administration of the BEXXAR therapeutic regimen.

28 DESCRIPTION

29 The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131
30 Tositumomab) is an anti-neoplastic radioimmunotherapeutic monoclonal
31 antibody-based regimen composed of the monoclonal antibody,
32 Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131
33 Tositumomab.

34 Tositumomab

35 Tositumomab is a murine IgG_{2a} lambda monoclonal antibody directed
36 against the CD20 antigen, which is found on the surface of normal and
37 malignant B lymphocytes. Tositumomab is produced in an antibiotic-free
38 culture of mammalian cells and is composed of two murine gamma 2a
39 heavy chains of 451 amino acids each and two lambda light chains of 220
40 amino acids each. The approximate molecular weight of Tositumomab is
41 150 kD.

42 Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent,
43 colorless to slightly yellow, preservative-free liquid concentrate. It is
44 supplied at a nominal concentration of 14 mg/mL Tositumomab in 35 mg
45 and 225 mg single-use vials. The formulation contains 10% (w/v) maltose,
46 145 mM sodium chloride, 10 mM phosphate, and Water for Injection, USP.
47 The pH is approximately 7.2.

48 Iodine I 131 Tositumomab

49 Iodine I 131 Tositumomab is a radio-iodinated derivative of Tositumomab
50 that has been covalently linked to Iodine-131. Unbound radio-iodine and
51 other reactants have been removed by chromatographic purification steps.
52 Iodine I 131 Tositumomab is supplied as a sterile, clear, preservative-free
53 liquid for IV administration. The dosimetric dosage form is supplied at
54 nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL
55 (at date of calibration), respectively. The therapeutic dosage form is
56 supplied at nominal protein and activity concentrations of 1.1 mg/mL and
57 5.6 mCi/mL (at date of calibration), respectively. The formulation for the
58 dosimetric and the therapeutic dosage forms contains 4.4%–6.6% (w/v)
59 povidone, 1–2 mg/mL maltose (dosimetric dose) or 9–15 mg/mL maltose

**Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)
BLA STN 125011**

60 (therapeutic dose), 0.85–0.95 mg/mL sodium chloride, and 0.9–1.3 mg/mL
61 ascorbic acid. The pH is approximately 7.0.

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BEXXAR Therapeutic Regimen

64 The BEXXAR therapeutic regimen is administered in two discrete steps:
65 the dosimetric and therapeutic steps. Each step consists of a sequential
66 infusion of Tositumomab followed by Iodine I 131 Tositumomab. The
67 therapeutic step is administered 7-14 days after the dosimetric step. The
68 BEXXAR therapeutic regimen is supplied in two distinct package
69 configurations as follows:

BEXXAR Dosimetric Packaging

- 71 • A carton containing two single-use 225 mg vials and one single-use
72 35 mg vial of Tositumomab supplied by McKesson BioServices and
- 73 • A package containing a single-use vial of Iodine I 131 Tositumomab
74 (0.61 mCi/mL at calibration), supplied by MDS Nordion.

BEXXAR Therapeutic Packaging

- 76 • A carton containing two single-use 225 mg vials and one single-use
77 35 mg vial of Tositumomab, supplied by McKesson BioServices
78 and
- 79 • A package containing one or two single-use vials of Iodine I 131
80 Tositumomab (5.6 mCi/mL at calibration), supplied by MDS
81 Nordion.

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Physical/Radiochemical Characteristics of Iodine-131

84 Iodine-131 decays with beta and gamma emissions with a physical
85 half-life of 8.04 days. The principal beta emission has a mean energy of
86 191.6 keV and the principal gamma emission has an energy of 364.5 keV
87 (Ref 1).

88 **External Radiation:** The specific gamma ray constant for Iodine-131 is
89 2.2 R/millicurie hour at 1 cm. The first half-value layer is 0.24 cm lead

90 (Pb) shielding. A range of values is shown in Table 1 for the relative
91 attenuation of the radiation emitted by this radionuclide that results from
92 interposition of various thicknesses of Pb. To facilitate control of the
93 radiation exposure from this radionuclide, the use of a 2.55 cm thickness
94 of Pb will attenuate the radiation emitted by a factor of about 1,000.

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Table 1
Radiation Attenuation by Lead Shielding

| Shield Thickness (Pb) cm | Attenuation Factor |
|-------------------------------------|-------------------------------|
| 0.24 | 0.5 |
| 0.89 | 10 ⁻¹ |
| 1.60 | 10 ⁻² |
| 2.55 | 10 ⁻³ |
| 3.7 | 10 ⁻⁴ |

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99 The fraction of Iodine-131 radioactivity that remains in the vial after the
100 date of calibration is calculated as follows:

101 Fraction of remaining radioactivity of Iodine-131 after x days = $2^{-(x/8.04)}$

102 Physical decay is presented in Table 2.

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Table 2
Physical Decay Chart: Iodine-131: Half-Life 8.04 Days

| Days | Fraction Remaining |
|------|--------------------|
| 0* | 1.000 |
| 1 | 0.917 |
| 2 | 0.842 |
| 3 | 0.772 |
| 4 | 0.708 |
| 5 | 0.650 |
| 6 | 0.596 |
| 7 | 0.547 |
| 8 | 0.502 |
| 9 | 0.460 |
| 10 | 0.422 |
| 11 | 0.387 |
| 12 | 0.355 |
| 13 | 0.326 |
| 14 | 0.299 |

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*(Calibration day)

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CLINICAL PHARMACOLOGY

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General Pharmacology

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Tositumomab binds specifically to the CD20 (human B-lymphocyte-restricted differentiation antigen, Bp 35 or B1) antigen. This antigen is a transmembrane phosphoprotein expressed on pre-B lymphocytes and at higher density on mature B lymphocytes (Ref. 2). The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL) (Ref. 3). The recognition epitope for Tositumomab is found within the extracellular domain of the CD20 antigen. CD20 does not shed from the cell surface and does not internalize following antibody binding (Ref. 4).

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Mechanism of Action: Possible mechanisms of action of the BEXXAR therapeutic regimen include induction of apoptosis (Ref. 5), complement-dependent cytotoxicity (CDC) (Ref. 6), and antibody-dependent cellular cytotoxicity (ADCC) (Ref. 5) mediated by the antibody. Additionally, cell death is associated with ionizing radiation from the radioisotope.

123 Pharmacokinetics/Pharmacodynamics

124 The phase 1 study of Iodine I 131 Tositumomab determined that a 475 mg
125 predose of unlabeled antibody decreased splenic targeting and increased
126 the terminal half-life of the radiolabeled antibody. The median blood
127 clearance following administration of 485 mg of Tositumomab in
128 110 patients with NHL was 68.2 mg/hr (range: 30.2–260.8 mg/hr).
129 Patients with high tumor burden, splenomegaly, or bone marrow
130 involvement were noted to have a faster clearance, shorter terminal half-
131 life, and larger volume of distribution. The total body clearance, as
132 measured by total body gamma camera counts, was dependent on the
133 same factors noted for blood clearance. Patient-specific dosing, based on
134 total body clearance, provided a consistent radiation dose, despite
135 variable pharmacokinetics, by allowing each patient's administered activity
136 to be adjusted for individual patient variables. The median total body
137 effective half-life, as measured by total body gamma camera counts, in
138 980 patients with NHL was 67 hours (range: 28-115 hours).

139 Elimination of Iodine-131 occurs by decay (see Table 2) and excretion in
140 the urine. Urine was collected for 49 dosimetric doses. After 5 days, the
141 whole body clearance was 67% of the injected dose. Ninety-eight percent
142 of the clearance was accounted for in the urine.

143 Administration of the BEXXAR therapeutic regimen results in sustained
144 depletion of circulating CD20 positive cells. The impact of administration
145 of the BEXXAR therapeutic regimen on circulating CD20 positive cells was
146 assessed in two clinical studies, one conducted in chemotherapy naïve
147 patients and one in heavily pretreated patients. The assessment of
148 circulating lymphocytes did not distinguish normal from malignant cells.
149 Consequently, assessment of recovery of normal B cell function was not
150 directly assessed. At seven weeks, the median number of circulating
151 CD20 positive cells was zero (range: 0-490 cells/mm³). Lymphocyte
152 recovery began at approximately 12 weeks following treatment. Among
153 patients who had CD20 positive cell counts recorded at baseline and at 6
154 months, 8 of 58 (14%) chemotherapy naïve patients had CD20 positive
155 cell counts below normal limits at six months and 6 of 19 (32%) heavily
156 pretreated patients had CD20 positive cell counts below normal limits at

157 six months. There was no consistent effect of the BEXXAR therapeutic
158 regimen on post-treatment serum IgG, IgA, or IgM levels.

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160 **Radiation Dosimetry**

161 Estimations of radiation-absorbed doses for Iodine I 131 Tositumomab
162 were performed using sequential whole body images and the MIRDSE 3
163 software program. Patients with apparent thyroid, stomach, or intestinal
164 imaging were selected for organ dosimetry analyses. The estimated
165 radiation-absorbed doses to organs and marrow from a course of the
166 BEXXAR therapeutic regimen are presented in Table 3.

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Table 3

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Estimated Radiation-Absorbed Organ Doses

| From Organ ROIs | BEXXAR | BEXXAR |
|-----------------------------|-------------------|------------------|
| | mGy/MBq Median | mGy/MBq Range |
| Thyroid | 2.71 | 1.4 - 6.2 |
| Kidneys | 1.96 | 1.5 - 2.5 |
| ULI Wall | 1.34 | 0.8 - 1.7 |
| LLI Wall | 1.30 | 0.8 - 1.6 |
| Heart Wall | 1.25 | 0.5 - 1.8 |
| Spleen | 1.14 | 0.7 - 5.4 |
| Testes | 0.83 | 0.3 - 1.3 |
| Liver | 0.82 | 0.6 - 1.3 |
| Lungs | 0.79 | 0.5 - 1.1 |
| Red Marrow | 0.65 | 0.5 - 1.1 |
| Stomach Wall | 0.40 | 0.2 - 0.8 |
| From Whole Body ROIs | | |
| Urine Bladder Wall | 0.64 | 0.6 - 0.9 |
| Bone Surfaces | 0.41 | 0.4 - 0.6 |
| Pancreas | 0.31 | 0.2 - 0.4 |
| Gall Bladder Wall | 0.29 | 0.2 - 0.3 |
| Adrenals | 0.28 | 0.2 - 0.3 |
| Ovaries | 0.25 | 0.2 - 0.3 |
| Small Intestine | 0.23 | 0.2 - 0.3 |
| Thymus | 0.22 | 0.1 - 0.3 |
| Uterus | 0.20 | 0.2 - 0.2 |
| Muscle | 0.18 | 0.1 - 0.2 |
| Breasts | 0.16 | 0.1 - 0.2 |
| Skin | 0.13 | 0.1 - 0.2 |
| Brain | 0.13 | 0.1 - 0.2 |
| Total Body | 0.24 | 0.2 - 0.3 |

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BLA STN 125011

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CLINICAL STUDIES

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The efficacy of the BEXXAR therapeutic regimen was evaluated in 2 studies conducted in patients with low-grade, transformed low-grade, or follicular large-cell lymphoma. Determination of clinical benefit of the BEXXAR therapeutic regimen was based on evidence of durable responses without evidence of an effect on survival. All patients had received prior treatment without an objective response or had progression of disease following treatment. Patients were required to have a granulocyte count >1500 cells/mm³, a platelet count $\geq 100,000$ /mm³, an average of $\leq 25\%$ of the intratrabecular marrow space involved by lymphoma, and no evidence of progressive disease arising in a field irradiated with >3500 cGy within 1 year of completion of irradiation.

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Study 1 was a multicenter, single-arm study of 40 patients whose disease had not responded to or had progressed after at least four doses of Rituximab therapy. The median age was 57 (range: 35–78); the median time from diagnosis to protocol entry was 50 months (range: 12–170); and the median number of prior chemotherapy regimens was 4 (range: 1–11). The efficacy outcome data from this study, as determined by an independent panel that reviewed patient records and radiologic studies, are summarized in Table 4.

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Among the forty patients in the study, twenty-four patients had disease that did not respond to their last treatment with Rituximab, 11 patients had disease that responded to Rituximab for less than 6 months, and five patients had disease that responded to Rituximab, with a duration of response of 6 months or greater. Overall, 35 of the 40 patients met the definition of "Rituximab refractory", defined as no response or a response of less than 6 months duration. In this subset of patients the overall objective response was 63% (95% confidence interval 45%, 79%) with a median duration of 25 months (range of 4 - 38+ months). The complete response in this subset of patients was 29% (95% CI of 15%, 46%) with a median duration of response not yet reached (range of 4 - 38+ months).

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Study 2 was a multicenter, single arm, open-label study of 60 chemotherapy refractory patients. The median age was 60 (range 38-82),

204 the median time from diagnosis to protocol entry was 53 months (range: 9-
 205 334), and the median number of prior chemotherapy regimens was 4
 206 (range 2-13). Fifty-three patients had not responded to prior therapy and
 207 7 patients had responded with a duration of response of <6 months. The
 208 efficacy outcome data from this study, as determined by an independent
 209 panel that reviewed patient records and radiologic studies are also
 210 summarized in Table 4. Investigators continued to follow eight patients
 211 with complete response after the last independent review panel
 212 assessment. The updated duration of ongoing response as per
 213 investigators was reported to range from 42 to 85 months.

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Table 4: Efficacy Outcomes in Bexxar Clinical Studies

| | Study 1 (n=40) | Study 2 (n=60) |
|---|---|---------------------------|
| Overall Response Rate 95% CI ^a | 68% (51%, 81%) | 47% (34%, 60%) |
| Response Duration (mos) Median 95% CI ^a Range | 16 (10, NR ^b) 1+ to 38+ | 12 (7, 47) 2 to 47 |
| Complete Response ^c Rate 95% CI ^a | 33% (19%, 49%) | 20% (11%, 32%) |
| Complete response ^c duration (mos) Median 95% CI ^a Range | NR ^b (15, NR) 4 to 38+ | 47 (47, NR) 9 to 47 |

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^a CI = Confidence Interval

^b NR = Not reached, Median duration of follow up: Study 1 = 26 months; Study 2 = 30 months

^c Complete response rate = Pathologic and clinical complete responses

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The results of these studies were supported by demonstration of durable objective responses in three single-arm studies. In these studies, 130 patients with Rituximab-naïve follicular non-Hodgkin's lymphoma with or without transformation were evaluated for efficacy. All patients had relapsed following, or were refractory to, chemotherapy. The overall response rates ranged from 49% to 64% and the median durations of

230 response ranged from 13 to 16 months. Due to small sample sizes in the
231 supportive studies, as in studies 1 and 2, the 95% confidence intervals for
232 the median durations of response are wide.

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234 **INDICATIONS AND USAGE**

235 The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131
236 Tositumomab) is indicated for the treatment of patients with CD20 antigen-
237 expressing relapsed or refractory, low grade, follicular, or transformed
238 non-Hodgkin's lymphoma, including patients with Rituximab-refractory
239 non-Hodgkin's lymphoma. Determination of the effectiveness of the
240 BEXXAR therapeutic regimen is based on overall response rates in
241 patients whose disease is refractory to chemotherapy alone or to
242 chemotherapy and Rituximab. The effects of the BEXXAR therapeutic
243 regimen on survival are not known.

244 The BEXXAR therapeutic regimen is not indicated for the initial treatment
245 of patients with CD20 positive non-Hodgkin's lymphoma. (see **ADVERSE**
246 **REACTIONS, Immunogenicity**)

247 The BEXXAR therapeutic regimen is intended as a single course of
248 treatment. The safety of multiple courses of the BEXXAR therapeutic
249 regimen, or combination of this regimen with other forms of irradiation or
250 chemotherapy, has not been evaluated.

251 **CONTRAINDICATIONS**

252 The BEXXAR therapeutic regimen is contraindicated in patients with
253 known hypersensitivity to murine proteins or any other component of the
254 BEXXAR therapeutic regimen.

255 **PREGNANCY CATEGORY X**

256 Iodine I 131 Tositumomab (a component of the BEXXAR therapeutic
257 regimen) is contraindicated for use in women who are pregnant. Iodine-
258 131 may cause harm to the fetal thyroid gland when administered to
259 pregnant women. Review of the literature has shown that transplacental

260 passage of radioiodide may cause severe, and possibly irreversible,
261 hypothyroidism in neonates. While there are no adequate and well-
262 controlled studies of the BEXXAR therapeutic regimen in pregnant
263 animals or humans, use of the BEXXAR therapeutic regimen in women of
264 childbearing age should be deferred until the possibility of pregnancy has
265 been ruled out. If the patient becomes pregnant while being treated with
266 the BEXXAR therapeutic regimen, the patient should be apprised of the
267 potential hazard to the fetus (see **BOXED WARNING, Pregnancy**
268 **Category X**).

269 **WARNINGS**

270 **Prolonged and Severe Cytopenias (see **BOXED WARNINGS;****
271 **ADVERSE REACTIONS, Hematologic Events):**

272 The most common adverse reactions associated with the BEXXAR
273 therapeutic regimen were severe or life-threatening cytopenias (NCI CTC
274 grade 3 or 4) with 71% of the 230 patients enrolled in clinical studies
275 experiencing grade 3 or 4 cytopenias. These consisted primarily of grade
276 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The
277 time to nadir was 4 to 7 weeks and the duration of cytopenias was
278 approximately 30 days. Thrombocytopenia, neutropenia, and anemia
279 persisted for more than 90 days following administration of the BEXXAR
280 therapeutic regimen in 16 (7%), 15 (7%), and 12 (5%) patients
281 respectively (this includes patients with transient recovery followed by
282 recurrent cytopenia). Due to the variable nature in the onset of cytopenias,
283 complete blood counts should be obtained weekly for 10-12 weeks. The
284 sequelae of severe cytopenias were commonly observed in the clinical
285 studies and included infections (45% of patients), hemorrhage (12%), a
286 requirement for growth factors (12% G- or GM-CSF; 7% Epoetin alfa) and
287 blood product support (15% platelet transfusions; 16% red blood cell
288 transfusions). Prolonged cytopenias may also influence subsequent
289 treatment decisions.

290 The safety of the BEXXAR therapeutic regimen has not been established
291 in patients with >25% lymphoma marrow involvement, platelet count
292 <100,000 cells/mm³ or neutrophil count <1,500 cells/mm³.

293 **Hypersensitivity Reactions Including Anaphylaxis (see BOXED**
294 **WARNINGS; ADVERSE REACTIONS, Hypersensitivity Reactions and**
295 **Immunogenicity):** Serious hypersensitivity reactions, including some
296 with fatal outcome, were reported during and following administration of
297 the BEXXAR therapeutic regimen. Emergency supplies including
298 medications for the treatment of hypersensitivity reactions, e.g.,
299 epinephrine, antihistamines and corticosteroids, should be available for
300 immediate use in the event of an allergic reaction during administration of
301 the BEXXAR therapeutic regimen. Patients who have received murine
302 proteins should be screened for human anti-mouse antibodies (HAMA).
303 Patients who are positive for HAMA may be at increased risk of
304 anaphylaxis and serious hypersensitivity reactions during administration of
305 the BEXXAR therapeutic regimen.

306 **Secondary Malignancies:** Myelodysplastic syndrome (MDS) and/or
307 acute leukemia were reported in 10% (24/230) of patients enrolled in the
308 clinical studies and 3% (20/765) of patients included in expanded access
309 programs, with median follow-up of 39 and 27 months, respectively.
310 Among the 44 reported cases, the median time to development of
311 MDS/leukemia was 31 months following treatment; however, the
312 cumulative rate continues to increase.

313 Additional non-hematological malignancies were also reported in 54 of the
314 995 patients enrolled in clinical studies or included in the expanded
315 access program. Approximately half of these were non-melanomatous
316 skin cancers. The remainder, which occurred in 2 or more patients,
317 included colorectal cancer (7), head and neck cancer (6), breast cancer
318 (5), lung cancer (4), bladder cancer (4), melanoma (3), and gastric cancer
319 (2). The relative risk of developing secondary malignancies in patients
320 receiving the BEXXAR therapeutic regimen over the background rate in
321 this population cannot be determined, due to the absence of controlled
322 studies (see ADVERSE REACTIONS).

323 **Pregnancy Category X: (see BOXED WARNINGS;**
324 **CONTRAINDICATIONS).**

325 **Hypothyroidism:** Administration of the BEXXAR therapeutic regimen
326 may result in hypothyroidism (see **ADVERSE REACTIONS,**
327 **Hypothyroidism**). Thyroid-blocking medications should be initiated at
328 least 24 hours before receiving the dosimetric dose and continued until
329 14 days after the therapeutic dose (see **DOSAGE and**
330 **ADMINISTRATION**). All patients must receive thyroid-blocking agents;
331 any patient who is unable to tolerate thyroid-blocking agents should not
332 receive the BEXXAR therapeutic regimen. Patients should be evaluated
333 for signs and symptoms of hypothyroidism and screened for biochemical
334 evidence of hypothyroidism annually.

335

336 **PRECAUTIONS**

337 **Radionuclide Precautions:** Iodine I 131 Tositumomab is radioactive.
338 Care should be taken, consistent with the institutional radiation safety
339 practices and applicable federal guidelines, to minimize exposure of
340 medical personnel and other patients.

341 **Renal Function:** Iodine I 131 Tositumomab and Iodine-131 are excreted
342 primarily by the kidneys. Impaired renal function may decrease the rate of
343 excretion of the radiolabeled iodine and increase patient exposure to the
344 radioactive component of the BEXXAR therapeutic regimen. There are no
345 data regarding the safety of administration of the BEXXAR therapeutic
346 regimen in patients with impaired renal function.

347 **Immunization:** The safety of immunization with live viral vaccines
348 following administration of the BEXXAR therapeutic regimen has not been
349 studied. The ability of patients who have received the BEXXAR
350 therapeutic regimen to generate a primary or anamnestic humoral
351 response to any vaccine has not been studied.

352 **Information for Patients:** Prior to administration of the BEXXAR
353 therapeutic regimen, patients should be advised that they will have a
354 radioactive material in their body for several days upon their release from
355 the hospital or clinic. After discharge, patients should be provided with
356 both oral and written instructions for minimizing exposure of family
357 members, friends and the general public. Patients should be given a copy

358 of the written instructions for use as a reference for the recommended
359 precautionary actions.

360 The pregnancy status of women of childbearing potential should be
361 assessed and these women should be advised of the potential risks to the
362 fetus (see **CONTRAINDICATIONS**). Women who are breastfeeding
363 should be instructed to discontinue breastfeeding and should be apprised
364 of the resultant potential harmful effects to the infant if these instructions
365 are not followed.

366 Patients should be advised of the potential risk of toxic effects on the male
367 and female gonads following the BEXXAR therapeutic regimen, and be
368 instructed to use effective contraceptive methods during treatment and for
369 12 months following the administration of the BEXXAR therapeutic
370 regimen.

371 Patients should be informed of the risks of hypothyroidism and be advised
372 of the importance of compliance with thyroid blocking agents and need for
373 life-long monitoring.
374

375 Patients should be informed of the possibility of developing a HAMA
376 immune response and that HAMA may affect the results of *in vitro* and
377 *in vivo* diagnostic tests as well as results of therapies that rely on murine
378 antibody technology.
379

380 Patients should be informed of the risks of cytopenias and symptoms
381 associated with cytopenia, the need for frequent monitoring for up to
382 12 weeks after treatment, and the potential for persistent cytopenias
383 beyond 12 weeks.
384

385 Patients should be informed that MDS, secondary leukemia, and solid
386 tumors have also been observed in patients receiving the BEXXAR
387 therapeutic regimen.
388

389 Due to lack of controlled clinical studies, and high background incidence in
390 the heavily pretreated patient population, the relative risk of development
391

392 of myelodysplastic syndrome/acute leukemia and solid tumors due to the
393 BEXXAR therapeutic regimen cannot be determined.

394

395 **Laboratory Monitoring:** A complete blood count (CBC) with differential
396 and platelet count should be obtained prior to, and at least weekly
397 following administration of the BEXXAR therapeutic regimen. Weekly
398 monitoring of blood counts should continue for a minimum of 10 weeks or,
399 if persistent, until severe cytopenias have completely resolved. More
400 frequent monitoring is indicated in patients with evidence of moderate or
401 more severe cytopenias (see **BOXED WARNINGS** and **WARNINGS**).
402 Thyroid stimulating hormone (TSH) level should be monitored before
403 treatment and annually thereafter. Serum creatinine levels should be
404 measured immediately prior to administration of the BEXXAR therapeutic
405 regimen.

406 **Drug Interactions:** No formal drug interaction studies have been
407 performed. Due to the frequent occurrence of severe and prolonged
408 thrombocytopenia, the potential benefits of medications that interfere with
409 platelet function and/or anticoagulation should be weighed against the
410 potential increased risk of bleeding and hemorrhage.

411 **Drug/Laboratory Test Interactions:** Administration of the BEXXAR
412 therapeutic regimen may result in the development of human anti-murine
413 antibodies (HAMA). The presence of HAMA may affect the accuracy of the
414 results of *in vitro* and *in vivo* diagnostic tests and may affect the toxicity
415 profile and efficacy of therapeutic agents that rely on murine antibody
416 technology. Patients who are HAMA positive may be at increased risk for
417 serious allergic reactions and other side effects if they undergo *in vivo*
418 diagnostic testing or treatment with murine monoclonal antibodies.

419 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term
420 animal studies have been performed to establish the carcinogenic or
421 mutagenic potential of the BEXXAR therapeutic regimen or to determine
422 its effects on fertility in males or females. However, radiation is a potential
423 carcinogen and mutagen. Administration of the BEXXAR therapeutic
424 regimen results in delivery of a significant radiation dose to the testes.

425 The radiation dose to the ovaries has not been established. There have
426 been no studies to evaluate whether administration of the BEXXAR
427 therapeutic regimen causes hypogonadism, premature menopause,
428 azoospermia and/or mutagenic alterations to germ cells. There is a
429 potential risk that the BEXXAR therapeutic regimen may cause toxic
430 effects on the male and female gonads. Effective contraceptive methods
431 should be used during treatment and for 12 months following
432 administration of the BEXXAR therapeutic regimen.

433 **Pregnancy Category X: (see CONTRAINDICATIONS; WARNINGS).**

434 **Nursing Mothers:** Radioiodine is excreted in breast milk and may reach
435 concentrations equal to or greater than maternal plasma concentrations.
436 Immunoglobulins are also known to be excreted in breast milk. The
437 absorption potential and potential for adverse effects of the monoclonal
438 antibody component (Tositumomab) in the infant are not known.
439 Therefore, formula feedings should be substituted for breast feedings
440 before starting treatment. Women should be advised to discontinue
441 nursing.

442 **Pediatric Use:** The safety and effectiveness of the BEXXAR therapeutic
443 regimen in children have not been established.

444 **Geriatric Use:** Clinical studies of the BEXXAR therapeutic regimen did
445 not include sufficient numbers of patients aged 65 and over to determine
446 whether they respond differently from younger patients. In clinical studies,
447 230 patients received the BEXXAR therapeutic regimen at the
448 recommended dose. Of these, 27% (61 patients) were age 65 or older
449 and 4% (10 patients) were age 75 or older. Across all studies, the overall
450 response rate was lower in patients age 65 and over (41% vs. 61%) and
451 the duration of responses was shorter (10 months vs. 16 months);
452 however, these findings are primarily derived from 2 of the 5 studies.
453 While the incidence of severe hematologic toxicity was lower, the duration
454 of severe hematologic toxicity was longer in those age 65 or older as
455 compared to patients less than 65 years of age. Due to the limited
456 experience greater sensitivity of some older individuals cannot be ruled
457 out.

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ADVERSE REACTIONS

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The most serious adverse reactions observed in the clinical trials were severe and prolonged cytopenias and the sequelae of cytopenias which included infections (sepsis) and hemorrhage in thrombocytopenic patients, allergic reactions (bronchospasm and angioedema), secondary leukemia and myelodysplasia (see **BOXED WARNINGS** and **WARNINGS**).

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The most common adverse reactions occurring in the clinical trials included neutropenia, thrombocytopenia, and anemia that are both prolonged and severe. Less common but severe adverse reactions included pneumonia, pleural effusion and dehydration.

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Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Patients had a median follow-up of 39 months and 79% of the patients were followed at least 12 months for survival and selected adverse events. Patients had a median of 3 prior chemotherapy regimens, a median age of 55 years, 60% male, 27% had transformation to a higher grade histology, 29% were intermediate grade and 2% high grade histology (IWF) and 68% had Ann Arbor stage IV disease. Patients enrolled in these studies were not permitted to have prior hematopoietic stem cell transplantation or irradiation to more than 25% of the red marrow. In the expanded access program, which included 765 patients, data regarding clinical serious adverse events and HAMA and TSH levels were used to supplement the characterization of delayed adverse events (see **ADVERSE REACTIONS, Hypothyroidism, Secondary Leukemia and Myelodysplastic Syndrome, Immunogenicity**).

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Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

491 **Hematologic Events:** Hematologic toxicity was the most frequently
492 observed adverse event in clinical trials with the BEXXAR therapeutic
493 regimen (Table 6). Sixty-three (27%) of 230 patients received one or
494 more hematologic supportive care measures following the therapeutic
495 dose: 12% received G-CSF; 7% received Epoetin alfa; 15% received
496 platelet transfusions; and 16% received packed red blood cell
497 transfusions. Twenty-eight (12%) patients experienced hemorrhagic
498 events; the majority were mild to moderate.

499 **Infectious Events:** One hundred and four of the 230 (45%) patients
500 experienced one or more adverse events possibly related to infection.
501 The majority were viral (e.g. rhinitis, pharyngitis, flu symptoms, or herpes)
502 or other minor infections. Twenty of 230 (9%) patients experienced
503 infections that were considered serious because the patient was
504 hospitalized to manage the infection. Documented infections included
505 pneumonia, bacteremia, septicemia, bronchitis, and skin infections.

506 **Hypersensitivity Reactions:** Fourteen patients (6%) experienced one or
507 more of the following adverse events: allergic reaction, face edema,
508 injection site hypersensitivity, anaphylactic reaction, laryngismus, and
509 serum sickness. In the post-marketing setting, severe hypersensitivity
510 reactions, including fatal anaphylaxis have been reported.

511 **Gastrointestinal Toxicity:** Eighty-seven patients (38%) experienced one
512 or more gastrointestinal adverse events, including nausea, emesis,
513 abdominal pain, and diarrhea. These events were temporally related to
514 the infusion of the antibody. Nausea, vomiting, and abdominal pain were
515 often reported within days of infusion, whereas diarrhea was generally
516 reported days to weeks after infusion.

517 **Infusional Toxicity:** A constellation of symptoms, including fever, rigors
518 or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea,
519 have been reported during or within 48 hours of infusion. Sixty-seven
520 patients (29%) reported fever, rigors/chills, or sweating within 14 days
521 following the dosimetric dose. Although all patients in the clinical studies
522 received pretreatment with acetaminophen and an antihistamine, the
523 value of premedication in preventing infusion-related toxicity was not

524 evaluated in any of the clinical studies. Infusional toxicities were managed
525 by slowing and/or temporarily interrupting the infusion. Symptomatic
526 management was required in more severe cases. Adjustment of the rate
527 of infusion to control adverse reactions occurred in 16 patients (7%);
528 seven patients required adjustments for only the dosimetric infusion, two
529 required adjustments for only the therapeutic infusion, and seven required
530 adjustments for both the dosimetric and the therapeutic infusions.
531 Adjustments included reduction in the rate of infusion by 50%, temporary
532 interruption of the infusion, and in 2 patients, infusion was permanently
533 discontinued.

534 Table 5 lists clinical adverse events that occurred in $\geq 5\%$ of patients.
535 Table 6 provides a detailed description of the hematologic toxicity.

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Table 5
Incidence of Clinical Adverse Experiences Regardless of Relationship to
Study Drug Occurring in $\geq 5\%$ of the Patients Treated with BEXXAR
Therapeutic Regimen^a
(N = 230)

| Body System Preferred Term | All Grades | Grade 3/4 |
|--|------------|-----------|
| Total | (96%) | (48%) |
| Non-Hematologic AEs | | |
| Body as a Whole | 81% | 12% |
| Asthenia | 46% | 2% |
| Fever | 37% | 2% |
| Infection ^b | 21% | <1% |
| Pain | 19% | 1% |
| Chills | 18% | 1% |
| Headache | 16% | 0% |
| Abdominal pain | 15% | 3% |
| Back pain | 8% | 1% |
| Chest pain | 7% | 0% |
| Neck pain | 6% | 1% |
| Cardiovascular System | 26% | 3% |
| Hypotension | 7% | 1% |
| Vasodilatation | 5% | 0% |
| Digestive System | 56% | 9% |
| Nausea | 36% | 3% |
| Vomiting | 15% | 1% |
| Anorexia | 14% | 0% |
| Diarrhea | 12% | 0% |
| Constipation | 6% | 1% |
| Dyspepsia | 6% | <1% |
| Endocrine System | 7% | 0% |
| Hypothyroidism | 7% | 0% |
| Metabolic and Nutritional Disorders | 21% | 3% |
| Peripheral edema | 9% | 0% |
| Weight loss | 6% | <1% |
| Musculoskeletal System | 23% | 3% |
| Myalgia | 13% | <1% |
| Arthralgia | 10% | 1% |
| Nervous System | 26% | 3% |
| Dizziness | 5% | 0% |
| Somnolence | 5% | 0% |

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Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)
 BLA STN 125011

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Table 5 (cont'd)
Incidence of Clinical Adverse Experiences Regardless of Relationship to
Study Drug Occurring in $\geq 5\%$ of the Patients Treated with BEXXAR
Therapeutic Regimen^a
(N =230)

| | | |
|----------------------------|-----|-----|
| Respiratory System | 44% | 8% |
| Cough increased | 21% | 1% |
| Pharyngitis | 12% | 0% |
| Dyspnea | 11% | 3% |
| Rhinitis | 10% | 0% |
| Pneumonia | 6% | 0% |
| Skin and Appendages | 44% | 5% |
| Rash | 17% | <1% |
| Pruritus | 10% | 0% |
| Sweating | 8% | <1% |

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^a Excludes laboratory derived hematologic adverse events (see Table 6).

^b The COSTART term for infection includes a subset of infections (e.g., upper respiratory infection). Other terms are mapped to preferred terms (e.g., pneumonia and sepsis). For a more inclusive summary see ADVERSE REACTIONS, Infectious Events.

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Table 6
Hematologic Toxicity^a (N=230)

| Endpoint | Values |
|--|-------------|
| <u>Platelets</u> | |
| Median nadir (cells/mm ³) | 43,000 |
| Per patient incidence ^a platelets <50,000/mm ³ | 53% (n=123) |
| Median ^b duration of platelets <50,000/mm ³ (days) | 32 |
| Grade 3/4 without recovery to Grade 2, N (%) | 16 (7%) |
| Per patient incidence ^c platelets <25,000/mm ³ | 21% (n=47) |
| <u>ANC</u> | |
| Median nadir (cells/mm ³) | 690 |
| Per patient incidence ^a ANC<1,000 cells/mm ³ | 63% (n=145) |
| Median ^b duration of ANC<1,000 cells/mm ³ (days) | 31 |
| Grade 3/4 without recovery to Grade 2, N (%) | 15 (7%) |
| Per patient incidence ^c ANC<500 cells/mm ³ | 25% (n=57) |
| <u>Hemoglobin</u> | |
| Median nadir (gm/dL) | 10 |
| Per patient incidence ^a <8 gm/dL | 29% (n=66) |
| Median ^b duration of hemoglobin <8.0 gm/dL (days) | 23 |
| Grade 3/4 without recovery to Grade 2, N (%) | 12 (5%) |
| Per patient incidence ^a hemoglobin <6.5 gm/dL | 5% (n=11) |

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^a Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data between Week 5 and Week 9.

^b Duration of Grade 3/4 of 1000+ days (censored) was assumed for those patients with undocumented Grade 3/4 and no hematologic data on or after Week 9.

^c Grade 4 toxicity was assumed if patient had documented Grade 3 toxicity and was missing 2 or more weeks of hematology data between Week 5 and Week 9.

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Delayed Adverse Reactions

Delayed adverse reactions, including hypothyroidism, HAMA, and myelodysplasia/leukemia, were assessed in 230 patients included in clinical studies and 765 patients included in expanded access programs. The entry characteristics of patients included from the expanded access programs were similar to the characteristics of patients enrolled in the clinical studies, except that the median number of prior chemotherapy regimens was fewer (2 vs. 3) and the proportion with low-grade histology

568 was higher (77% vs. 70%) in patients from the expanded access
569 programs.

570 **Secondary Leukemia and Myelodysplastic Syndrome (MDS):** There
571 were 44 cases of MDS/secondary leukemia reported among 995 (4.0%)
572 patients included in clinical studies and expanded access programs, with a
573 median follow-up of 29 months. The overall incidence of MDS/secondary
574 leukemia among the 230 patients included in the clinical studies was 10%
575 (24/230), with a median follow-up of 39 months and a median time to
576 development of MDS of 34 months. The cumulative incidence of
577 MDS/secondary leukemia in this patient population was 4.7% at 2 years
578 and 15% at 5 years. The incidence of MDS/secondary leukemia among
579 the 765 patients in the expanded access programs was 3% (20/765), with
580 a median follow-up of 27 months and a median time to development of
581 MDS of 31 months. The cumulative incidence of MDS/secondary
582 leukemia in this patient population was 1.6% at 2 years and 6% at 5 years.

583 **Secondary Malignancies:** Of the 995 patients in clinical studies and the
584 expanded access programs, there were 65 reports of second
585 malignancies in 54 patients, excluding secondary leukemias. The most
586 common included non-melanomatous skin cancers (26), colorectal cancer
587 (7) head and neck cancer (6), breast cancer (5), lung cancer (4), bladder
588 cancer (4), melanoma (3), and gastric cancer (2). Some of these events
589 included recurrence of an earlier diagnosis of cancer.

590 **Hypothyroidism:** Of the 230 patients in the clinical studies, 203 patients
591 did not have elevated TSH upon study entry. Of these, 137 patients had
592 at least one post-treatment TSH value available and were not taking
593 thyroid hormonal treatment upon study entry. With a median follow up
594 period of 46 months, the incidence of hypothyroidism based on elevated
595 TSH or initiation of thyroid replacement therapy in these patients was 18%
596 with a median time to development of hypothyroidism of 16 months. The
597 cumulative incidences of hypothyroidism at 2 and 5 years in these 137
598 patients were 11% and 19% respectively. New events have been
599 observed up to 90 months post treatment.

600 Of the 765 patients in the expanded access programs, 670 patients did
601 not have elevated TSH upon study entry. Of these, 455 patients had at
602 least one post-treatment TSH value available and were not taking thyroid
603 hormonal treatment upon study entry. With a median follow up period of
604 33 months, the incidence of hypothyroidism based on elevated TSH or
605 initiation of thyroid replacement therapy in these 455 patients was 13%
606 with a median time to development of hypothyroidism of 15 months. The
607 cumulative incidences of hypothyroidism at 2 and 5 years in these patients
608 were 9% and 17%, respectively.

609 **Immunogenicity:** One percent (11/989) of the chemotherapy-relapsed or
610 refractory patients included in the clinical studies or the expanded access
611 program had a positive serology for HAMA prior to treatment and six
612 patients had no baseline assessment for HAMA. Of the 230 patients in
613 the clinical studies, 220 patients were seronegative for HAMA prior to
614 treatment, and 219 had at least one post-treatment HAMA value obtained.
615 With a median observation period of 6 months, a total of 23 patients (11%)
616 became seropositive for HAMA post-treatment. The median time of
617 HAMA development was 6 months. The cumulative incidences of HAMA
618 seropositivity at 6 months, 12 months, and 18 months were 6%, 17% and
619 21% respectively.

620 Of the 765 patients in the expanded access programs, 758 patients were
621 seronegative for HAMA prior to treatment, and 569 patients had at least
622 one post-treatment HAMA value obtained. With a median observation
623 period of 7 months, a total of 57 patients (10%) became seropositive for
624 HAMA post-treatment. The median time of HAMA development was 5
625 months. The cumulative incidences of HAMA seropositivity at 6 months,
626 12 months, and 18 months were 7%, 12% and 13%, respectively.

627 In a study of 76 previously untreated patients with low-grade non-
628 Hodgkin's lymphoma who received the BEXXAR therapeutic regimen, the
629 incidence of conversion to HAMA seropositivity was 70%, with a median
630 time to development of HAMA of 27 days.

631 The data reflect the percentage of patients whose test results were
632 considered positive for HAMA in an ELISA assay that detects antibodies

633 to the Fc portion of IgG₁ murine immunoglobulin and are highly dependent
634 on the sensitivity and specificity of the assay. Additionally, the observed
635 incidence of antibody positivity in an assay may be influenced by several
636 factors including sample handling, concomitant medications, and
637 underlying disease. For these reasons, comparison of the incidence of
638 HAMA in patients treated with the BEXXAR therapeutic regimen with the
639 incidence of HAMA in patients treated with other products may be
640 misleading.

641 **OVERDOSAGE**

642 The maximum dose of the BEXXAR therapeutic regimen that was
643 administered in clinical trials was 88 cGy. Three patients were treated with
644 a total body dose of 85 cGy of Iodine I 131 Tositumomab in a dose
645 escalation study. Two of the 3 patients developed Grade 4 toxicity of 5
646 weeks duration with subsequent recovery. In addition, accidental
647 overdose of the BEXXAR therapeutic regimen occurred in one patient at a
648 total body dose of 88 cGy. The patient developed Grade 3 hematologic
649 toxicity of 18 days duration. Patients who receive an accidental overdose
650 of Iodine I 131 Tositumomab should be monitored closely for cytopenias
651 and radiation-related toxicity. The effectiveness of hematopoietic stem
652 cell transplantation as a supportive care measure for marrow injury has
653 not been studied; however, the timing of such support should take into
654 account the pharmacokinetics of the BEXXAR therapeutic regimen and
655 decay rate of the Iodine-131 in order to minimize the possibility of
656 irradiation of infused hematopoietic stem cells.

657

658 **DOSAGE AND ADMINISTRATION**

659 **Recommended Dose**

660 The BEXXAR therapeutic regimen consists of four components
661 administered in two discrete steps: the dosimetric step, followed 7-14 days
662 later by a therapeutic step.

663 Note: the safety of the BEXXAR therapeutic regimen was established only
664 in the setting of patients receiving thyroid blocking agents and
665 premedication to ameliorate/prevent infusion reactions (see **Concomitant**
666 **Medications**).

667 **Dosimetric step**

668 • Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride
669 over 60 minutes. Reduce the rate of infusion by 50% for mild to
670 moderate infusional toxicity; interrupt infusion for severe infusional
671 toxicity. After complete resolution of severe infusional toxicity, infusion
672 may be resumed with a 50% reduction in the rate of infusion.

673 • Iodine I 131 Tositumomab (containing 5.0 mCi Iodine-131 and 35 mg
674 tositumomab) intravenously in 30 ml 0.9% Sodium Chloride over 20
675 minutes. Reduce the rate of infusion by 50% for mild to moderate
676 infusional toxicity; interrupt infusion for severe infusional toxicity. After
677 complete resolution of severe infusional toxicity, infusion may be
678 resumed with a 50% reduction in the rate of infusion.

679 **Therapeutic step**

680 Note: Do not administer the therapeutic step if biodistribution is altered
681 (see **Assessment of Biodistribution of Iodine I 131 Tositumomab**).

682 • Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride
683 over 60 minutes. Reduce the rate of infusion by 50% for mild to
684 moderate infusional toxicity; interrupt infusion for severe infusional
685 toxicity. After complete resolution of severe infusional toxicity, infusion
686 may be resumed with a 50% reduction in the rate of infusion.

687 • Iodine I 131 Tositumomab (see **CALCULATION OF IODINE-131**
688 **ACTIVITY FOR THE THERAPEUTIC DOSE**). Reduce the rate of
689 infusion by 50% for mild to moderate infusional toxicity; interrupt
690 infusion for severe infusional toxicity. After complete resolution of
691 severe infusional toxicity, infusion may be resumed with a 50%
692 reduction in the rate of infusion.

693 • Patients with $\geq 150,000$ platelets/ mm^3 : The recommended dose is
694 the activity of Iodine-131 calculated to deliver 75 cGy total body
695 irradiation and 35 mg Tositumomab, administered intravenously
696 over 20 minutes.

697 • Patients with NCI Grade 1 thrombocytopenia (platelet counts
698 $\geq 100,000$ but $< 150,000$ platelets/ mm^3): The recommended dose is
699 the activity of Iodine-131 calculated to deliver 65 cGy total body
700 irradiation and 35 mg Tositumomab, administered intravenously
701 over 20 minutes.

702 **Concomitant Medications:** The safety of the BEXXAR therapeutic
703 regimen was established in studies in which all patients received the
704 following concurrent medications:

705 • Thyroid protective agents: Saturated solution of potassium iodide
706 (SSKI) 4 drops orally t.i.d; Lugol's solution 20 drops orally t.i.d.; or
707 potassium iodide tablets 130 mg orally q.d. Thyroid protective agents
708 should be initiated at least 24 hours prior to administration of the Iodine
709 I 131 Tositumomab dosimetric dose and continued until 2 weeks after
710 administration of the Iodine I 131 Tositumomab therapeutic dose.

711 **Patients should not receive the dosimetric dose of Iodine I 131**
712 **Tositumomab if they have not yet received at least three doses of**
713 **SSKI, three doses of Lugol's solution, or one dose of 130 mg**
714 **potassium iodide tablet (at least 24 hours prior to the dosimetric**
715 **dose).**

716 • Acetaminophen 650 mg orally and diphenhydramine 50 mg orally 30
717 minutes prior to administration of Tositumomab in the dosimetric and
718 therapeutic steps.

719 The BEXXAR therapeutic regimen is administered via an IV tubing set
720 with an in-line 0.22 micron filter. **THE SAME IV TUBING SET AND**
721 **FILTER MUST BE USED THROUGHOUT THE ENTIRE DOSIMETRIC**
722 **OR THERAPEUTIC STEP. A CHANGE IN FILTER CAN RESULT IN**
723 **LOSS OF DRUG.**

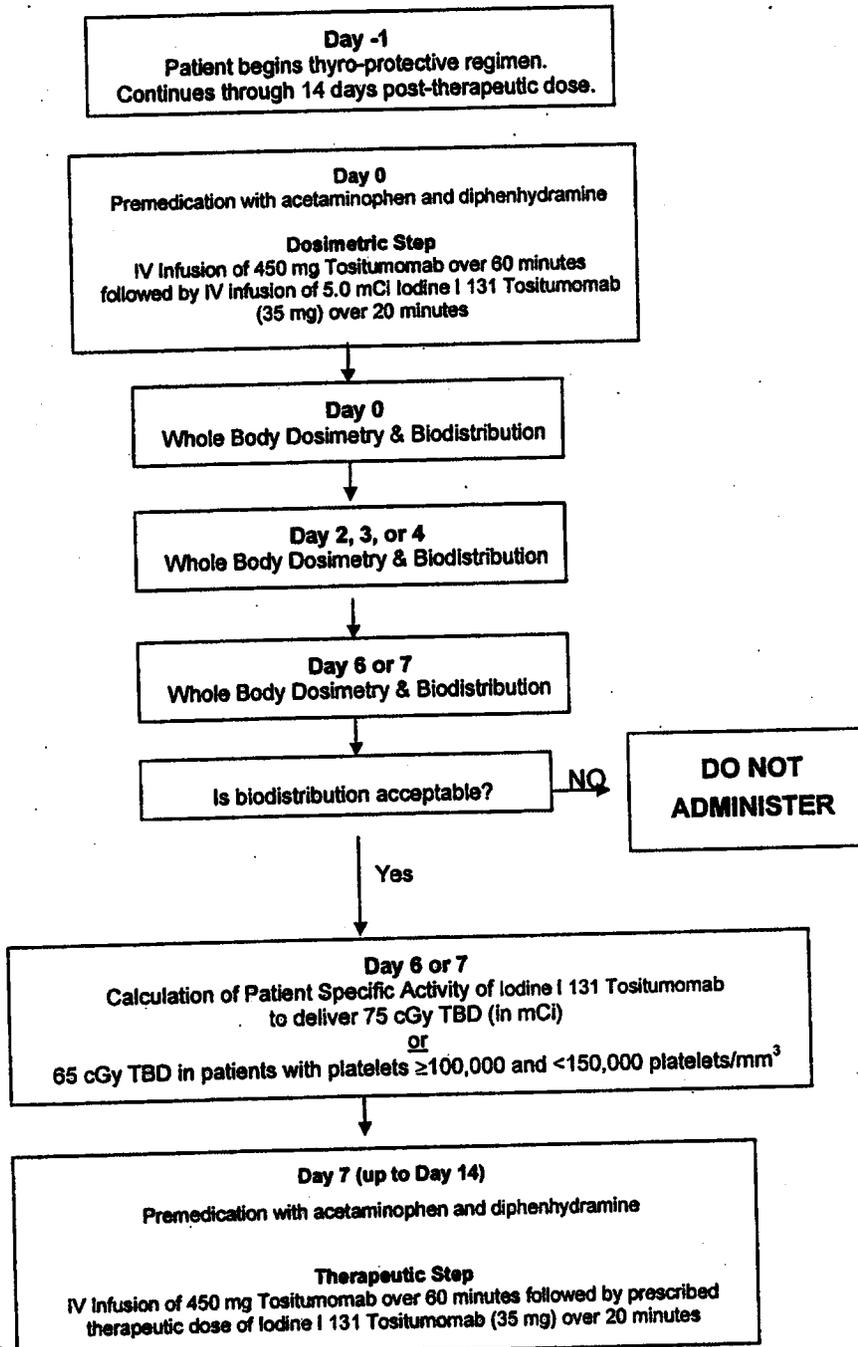
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Figure 1 shows an overview of the dosing schedule.

**Figure 1
Dosing Schedule**

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773 **PREPARATION OF THE BEXXAR THERAPEUTIC REGIMEN**

774 **GENERAL**

775 **Read all directions thoroughly and assemble all materials before**
776 **preparing the dose for administration.**

777 **The Iodine I 131 Tositumomab dosimetric and therapeutic doses**
778 **should be measured by a suitable radioactivity calibration system**
779 **immediately prior to administration. The dose calibrator must be**
780 **operated in accordance with the manufacturer's specifications and**
781 **quality control for the measurement of Iodine-131.**

782 **All supplies for preparation and administration of the BEXXAR**
783 **therapeutic regimen should be sterile. Use appropriate aseptic**
784 **technique and radiation precautions for the preparation of the components**
785 **of the BEXXAR therapeutic regimen.**

786 **Waterproof gloves should be utilized in the preparation and administration**
787 **of the product. Iodine I 131 Tositumomab doses should be prepared,**
788 **assayed, and administered by personnel who are licensed to handle**
789 **and/or administer radionuclides. Appropriate shielding should be used**
790 **during preparation and administration of the product.**

791 **Restrictions on patient contact with others and release from the hospital**
792 **must follow all applicable federal, state, and institutional regulations.**

793

794 **Preparation for the Dosimetric Step**

795 **Tositumomab Dose**

796 **Required materials not supplied:**

797 **A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450**
798 **mg of Tositumomab from two vials each containing 225 mg**
799 **Tositumomab)**

800 **B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP**

801 C. One 50 mL syringe for drawing up 32 mL of saline for disposal from
802 the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

803 **Method:**

- 804 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile
805 0.9% Sodium Chloride for Injection, USP.
- 806 2. Withdraw the entire contents from each of the two 225 mg vials (a total
807 of 450 mg Tositumomab in 32 mL) and transfer to the infusion bag
808 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a
809 final volume of 50 mL.
- 810 3. Gently mix the solution by inverting/rotating the bag. DO NOT SHAKE.
- 811 4. The diluted Tositumomab may be stored for up to 24 hours when
812 stored refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at
813 room temperature.

814 **Note:** Tositumomab solution may contain particulates that are generally
815 white in nature. The product should appear clear to opalescent, colorless
816 to slightly yellow.

817 **Preparation of Iodine I 131 Tositumomab Dosimetric Dose**

818 **Required materials not supplied:**

- 819 A. Lead shielding for preparation vial and syringe pump
- 820
- 821 B. One 30 mL syringe with 18 gauge needle to withdraw the
822 calculated volume of Iodine I 131 Tositumomab from the Iodine I
823 131 Tositumomab vial. One 60 mL syringe with 18 gauge needle to
824 withdraw the volume from the preparation vial for administration
- 825 C. One 20 mL syringe with attached needle, filled with 0.9% Sodium
826 Chloride for Injection, USP
- 827 D. One 3 mL syringe with attached needle to withdraw Tositumomab
828 from 35 mg vial
- 829 E. One sterile, 30 or 50 mL preparation vial
- 830 F. Two lead pots, both kept at room temperature. One pot is used to
831 thaw the labeled antibody and the second pot is used to hold the
832 preparation vial

- 833 **Method:**
- 834 1. Allow approximately 60 minutes for thawing (at ambient temperature)
- 835 of the Iodine I 131 Tosiumomab dosimetric vial with appropriate lead
- 836 shielding.
- 837 2. Based on the activity concentration of the vial (see actual product
- 838 specification sheet for the vial supplied in the dosimetric package),
- 839 calculate the volume required for an Iodine I 131 Tosiumomab activity
- 840 of 5.0 mCi.
- 841 3. Withdraw the calculated volume from the Iodine I 131 Tosiumomab
- 842 vial.
- 843 4. Transfer this volume to the shielded preparation vial.
- 844 5. Assay the dose to ensure that the appropriate activity (mCi) has been
- 845 prepared.
- 846 a. If the assayed dose is 5.0 mCi (+/- 10%) proceed with step 6.
- 847 b. If the assayed dose does not contain 5.0 mCi (+/- 10%) recalculate
- 848 the activity concentration of the Iodine I 131 Tosiumomab at this
- 849 time, based on the volume and the activity in the preparation vial.
- 850 Recalculate the volume required for an Iodine I 131 Tosiumomab
- 851 activity of 5.0 mCi. Using the same 30 mL syringe, add or subtract
- 852 the appropriate volume from the Iodine I 131 Tosiumomab vial so
- 853 that the preparation vial contains the volume required for an Iodine I
- 854 131 Tosiumomab activity of 5.0 mCi (+/- 10%). Re-assay the
- 855 preparation vial and proceed with step 6.
- 856 6. Calculate the amount of Tosiumomab contained in the solution of
- 857 Iodine I 131 Tosiumomab in the shielded preparation vial, based on
- 858 the volume and protein concentration (see actual product specification
- 859 sheet supplied in the dosimetric package).
- 860 7. If the shielded preparation vial contains less than 35 mg, calculate the
- 861 amount of additional Tosiumomab needed to yield a total of 35 mg
- 862 protein. Calculate the volume needed from the 35 mg vial of
- 863 Tosiumomab, based on the protein concentration. Withdraw the
- 864 calculated volume of Tosiumomab from the 35 mg vial of
- 865 Tosiumomab, and transfer this volume to the shielded preparation vial.
- 866 The preparation vial should now contain a total of 35 mg of
- 867 Tosiumomab.
- 868 8. Using the 20 mL syringe containing 0.9% Sodium Chloride for
- 869 Injection, USP, add a sufficient quantity to the shielded preparation vial
- 870 to yield a final volume of 30 mL. Gently mix the solutions.

- 871 9. Withdraw the entire contents from the preparation vial into a 60 mL
872 syringe using a large bore needle (18 gauge).
- 873 10. Assay and record the activity.

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Administration of the Dosimetric Step

877 **Required materials not supplied: For questions about required materials call**
878 **the BEXXAR Service Center at 1-877-423-9927.**

- 879 A. One IV Filter set (0.22 micron filter), 15 inch with injection site (port)
880 and luer lock
- 881 B. One Primary IV infusion set
- 882 C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 883 D. Two Secondary IV infusion sets
- 884 E. One IV Extension set, 30 inch luer lock
- 885 F. One 3-way stopcock
- 886 G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 887 H. One Infusion pump for Tositumomab infusion
- 888 I. One Syringe Pump for Iodine I 131 Tositumomab infusion
- 889 J. Lead shielding for use in the administration of the dosimetric dose

890 **Tositumomab Infusion:**

891 (See Figure 1 in the "Workbook for Dosimetry Methodology and
892 Administration Set-Up" for diagrammatic illustration of the configuration of
893 the infusion set components.)
894

- 895 1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set
896 (Item A) and the 100 mL bag of sterile 0.9% Sodium Chloride for Injection,
897 USP (Item C).
- 898 2. After priming the primary IV infusion set (Item B) and IV filter set (Item A),
899 connect the infusion bag containing 450 mg Tositumomab (50 mL) via a
900 secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at
901 a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60
902 minutes.

903

904 3. After completion of the Tositumomab infusion, disconnect the secondary
905 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and
906 the in-line IV filter set (Item A) with sterile 0.9% Sodium Chloride for
907 Injection, USP. Discard the Tositumomab bag and secondary IV infusion
908 set.

909

910 **Iodine I 131 Tositumomab Dosimetric Infusion:**

911 (See Figure 2 in the "Workbook for Dosimetry Methodology and
912 Administration Set-Up" for diagrammatic illustration of the configuration of
913 the infusion set components.)

914 1. Appropriate shielding should be used in the administration of the
915 dosimetric dose.

916 2. The dosimetric dose is delivered in a 60 mL syringe.

917 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).

918 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
919 (Item G) to a secondary IV infusion set (Item D) and connect the infusion
920 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set
921 (Item D) and the extension set (Item E). Connect the extension set (Item
922 E) to a port in the primary IV infusion set (Item B), distal to the filter.

923 (Note: You must use the same primary infusion set (Item B) and IV filter
924 set (Item A) with pre-wetted filter that was used for the Tositumomab
925 infusion. A change in filter can result in loss of up to 7% of the Iodine I
926 131 Tositumomab dose.)

927

928 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way
929 stopcock (Item F).

930 6. Set syringe pump to deliver the entire 5.0 mCi (35 mg) dose of Iodine I
931 131 Tositumomab over 20 minutes.

932 7. After completion of the infusion of Iodine I 131 Tositumomab, close the
933 stopcock (Item F) to the syringe. Flush the extension set (Item E) and the
934 secondary IV infusion set (Item D) with 0.9% Sodium Chloride for
935 Injection, USP from the 50 mL bag (Item G).

- 936 8. After the flush, disconnect the extension set (Item E), 3-way stopcock
937 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and
938 in-line filter set (Item A). Determine the combined residual activity of the
939 syringe and infusion set components (stopcock, extension set, primary
940 infusion set and in-line filter set) by assaying these items in a suitable
941 radioactivity calibration system immediately following completion of
942 administration of all components of the dosimetric step. Calculate and
943 record the dose delivered to the patient by subtracting the residual activity
944 in the syringe and the infusion set components from the activity of Iodine I
945 ¹³¹Tositumomab in the syringe prior to infusion.
- 946 9. Discard all materials used to deliver the Iodine I ¹³¹Tositumomab (e.g.,
947 syringes, vials, in-line filter set, extension set and infusion sets) in
948 accordance with local, state, and federal regulations governing radioactive
949 and biohazardous waste.

950 **Determination of Dose for the Therapeutic Step (see CALCULATION OF**
951 **IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE):**

952 The method for determining and calculating the patient-specific dose of
953 Iodine-131 activity (mCi) to be administered in the therapeutic step is
954 described below. The derived values obtained in steps 3 and 4 and
955 calculation of the therapeutic dose as described in step 6 may be determined
956 manually [see **Workbook for Dosimetry Methodology and Administration**
957 **Set-up**] or calculated automatically using the Corixa proprietary software
958 program [BEXXAR Patient Management Templates]. To receive training and
959 to obtain the "BEXXAR Patient Management Templates" call the BEXXAR
960 Service Center at 1-877-423-9927. For assistance with either manual or
961 automated calculations call the BEXXAR Service Center at 1-877-423-9927.

- 962 1. Following infusion of the Iodine I ¹³¹Tositumomab dosimetric dose,
963 obtain total body gamma camera counts and whole body images at the
964 following timepoints:
- 965 a. Within one hour of infusion and prior to urination
- 966 b. 2-4 days after infusion of the dosimetric dose, following urination
- 967 c. 6-7 days after infusion of the dosimetric dose, following urination
- 968 2. Assess biodistribution. If biodistribution is altered, the therapeutic step
969 should not be administered.

- 970 3. Determine total body residence time (see Graph 1, "Determination of
971 Residence Time", in the "Workbook for Dosimetry Methodology and
972 Administration Set-Up").
- 973 4. Determine activity hours (see Table 2, "Determination of Activity
974 Hours", in the "Workbook for Dosimetry Methodology and
975 Administration Set-Up"), according to gender. Use actual patient mass
976 (in kg) or maximum effective mass (in kg) whichever is lower (see Table 1,
977 "Determination of Maximum Effective Mass", in the "Workbook for
978 Dosimetry Methodology and Administration Set-Up").
- 979 5. Determine whether the desired total body dose should be reduced (to 65
980 cGy) due to a platelet count of 100,000 to <150,000 cells/mm³.
- 981 6. Based on the total body residence time and activity hours, calculate the
982 Iodine-131 activity (mCi) to be administered to deliver the therapeutic dose
983 of 65 or 75 cGy.

984 The following equation is used to calculate the activity of Iodine-131
985 required for delivery of the desired total body dose of radiation.

986 Iodine-131 Activity (mCi) = $\frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$
987

988 **Preparation for the Therapeutic Step**989 **Tositumomab Dose**990 **Required materials not supplied:**

- 991 A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450
992 mg of Tositumomab from two vials each containing 225 mg
993 Tositumomab)
- 994 B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 995 C. One 50 mL syringe for drawing up 32 mL of saline for disposal from the
996 50 mL bag of sterile 0.9% Sodium Chloride for Injection USP

997 **Method:**

- 998 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile 0.9%
999 Sodium Chloride for Injection, USP.
- 1000 2. Withdraw the entire contents from each of the two 225 mg vials (a total of
1001 450 mg Tositumomab in 32 mL) and transfer to the infusion bag
1002 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a
1003 final volume of 50 mL.
- 1004 3. Gently mix the solutions by inverting/rotating the bag. DO NOT SHAKE.
- 1005 4. The diluted Tositumomab may be stored for up to 24 hours when stored
1006 refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at room
1007 temperature.

1008 Note: Tositumomab solution may contain particulates that are generally
1009 white in nature. The product should appear clear to opalescent, colorless
1010 to slightly yellow.

1011 **Preparation of Iodine I 131 Tositumomab Therapeutic Dose**1012 **Required materials not supplied:**

- 1013 A. Lead shielding for preparation vial and syringe pump

- 1016 B. One or two 30 mL syringes with 18 gauge needles to withdraw the
1017 calculated volume of Iodine I 131 Tositumomab from the Iodine I 131
1018 Tositumomab vial(s). One or two 60 mL syringes with 18 gauge
1019 needles to withdraw the volume from the preparation vial for
1020 administration
- 1021 C. One 20 mL syringe with attached needle filled with 0.9% Sodium
1022 Chloride for Injection, USP
- 1023 D. One 3 mL sterile syringe with attached needle to draw up
1024 Tositumomab from the 35 mg vial
- 1025 E. One sterile, 30 or 50 mL preparation vial
- 1026 F. Two lead pots both kept at room temperature. One pot is used to thaw
1027 the labeled antibody, and the second pot is used to hold the
1028 preparation vial

1029 **Method:**

- 1030
- 1031 1. Allow approximately 60 minutes for thawing (at ambient temperature) of
1032 the Iodine I 131 Tositumomab therapeutic vial with appropriate lead
1033 shielding.
- 1034 2. Calculate the dose of Iodine I 131 Tositumomab required (see
1035 **CALCULATION OF IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE**).
- 1036 3. Based on the activity concentration of the vial (see actual product
1037 specification sheet for each vial supplied in the therapeutic package),
1038 calculate the volume required for the Iodine I 131 Tositumomab activity
1039 required for the therapeutic dose.
- 1040 4. Using one or more 30 mL syringes with an 18-gauge needle, withdraw the
1041 calculated volume from the Iodine I 131 Tositumomab vial.
- 1042 5. Transfer this volume to the shielded preparation vial.
- 1043 6. Assay the dose to ensure that the appropriate activity (mCi) has been
1044 prepared.
- 1045 a. If the assayed dose is the calculated dose (+/- 10%) needed for the
1046 therapeutic step, proceed with step 7.

- 1047 b. If the assayed dose does not contain the desired dose (+/- 10%), re-
1048 calculate the activity concentration of the Iodine I 131 Tosiumomab at
1049 this time, based on the volume and the activity in the preparation vial.
1050 Re-calculate the volume required for an Iodine I 131 Tosiumomab
1051 activity for the therapeutic dose. Using the same 30 mL syringe, add
1052 or subtract the appropriate volume from the Iodine I 131 Tosiumomab
1053 vial so that the preparation vial contains the volume required for the
1054 Iodine I 131 Tosiumomab activity required for the therapeutic dose.
1055 Re-assay the preparation vial. Proceed to step 7.
- 1056 7. Calculate the amount of Tosiumomab protein contained in the solution of
1057 Iodine I 131 Tosiumomab in the shielded preparation vial, based on the
1058 volume and protein concentration (see product specification sheet).
- 1059 8. If the shielded preparation vial contains less than 35 mg, calculate the
1060 amount of additional Tosiumomab needed to yield a total of 35 mg
1061 protein. Calculate the volume needed from the 35 mg vial of
1062 Tosiumomab, based on the protein concentration. Withdraw the
1063 calculated volume of Tosiumomab from the 35 mg vial of Tosiumomab,
1064 and transfer this volume to the shielded preparation vial. The preparation
1065 vial should now contain a total of 35 mg of Tosiumomab.
- 1066 **Note:** If the dose of Iodine I 131 Tosiumomab requires the use of 2 vials
1067 of Iodine I 131 Tosiumomab or the entire contents of a single vial of
1068 Iodine I 131 Tosiumomab, there may be no need to add protein from the
1069 35 mg vial of Tosiumomab.
- 1070 9. Using the 20 mL syringe containing 0.9% Sodium Chloride for Injection,
1071 USP, add a sufficient volume (if needed) to the shielded preparation vial to
1072 yield a final volume of 30 mL. Gently mix the solution.
- 1073 10. Withdraw the entire volume from the preparation vial into a one or more
1074 sterile 60 mL syringes using a large bore needle (18 gauge).
- 1075 11. Assay and record the activity.

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Administration of the Therapeutic Step

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Note: Restrictions on patient contact with others and release from the hospital must follow all applicable federal, state, and institutional regulations.

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1083

Required materials not supplied: For questions about required materials call the BEXXAR Service Center at 1-877-423-9927.

1084
1085

A. One IV Filter set (0.22 micron, filter), 15 inch with injection site (port) and luer lock

1086

B. One Primary IV infusion set

- 1087 C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
1088 D. Two Secondary IV infusion sets
1089 E. One IV extension set, 30 inch luer lock
1090 F. One 3-way stopcock
1091 G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
1092 H. One Infusion pump for Tositumomab infusion
1093 I. One Syringe Pump for Iodine I 131 Tositumomab infusion
1094 J. Lead shielding for use in the administration of the therapeutic dose
1095

1096 **Tositumomab Infusion:**

1097 (See Figure 1 in the "Workbook for Dosimetry Methodology and
1098 Administration Set-Up" for diagrammatic illustration of the configuration of
1099 the infusion set components.)

- 1100 1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set
1101 (Item A) and a 100 mL bag of sterile 0.9% Sodium Chloride for Injection,
1102 USP (Item C).
1103 2. After priming the primary IV infusion set (Item B) and filter set (Item A),
1104 connect the infusion bag containing 450 mg Tositumomab (50 mL) via a
1105 secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at
1106 a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60
1107 minutes.
1108 3. After completion of the Tositumomab infusion, disconnect the secondary
1109 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and
1110 the IV filter set (Item A) with sterile 0.9% Sodium Chloride for Injection,
1111 USP. Discard the Tositumomab bag and secondary IV infusion set.

1112 **Iodine I 131 Tositumomab Therapeutic Infusion:**

1113 (See Figure 2 in the "Workbook for Dosimetry Methodology and
1114 Administration Set-Up" for diagrammatic illustration of the configuration of
1115 the infusion set components.)

- 1116
1117 1. Appropriate shielding should be used in the administration of the
1118 therapeutic dose.

- 1119 2. The therapeutic dose is delivered in one or more 60 mL syringes.
- 1120 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).
- 1121 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
1122 (Item G) to a secondary IV infusion set (Item D) and connect the infusion
1123 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set
1124 (Item D) and the extension set (Item E). Connect the extension set (Item
1125 E) to a port in the primary IV infusion set (Item B), distal to the filter.
- 1126 (Note: You must use the same primary infusion set (Item B) and IV filter
1127 set (Item A) with pre-wetted filter that was used for the Tositumomab
1128 infusion. A change in filter can result in loss of up to 7% of the Iodine I
1129 131 Tositumomab dose.)
- 1130
- 1131 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way
1132 stopcock (Item F).
- 1133 6. Set syringe pump to deliver the entire therapeutic dose of Iodine I 131
1134 Tositumomab over 20 minutes. (Note: if more than one syringe is
1135 required, remove the syringe and repeat steps 5 and 6.)
- 1136 7. After completion of the infusion of Iodine I 131 Tositumomab, close the
1137 stopcock (Item F) to the syringe. Flush the secondary IV infusion set (Item
1138 D) and the extension set (Item E) with 0.9% Sodium Chloride from the 50
1139 mL bag of sterile, 0.9% Sodium Chloride for Injection, USP (Item G).
- 1140 8. After the flush, disconnect the extension set (Item E), 3-way stopcock
1141 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and
1142 in-line filter set (Item A). Determine the combined residual activity of the
1143 syringe(s) and infusion set components (stopcock, extension set, primary
1144 infusion set and in-line filter set) by assaying these items in a suitable
1145 radioactivity calibration system immediately following completion of
1146 administration of all components of the therapeutic step. Calculate and
1147 record the dose delivered to the patient by subtracting the residual activity
1148 in the syringe and infusion set components from the activity of Iodine I 131
1149 Tositumomab in the syringe prior to infusion.
- 1150 9. Discard all materials used to deliver the Iodine I 131 Tositumomab (e.g.,
1151 syringes, vials, in-line filter set, extension set and infusion sets) in
1152 accordance with local, state, and federal regulations governing radioactive
1153 and biohazardous waste.
- 1154

1155 DOSIMETRY

1156 The following sections describe the procedures for image acquisition for
1157 collection of dosimetry data, interpretation of biodistribution images,
1158 calculation of residence time, and calculation of activity hours. Please read
1159 all sections carefully.

1160 IMAGE ACQUISITION AND INTERPRETATION**1161 Gamma Camera and Dose Calibrator Procedures**

1162 Manufacturer-specific quality control procedures should be followed for the
1163 gamma camera/computer system, the collimator, and the dose calibrator.
1164 Less than 20% variance between maximum and minimum pixel count values
1165 in the useful field of view is acceptable on Iodine-131 intrinsic flood fields and
1166 variability <10% is preferable. Iodine-131-specific camera uniformity
1167 corrections are strongly recommended, rather than applying lower energy
1168 correction to the Iodine-131 window. Camera extrinsic uniformity should be
1169 assessed at least monthly using ^{99m}Tc or ⁵⁷Co as a source with imaging at the
1170 appropriate window.
1171

1172 Additional (non-routine) quality control procedures are required. To assure
1173 the accuracy and precision of the patient total body counts, the gamma
1174 camera must undergo validation and daily quality control on each day it is
1175 used to collect patient images.

1176

1177

1178 Use the same setup and region of interest (ROI) for calibration, determination
1179 of background, and whole body patient studies.

1180 Gamma Camera Set-Up

1181 The same camera, collimator, scanning speed, energy window, and setup
1182 must be used for all studies. The gamma camera must be capable of whole
1183 body imaging and have a large or extra large field of view with a digital
1184 interface. It must be equipped with a parallel-hole collimator rated to at least
1185 364 keV by the manufacturer with a septal penetration for Iodine-131 of <7%.
1186 The camera and computer must be set up for scanning as follows:
1187

- 1188 • Parallel hole collimator rated to at least 364 keV with a septal penetration
- 1189 for Iodine-131 of <7%
- 1190 • Symmetric window (20-25%) centered on the 364 keV photo peak of
- 1191 Iodine-131 (314-414 keV)
- 1192 • Matrix: appropriate whole body matrix
- 1193 • Scanning speed: 10-30 cm/minute

1194

1195 Counts from Calibrated Source for Quality Control

- 1196 Camera sensitivity for Iodine-131 must be determined each day.
- 1197 Determination of the gamma camera's sensitivity is obtained by scanning a
- 1198 calibrated activity of Iodine-131 (e.g., 200–250 μCi in at least 20 mL of saline
- 1199 within a sealed pharmaceutical vial). The radioactivity of the Iodine-131
- 1200 source is first determined using a NIST-traceable-calibrated clinical dose
- 1201 calibrator at the Iodine-131 setting.

1202 Background Counts

- 1203 The background count is obtained from a scan with no radioactive source.
- 1204 This should be obtained following the count of the calibrated source and just
- 1205 prior to obtaining the patient count.

- 1206 If abnormally high background counts are measured, the source should be
- 1207 identified and, if possible, removed. If abnormally low background counts are
- 1208 measured, the camera energy window setting and collimator should be
- 1209 verified before repeating the background counts.

- 1210 The counts per μCi are obtained by dividing the background-corrected source
- 1211 count by the calibrated activity for that day. For a specific camera and
- 1212 collimator, the counts per μCi should be relatively constant. When values
- 1213 vary more than 10% from the established ratio, the reason for the discrepancy
- 1214 should be ascertained and corrected and the source count repeated.

1215 Patient Total Body Counts

- 1216 The source and background counts are obtained first and the camera
- 1217 sensitivity (i.e., constant counting efficiency) is established prior to obtaining
- 1218 the patient count. The same rectangular region of interest (ROI) must be

- 1219 used for the whole body counts, the quality control counts of the radioactive
1220 source, and the background counts.
- 1221 Acquire anterior and posterior whole body images for gamma camera counts.
1222 For any particular patient, the same gamma camera must be used for all
1223 scans. To obtain proper counts, extremities must be included in the images,
1224 and arms should not cross over the body. The scans should be centered on
1225 the midline of the patient. Record the time of the start of the radiolabeled
1226 dosimetric infusion and the time of the start of each count acquisition.
- 1227 Gamma camera counts will be obtained at the three imaging time points:
- 1228 • **Count 1: *Within an hour of end of the infusion*** of the Iodine I 131
1229 Tositumomab dosimetric dose prior to patient voiding.
 - 1230 • **Count 2: Two to 4 days after administration** of the Iodine I 131
1231 Tositumomab dosimetric dose and immediately following patient voiding.
 - 1232 • **Count 3: Six to 7 days after the administration** of the Iodine I 131
1233 Tositumomab dosimetric dose and immediately following patient voiding.
- 1234 **Assessment of Biodistribution of Iodine I 131 Tositumomab**
- 1235 The biodistribution of Iodine I 131 Tositumomab should be assessed by
1236 determination of total body residence time and by visual examination of whole
1237 body camera images from the first image taken at the time of Count 1 (within
1238 an hour of the end of the infusion) and from the second image taken at the
1239 time of Count 2 (at 2 to 4 days after administration). To resolve ambiguities,
1240 an evaluation of the third image at the time of Count 3 (6 to 7 days after
1241 administration) may be necessary. If either of these methods indicates that
1242 the biodistribution is altered, the Iodine I 131 Tositumomab therapeutic dose
1243 should not be administered.
- 1244 **Expected Biodistribution**
- 1245 • On the first imaging timepoint: Most of the activity is in the blood pool
1246 (heart and major blood vessels) and the uptake in normal liver and spleen
1247 is less than in the heart.
 - 1248 • On the second and third imaging timepoints: The activity in the blood pool
1249 decreases significantly and there is decreased accumulation of activity in

1250 normal liver and spleen. Images may show uptake by thyroid, kidney, and
1251 urinary bladder and minimal uptake in the lungs. Tumor uptake in soft
1252 tissues and in normal organs is seen as areas of increased intensity.

1253

1254 Results Indicating Altered Biodistribution

- 1255 • On the first imaging timepoint: If the blood pool is not visualized or if there
1256 is diffuse, intense tracer uptake in the liver and/or spleen or uptake
1257 suggestive of urinary obstruction the biodistribution is altered. Diffuse lung
1258 uptake greater than that of blood pool on the first day represents altered
1259 biodistribution.
- 1260 • On the second and third imaging timepoints: uptake suggestive of urinary
1261 obstruction and diffuse lung uptake greater than that of the blood pool
1262 represent altered biodistribution.
- 1263 • Total body residence times of less than 50 hours and more than 150 hours.

1264

1265 CALCULATION OF IODINE-131 ACTIVITY FOR THE THERAPEUTIC 1266 DOSE

1267 There are two options for calculation of the Iodine-131 activity for the
1268 therapeutic dose. The derived values and calculation of the therapeutic dose
1269 may be determined manually [see **Workbook for Dosimetry Methodology
1270 and Administration Set-up**] or calculated automatically using the Corixa
1271 proprietary software program [BEXXAR Patient Management Templates]. The
1272 following describes in greater detail the stepwise method for manual
1273 determination of the Iodine-131 activity for the therapeutic dose.

1274

1275 Residence Time (hr)

1276 For each time point, calculate the background corrected total body count at
1277 each timepoint (defined as the geometric mean). The following equation is
1278 used:

$$1279 \text{ Geometric mean of counts} = \sqrt{(C_A - C_{BA})(C_P - C_{BP})}$$

1280

1281 In this equation, C_A = the anterior counts, C_{BA} = the anterior background
1282 counts, C_P = the posterior counts, and C_{BP} = the posterior background counts.

1283

1284 Once the geometric mean of the counts has been calculated for each of the 3
1285 timepoints, the % injected activity remaining for each timepoint is calculated
1286 by dividing the geometric mean of the counts from that timepoint by the
1287 geometric mean of the counts from Day 0 and multiplying by 100.

1288

1289 The residence time (h) is then determined by plotting the time from the start of
1290 infusion and the % injected activity values for the 3 imaging timepoints on
1291 Graph 1 (see Worksheet "Determination of Residence Time" in the
1292 "Workbook for Dosimetry Methodology and Administration Set-Up"
1293 supplied with Dosimetric Dose Packaging). A best-fit line is then drawn from
1294 100% (the pre-plotted Day 0 value) through the other 2 plotted points (if the
1295 line does not intersect the two points, one point must lie above the best-fit line
1296 and one point must lie below the best-fit line). The residence time (h) is read
1297 from the x-axis of the graph at the point where the fitted line intersects with
1298 the horizontal 37% injected activity line.

1299

1300 **Activity Hours (mCi hr)**

1301 In order to determine the activity hours (mCi hr), look up the patient's
1302 maximum effective mass derived from the patient's sex and height (see
1303 Worksheet "Determination of Maximum Effective Mass" in the "Workbook
1304 for Dosimetry Methodology and Administration Set-Up" supplied with
1305 Dosimetric Dose Packaging). If the patient's actual weight is less than the
1306 maximum effective mass, the actual weight should be used in the activity
1307 hours table (see Worksheet "Determination of Activity Hours" in the
1308 "Workbook for Dosimetry Methodology and Administration Set-Up"
1309 supplied with Dosimetric Dose Packaging). If the patient's actual weight is
1310 greater than the maximum effective mass, the mass from the worksheet for
1311 "Determination of Maximum Effective Mass" should be used.

1312 **Calculation of Iodine-131 Activity for the Therapeutic Dose**

1313 The following equation is used to calculate the activity of Iodine-131 required
1314 for delivery of the desired total body dose of radiation.

1315

$$1316 \quad \text{Iodine-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

1317

1318 **HOW SUPPLIED**1319 **TOSITUMOMAB DOSIMETRIC PACKAGING**

1320 The components of the dosimetric step will be shipped **ONLY** to individuals
1321 who are participating in the certification program or have been certified in the
1322 preparation and administration of the BEXXAR therapeutic regimen. The
1323 components are shipped from separate sites; when ordering, ensure that the
1324 components are scheduled to arrive on the same day. The components of
1325 the Tositumomab Dosimetric Step include:

1326 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use
1327 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14 mg/mL
1328 supplied by McKesson BioServices.

1329 NDC 67800-101-31

1330 2. Iodine I 131 Tositumomab: A single-use vial of Iodine I 131 Tositumomab
1331 within a lead pot, supplied by MDS Nordion. Each single-use vial contains
1332 not less than 20 mL of Iodine I 131 Tositumomab at nominal protein and
1333 activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at calibration),
1334 respectively. (Refer to the product specification sheet for the lot-specific
1335 protein concentration, activity concentration, total activity and expiration date.)

1336 NDC 67800-111-10

1337

1338 **TOSITUMOMAB THERAPEUTIC PACKAGING**

1339 The components of the therapeutic step will be shipped **ONLY** to individuals
1340 who are participating in the certification program or have been certified in the
1341 preparation and administration of the BEXXAR therapeutic regimen for an
1342 individual patient who has completed the Dosimetric Step. The components of
1343 the therapeutic step are shipped from separate sites; when ordering, ensure
1344 that the components are scheduled to arrive on the same day. The
1345 components of the Tositumomab Therapeutic Step include:

Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)
BLA STN 125011

1346 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use
1347 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14
1348 mg/mL supplied by McKesson BioServices.

1349 NDC 67800-101-32

1350 2. Iodine I 131 Tositumomab: One or two single-use vials of Iodine I 131.
1351 Tositumomab within a lead pot(s), supplied by MDS Nordion. Each single-
1352 use vial contains not less than 20 mL of Iodine I 131 Tositumomab at
1353 nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL
1354 (at calibration), respectively. Refer to the product specification sheet for
1355 the lot-specific protein concentration, activity concentration, total activity
1356 and expiration date.

1357 NDC 67800-121-10

1358

1359 **STABILITY AND STORAGE**

1360 **TOSITUMOMAB**

1361 Vials of Tositumomab (35 mg and 225 mg) should be stored refrigerated at
1362 2°C-8°C (36°F-46°F) prior to dilution. Do not use beyond expiration date.
1363 Protect from strong light. **DO NOT SHAKE.** Do not freeze. Discard any
1364 unused portions left in the vial.

1365 Solutions of diluted Tositumomab are stable for up to 24 hours when stored
1366 refrigerated at 2°C-8°C (36°F-46°F) and for up to 8 hours at room
1367 temperature. However, it is recommended that the diluted solution be stored
1368 refrigerated at 2°C-8°C (36°F-46°F) prior to administration because it does
1369 not contain preservatives. Any unused portion must be discarded. Do not
1370 freeze solutions of diluted Tositumomab.

1371

1372 **IODINE I 131 TOSITUMOMAB**

1373 **Store frozen in the original lead pots.** The lead pot containing the product
1374 must be stored in a freezer at a temperature of -20°C or below until it is
1375 removed for thawing prior to administration to the patient. Do not use beyond
1376 the expiration date on the label of the lead pot.

Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)
BLA STN 125011

1377 Thawed dosimetric and therapeutic doses of Iodine I 131 Tositumomab are
1378 stable for up to 8 hours at 2°C–8°C (36°F–46°F) or at room temperature.
1379 Solutions of Iodine I 131 Tositumomab diluted for infusion contain no
1380 preservatives and should be stored refrigerated at 2°C–8°C (36°F–46°F) prior
1381 to administration (do not freeze). Any unused portion must be discarded
1382 according to federal and state laws.

1383

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1404

1405 Manufactured by

1406

1407

1408 Corixa Corporation

1409 1900 9th Ave Suite 1100

1410 Seattle, WA 98101

1411

1412 U.S. Lic. 1614

1413

1414

1415

1416

1417 **Jointly Marketed by:**

1418

1419 Corixa Corp.

GlaxoSmithKline

1420 Seattle, WA 98101

Research Triangle Park, NC 27709

1421

1422 . Issued: Revised Date

1423 © 2004 Corixa Corp. and GlaxoSmithKline

1424

1425

**Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)
BLA STN 125011**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

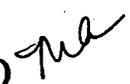
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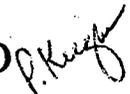
MEDICAL REVIEW

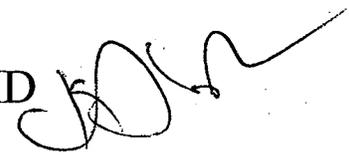
CLINICAL REVIEW

Application Type sBLA
Submission Number 125011
Submission Code 24

Letter Date 3 July 2004

Reviewer Name Mary Andrich, MD 

Through Patricia Keegan, MD 
Director, DTBOP

Kaushikkumar Shastri, MD 
Clinical Reviewer

V. Ellen Maher, MD
Acting Team Leader

Review Completion Date 5 November 2004

Established Name Bexxar®
Therapeutic Class Radiolabeled Antibody
Applicant Corixa Corporation

Priority Designation P

Formulation Injectable
Indication Non-Hodgkin's Lymphoma

Clinical Review
{Insert Reviewer Name}
{Insert Application and Submission Number}
{Insert Product Trade and Generic Name}

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**APPEARS THIS WAY
ON ORIGINAL**

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving the label supplement with revisions to the proposed label.

8 ADDITIONAL CLINICAL ISSUES

b(4)

8.1 Nuclear Medicine Review

[Redacted content]

b(4)

 1 Page(s) Withheld

 Trade Secret / Confidential (b4)

Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Clinical Review
{Insert Reviewer Name}
{Insert Application and Submission Number}
{Insert Product Trade and Generic Name}

9 OVERALL ASSESSMENT

9.1 Conclusions

The changes to the Package Insert are acceptable.

9.2 Recommendation on Regulatory Action

Recommend approving the label supplement with revisions to the proposed label.

**APPEARS THIS WAY
ON ORIGINAL**

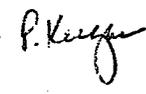
CLINICAL REVIEW

Application Type BLA prior approval supplement
Submission Number STN 125011.24
Submission Code PAS

Letter Date
Stamp Date
PDUFA Goal Date

Reviewer Name
Through

Kaushik Shastri, M.D. 

Patricia Keegan, M.D. 

Director, DTBOP

Review Completion Date

12/9/04

Established Name

Bexxar

(Proposed) Trade Name

Bexxar

Therapeutic Class

Radiolabeled antibody

Applicant

Corixa Corporation

Priority Designation

P

Formulation:

Tositumomab and Iodine I 131

Tositumomab anti CD20 murine

IgG_{2a} lambda monoclonal antibody

Dosing Regimen

Single course in two steps:

A: Dosimetric step: Tositumomab

450 mg intravenously in 50 ml

0.9% Sodium Chloride over 60 minutes, followed by Iodine I 131 Tositumomab (containing 5.0 mCi I-131 and 35 mg tositumomab) intravenously in 30 ml 0.9% Sodium Chloride over 20 minutes. B: Therapeutic step: administered 7-14 days after the dosimetric step and consists of Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes followed by Iodine I 131 Tositumomab containing the activity of Iodine-131 calculated to deliver 75cGy total body irradiation and 35 mg Tositumomab, administered intravenously over 20 minutes.

Indication: treatment of patients with CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with

b(4)

Intended Population: Patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without

transformation, whose disease
has relapsed or is refractory to
chemotherapy.

**APPEARS THIS WAY
ON ORIGINAL**

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Currently, Bexxar is indicated for use in patients with low grade or transformed follicular Non-Hodgkin's lymphoma, whose disease is refractory or has relapsed following chemotherapy and Rituximab treatment. I recommend approval of this application to expand the indication of Bexxar to include patients who are refractory to chemotherapy alone and _____ not have received prior Rituximab therapy for their low grade or transformed follicular lymphoma. This recommendation of approval is under accelerated approval guidelines based on the surrogate end point of response rate. The response rates seen in the pivotal study and the supportive studies exceed that which would be expected in chemotherapy refractory low grade or transformed follicular lymphoma. The long response duration and the high percentage of complete responses in the pivotal study and all the supportive studies suggest that the responses to Bexxar are likely to predict clinical benefit in terms of survival and/or symptom improvement.

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1.2 Recommendation on Postmarketing Actions

No specific post-marketing recommendations related to this application are deemed necessary. The sponsor of the application already has a study CCBX001-049 under way to confirm and further define the clinical benefits of the BEXXAR therapeutic regimen compared to Rituximab. The protocol for Study CCBX001-049 was reviewed and finalized under Special Protocol Assessment with FDA on 30 September 2003. This is a multi-center, randomized Phase 3 comparison of Rituximab and BEXXAR in the treatment of patients with relapsed follicular non-Hodgkin's B-cell lymphoma. A total of 506 patients, approximately 253 per arm, will be enrolled at sites in the United States and Europe. As per the sponsor, the study was opened to enrollment in March 2004 and twelve U.S. and 5 European sites have been initiated or are completing IRB/EC approvals. It should be noted that this study was also part of the post-marketing commitment of the full approval of Bexxar that was granted for chemotherapy and Rituximab refractory patients.

1.2.1 Risk Management Activity:

No specific risk management activity pertaining to this supplemental application is deemed necessary. The sponsor is already following patients for long term adverse events of myelodysplastic syndrome/acute leukemia in reference to the original approval In June 2003.

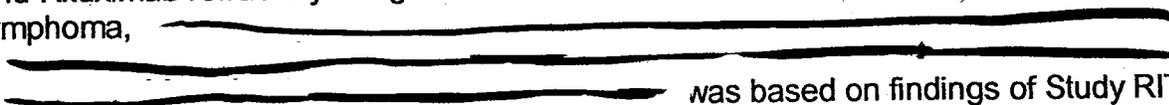
1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The primary data to support this expanded indication supplement comes from multicentered single arm Study RIT-II-004, conducted in a patient population whose lymphoma was refractory to chemotherapy. Eighty percent of patients had received three or more prior chemotherapy regimens and all patients had experienced either no response or progressed within 6 months of their last qualifying chemotherapy. All patients had multiple poor prognostic factors. The observed response rates and duration of response in this study form the basis of the application. The response rates and duration of responses were consistent through other 4 studies and bolster the conclusions of the primary study. These include : Study CP-97-002, which formed the basis for the original approval and the other supportive studies RIT-II-002, RIT-I-000 and RIT-II-001.

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

During the submission to BLA STN 125011 on July 23, 2001, which resulted in approval of Bexxar on June 27, 2003 for its indication in patients with chemotherapy and Rituximab refractory low grade and transformed low grade Non-Hodgkin's lymphoma,

 was based on findings of Study RIT-002-004 and other supportive studies that also contributed to the basis of full approval of Bexxar.

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such time as a clinical benefit has been confirmed.

b(4)

1.3.2 Efficacy

The overall response rates seen in the pivotal study (RIT-II-004) of 47% and response rate ranging from 49% to 64% among all the other studies exceed that which would be expected in chemotherapy refractory low grade or transformed follicular lymphoma. The long response duration (median 12 months; range 2 to 47 months) and 20% complete responses across the pivotal study and similarly high response durations and complete response rates across all the supportive studies suggest that the responses to Bexxar are likely to predict clinical benefit in the chemotherapy refractory population regardless of whether they have received prior Rituximab therapy.

1.3.3 Safety

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

The safety aspects regarding the early toxicity due to Bexxar were reviewed at the time of original application. Since all the five clinical trials which were used to describe the earlier occurring adverse events due to Bexxar have been closed to patient enrollment at least for approximately four years, the updated safety information regarding delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism were reviewed for this application.

Myelodysplastic syndrome (MDS) and/or acute leukemia were reported in 10% (24/230) of patients enrolled in the clinical studies and 3% (20/765) of patients included in expanded access programs, with median follow-up of 39 and 27 months, respectively. Among the 44 reported cases, the median time to development of MDS/leukemia was 31 months following treatment. Non-hematological malignancies were also reported in 54 of the 995 patients enrolled in clinical studies or included in the expanded access program. Approximately half of these were non-melanomatous skin cancers. The remainder, which occurred in 2 or more patients, included colorectal cancer (7), head and neck cancer (6), breast cancer (5), lung cancer (4), bladder cancer (4), melanoma (3), and gastric cancer (2). It should be noted that in this group of heavily

pretreated patients, who had received cytotoxic chemotherapy the background incidence of secondary leukemia is high. The relative risk of developing secondary malignancies in patients receiving the BEXXAR therapeutic regimen over the background rate in this population cannot be determined, due to the absence of controlled studies.

Regarding hypothyroidism, from the 230 patients in the clinical studies, with a median follow up period of 46 months, the incidence of hypothyroidism based on elevated TSH or initiation of thyroid replacement therapy in these patients was 18% with a median time to development of hypothyroidism of 16 months. Of the 765 patients in the expanded access programs, with less rigorous follow up, the incidence of hypothyroidism based on elevated TSH or initiation of thyroid replacement therapy in these 455 patients was 13% with a median time to development of hypothyroidism of 15 months. Because of the radioiodine hypothyroidism is an expected and manageable toxicity..

Regarding immunogenicity, from the 230 patients in the clinical studies, 220 patients were seronegative for HAMA prior to treatment, and 219 had at least one post-treatment HAMA value obtained. With a median observation period of 6 months, a total of 23 patients (11%) became seropositive for HAMA post-treatment. The median time of HAMA development was 6 months. The cumulative incidences of HAMA seropositivity at 6 months, 12 months, and 18 months were 6%, 17% and 21% respectively. Of the 765 patients in the expanded access programs, 758 patients were seronegative for HAMA prior to treatment, and 569 patients had at least one post-treatment HAMA value obtained. With a median observation period of 7 months, a total of 57 patients (10%) became seropositive for HAMA post-treatment. The median time of HAMA development was 5 months. The cumulative incidences of HAMA seropositivity at 6 months, 12 months, and 18 months were 7%, 12% and 13%, respectively. It should be noted that development of HAMA response is an integral aspect of the murine antibody therapy. The label contains adequate description of this adverse event.

1.3.4 Dosing Regimen and Administration

There has been no change in dosing regimen and administration as a result of this supplemental application.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies have been performed. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications that interfere with platelet function and/or anticoagulation should be weighed against the potential increased risk of bleeding and hemorrhage.

1.3.6 Special Populations

Iodine I 131 Tositumomab (a component of the BEXXAR therapeutic regimen) is contraindicated for use in women who are pregnant. The safety and effectiveness of the BEXXAR therapeutic regimen in children have not been established. Clinical studies of the BEXXAR therapeutic regimen did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

**APPEARS THIS WAY
ON ORIGINAL**

2 INTRODUCTION AND BACKGROUND

The data contained in this submission are the same as in the original application except for updated safety information primarily for delayed adverse events and additional investigator assessed response assessments of the study in primary support of this application (RIT-II-004). An extensive review of the studies was conducted during the review of the original application. Information directly relevant to the expanded indication and updated information forms the primary thrust of this review.

2.5 Presubmission Regulatory Activity

During the submission to BLA STN 125011 on July 23, 2001, which resulted in approval of Bexxar on June 27, 2003 for its indication in patients with chemotherapy and Rituximab refractory low grade and transformed low grade Non-Hodgkin's lymphoma, [REDACTED]

b(4)

[REDACTED] was based on findings of Study RIT-002-004 and other supportive studies that also contributed to the basis of full approval of Bexxar.

b(4)

b(4)

[REDACTED]

regimen. The goal of that meeting was agreement on the appropriate path for approval of an additional indication to supplement the current indication. At that meeting, agreement was reached on the contents of this efficacy supplement.

b(4)

5 CLINICAL PHARMACOLOGY

The proposed updated label contains the following additional statement in the Pharmacokinetics/Pharmacodynamics section regarding the total body effective half-life of I 131 Tositumomab:

The median total body effective half-life, as measured by total body gamma camera counts, in 980 patients with NHL was 67 hours (range: 28-115 hours).

For the review of the supportive data for addition of the above statement, please see Dr. Rajpal's review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Expanded Indication Sought in this application:

Bexxar is currently indicated for treatment of patients with CD20 positive, follicular NHL, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. The proposed new indication following this application is as follows:

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6.1.1 Methods

The data contained in this submission are the same as in the original application except for updated safety information particularly in regards to the delayed effects and additional investigator assessed response assessments. An extensive review of all the studies was conducted during the original application review and approval. Information directly relevant to the expanded indication and updated information forms the primary thrust of this review.

The primary data to support this expanded indication supplement comes from Study RIT-II-004, conducted in a patient population whose lymphoma was refractory to chemotherapy. Eighty percent of patients had received three or more prior chemotherapy regimens and all patients had experienced either no response or progressed within 6 months of their last qualifying chemotherapy. All patients had multiple poor prognostic factors. The observed response rates and duration of response in this study form the basis of the application. The response rates and duration of responses were consistent through other 4 studies and bolster the conclusions of the primary study. These include : Study

CP-97-002, which formed the basis for the original approval and the other supportive studies RIT-II-002, RIT-I-000 and RIT-II-001.

6.1.2 General Discussion of Endpoints

For the purposes of this review and the basis of recommendation for accelerated approval the end points of response rates and durations were utilized. Although the sponsor also conducted and submitted analysis based on comparison of response to Bexxar with the patients' response to last qualifying chemotherapy, such analysis does not form the basis of this reviewer's recommendation for approval. Using the patient's prior response as a comparator to response to Bexxar has the obvious flaw of selecting patients who did not respond satisfactorily to prior regimen, since they would not have been treated with Bexxar otherwise. The protocol entry criteria also defined refractory to chemotherapy as response of six months or less. Also, there is a general tendency among practicing physicians to treat the patients with the same regimen of chemotherapy if there was a prolonged response initially and such patients would not have been even considered for treatment with Bexxar.

Response rate and duration are reasonable surrogate endpoints as second and third line therapies to predict meaningful clinical benefit and have been routinely used in making regulatory decisions with other products (e.g. Zevalin). The sponsor employed an independent review panel consisting of radiologists and medical oncologists to minimize bias in interpretation of the results of this and the other supportive studies. The charter of the MIRROR panel (masked randomized radiology and oncology review panel) was reviewed previously during the original submission. In brief, 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.

Besides providing the MIRROR panel data submitted with the original application, the sponsor has also provided updated data with investigators' assessment after the last MIRROR panel review for Study RIT-II-004.

6.1.3 Study Design

The primary efficacy study RIT-II-004 was a single arm study in patients who had relapsed or were refractory to chemotherapy. The title of this Study (RIT-II-004) was

Multicenter, Pivotal Phase 3 Study of Iodine-131 Tositumomab (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas That Have Transformed to Higher Grade Histologies.

The study was a multicenter trial that enrolled patients from 22 November 1996 through 06 March 1998. The sponsor has submitted all patient visit data through 01 March 2004. The median follow-up was 30.1 months (range: 0.5-86.5 months).

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 on Iodine I 131 Tositumomab therapeutic regimen (Iodine I 131 Tositumomab) to the number of patients having a longer duration of response on their last qualifying chemotherapy regimen. Secondary efficacy endpoints were the Investigator-assessed response rates, complete response rates, time to progression, and time to treatment failure. The comparison of the response rate and time to treatment failure following Iodine I 131 Tositumomab with the response rate and the time to treatment failure following the last qualifying chemotherapy regimen were additional secondary efficacy endpoints. Quality of life, safety, and survival were also secondary endpoints. In addition, as requested by the FDA in October 1999, the MIRROR panel review was expanded to include efficacy evaluations of the secondary efficacy endpoints. Secondary endpoints of response; confirmed response; complete response; confirmed complete response; duration of response; duration of response for confirmed responders, complete responders, and confirmed complete responders; time to progression; and time to progression for responders following Iodine I 131 Tositumomab and the comparison of these endpoints with those following the last qualifying chemotherapy were added to the Protocol RIT-II-004 Analysis Plan. Patients continue to be followed by the Investigators for long-term efficacy and safety. Long-term efficacy has been incorporated in this submission by supplementing the MIRROR Panel assessments with Investigator assessments for those patients who were assessed to be in ongoing response at their last MIRROR Panel assessment.

As stated in this review under discussion of endpoints, the recommendation of this reviewer is based on response rate and response duration assessments and for reasons stated, does not rely on comparison to the patients response to last chemotherapy.

This study was designed to enroll 60 evaluable patients (i.e., patients who received at least part of the dosimetric dose). A total of 61 patients were enrolled in this study resulting in 60 evaluable patients; 1 patient withdrew consent prior to receiving study drug. The results of this study adequately supported by other studies in similar patient population and having similar findings regarding response rate and duration form the basis of this reviewer's recommendation.

The diagnosis and the main criteria for inclusion in the study are outlined below and form the framework for generalization to the indicated population:

1. Patients must have a histologically confirmed initial diagnosis of low grade non-Hodgkin's B-cell lymphoma or low-grade lymphoma that has transformed to intermediate- or high-grade histology (as defined in the International Working Formulation, IWF).
2. Patients must have evidence that their tumor tissue expresses the CD20 antigen.
3. Patients must have been treated with at least two different regimens of qualifying chemotherapy on separate occasions and have progressed on, failed to achieve an objective response (CR, CCR, or PR) on, or relapsed/progressed within 6 months after completion of the last qualifying chemotherapy regimen. Patients must have objective evidence of progression or failure to respond. Patients receiving additional therapy (such as steroids or a non-qualifying chemotherapy) after their last qualifying chemotherapy must have failed to achieve an objective response (CR, CCR, or PR) or progressed within 6 months of completion of this therapy.
4. Patients must have adequate renal and hepatic function and a performance status of at least 60% on the Karnofsky Performance Scale and an anticipated survival of at least 3 months.
5. Patients must have an absolute granulocyte count $>1500/\text{mm}^3$ and a platelet count $>100,000/\text{mm}^3$ within 14 days of study entry.
6. Patients must have bidimensionally measurable disease. At least one lesion must be $\geq 2 \times 2$ cm. They must also have adequate written documentation of type and response to prior chemotherapy regimens.
7. Patients who have low-grade non-Hodgkin's lymphoma which has transformed to a higher grade histology must have been treated with a prior therapy for intermediate-grade lymphoma. Rebiopsy of the patient's lymphoma to rule-out transformation and to confirm low-grade histology was required only for those patients who have not received appropriate prior therapy for intermediate-grade lymphoma.
8. Patients must have $\leq 25\%$ of the intratrabecular marrow space involved by lymphoma in bone marrow biopsy specimens as assessed microscopically at study entry. Verification of bone marrow status is required within 42 days of initial 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%.

6.1.4 Efficacy Findings

The efficacy findings of the primary study RIT-II-004 are described in the beginning of this section. There are supplemented by results from the other supportive studies and are presented and discussed at the end of this section. A complete study report for these and the other four studies was included in the review of the original application.

STUDY RIT-II-004:

A total of 61 patients male and female patients with histologically confirmed, chemotherapy refractory, low-grade or transformed low-grade NHL were enrolled in this study. One patient withdrew consent before receiving therapy culminating in 60 evaluable patients. The complete inclusion/exclusion criteria as stated in the protocol were:

Inclusion Criteria

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 were to be included: small lymphocytic (with or without plasmacytoid differentiation); follicular, small-cleaved; and follicular, 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 Tositumomab _____ 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 was acceptable.
3. Patients must have been treated with at least two different regimens of qualifying chemotherapy on separate occasions and have progressed on, failed to achieve an objective response (CR, CCR, or PR) on, or relapsed/progressed within 6 months after completion of the last qualifying chemotherapy regimen. Patients must have objective evidence of progression or failure to respond. Patients receiving additional therapy (such as steroids or a non-qualifying chemotherapy) after their last qualifying chemotherapy must have failed to achieve an objective response (CR, CCR, or PR) or progressed within 6 months of completion of this therapy.
4. Patients must have a performance status of at least 60% on the Karnofsky Performance Scale and an anticipated survival of at least 3 months.
5. Patients must have an absolute granulocyte count >1500/mm³ and a platelet count >100,000/mm³ within 14 days of study entry. These blood counts must be

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- sustained without support of hematopoietic cytokines or transfusion of blood products.
6. Patients must have adequate renal function (defined as serum creatinine $<1.5 \times$ upper limit of normal [ULN]) 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).
 7. Patients must have bidimensionally measurable disease. At least one lesion must be $\geq 2 \times 2$ cm.
 8. Patients must have written documentation (i.e., copies of original medical notes and radiographic reports from referring physician) that includes: 1) the agents which comprised their last qualifying chemotherapy regimen, 2) the number of courses of their last qualifying chemotherapy regimen, 3) the start and stop dates of their last qualifying chemotherapy regimen, 4) whether the patient responded to their last qualifying chemotherapy regimen, 5) if the patient responded, the date of first response, and 6) the date that stable disease or progressive disease occurred. In addition, the same written documentation must be provided for any non-qualifying chemotherapy that was administered after the last qualifying chemotherapy regimen. This written documentation must be provided to the Sponsor along with the eligibility checklist. Prior to enrollment, this information underwent independent review to determine if the documentation is adequate. In addition, all available radiographic evidence of their disease status at baseline, at best response (if applicable), and at progression from the patient's most recent qualifying chemotherapy regimen and, if applicable, baseline, at best response, and at progression for any non-qualifying regimens that were administered after the last qualifying regimen must be sent to _____ before a patient is enrolled. Evaluations which constitute evidence of progression after the last chemotherapy may also be used as the baseline for this study.
 9. Patients must be at least 18 years of age.
 10. Patients must give written informed consent and sign (an) approved informed consent form(s) prior to study entry.
 11. Patients who have low-grade NHL that has transformed to a higher grade histology must have been treated with a prior therapy for intermediate-grade lymphoma. Rebiopsy of the patient's lymphoma to rule-out transformation and to confirm low-grade histology was required only for those patients who have not received appropriate prior therapy for intermediate-grade lymphoma.

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Exclusion Criteria

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 at study entry. Verification of bone marrow status was required within 42 days of initial study entry. Bilateral posterior iliac crest core biopsies were 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%.

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.
3. Patients with prior hematopoietic stem cell transplant following high-dose chemotherapy or chemo/radiotherapy.
4. Patients with active obstructive hydronephrosis.
5. Patients with evidence of active infection requiring intravenous (IV) 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 the 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 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 dose.
11. Patients with previous allergic reactions to iodine. This does not include reacting to IV iodine-containing contrast materials.
12. Patients who were previously given any monoclonal or polyclonal antibodies of any non-human species for either diagnostic or therapeutic purposes. This includes engineered chimeric and humanized antibodies.
13. Patients who previously received radioimmunotherapy.
14. Patients with progressive disease within 1 year of irradiation arising in a field that has been previously irradiated with more than 3500 cGy.
15. Patients who are receiving either approved or non-approved (through another protocol) anti-cancer drugs or biologics.
16. Patients with *de novo* intermediate- or high-grade lymphoma.

Baseline Patient Demographics are shown below in the table. As shown, thirty-six of 60 (60%) patients had low-grade NHL: small lymphocytic lymphoma (4), follicular small cleaved (21), and follicular mixed small cleaved and large cell (11); 23 of 60 (38%) patients had transformed low-grade NHL: diffuse large cell lymphoma (8), diffuse mixed lymphoma (6), follicular large cell lymphoma (4), diffuse small cleaved cell lymphoma (2), and other transformed lymphomas (3). One of 60 (2%) patients had a *de novo* intermediate-grade lymphoma (i.e., mantle cell lymphoma). The patients had received a median of four prior chemotherapy regimens (range: 2–13). Fifty-one of 60 (85%) patients had received an anthracycline/anthracenedione containing regimen and 37 of 60 (26%) patients had received a fludarabine containing regimen.

Table: Baseline Demographics

| | |
|---|-------------|
| Gender | |
| Male | 38 (63%) |
| Female | 22 (37%) |
| Age (years): median (range) | 60 (38-82) |
| Time (months) since diagnosis | |
| Median (range) | 53 (9-354) |
| PROGNOSTIC INDICATORS | |
| Stage III/IV disease | 59 (98%) |
| Grade | |
| Low Grade | 36 (60%) |
| Transformed Low Grade | 23 (38%) |
| Intermediate | 1 (2%) |
| Elevated LDH | 26/59 (44%) |
| Lymph node ≥ 5 cm | 42 (70%) |
| Bulky disease (>500 g) | 23 (38%) |
| Bone marrow involvement | 33 (56%) |
| B-symptoms | 15 (25%) |
| IPI | |
| 0-1 | 18/59 (31%) |
| 2 | 22/59 (37%) |
| 3 | 13/59 (10%) |
| 4-5 | 6/59 (10%) |
| NUMBER OF PRIOR CHEMOTHERAPIES | |
| Median (range) | 4 (2-13) |
| INVESTIGATOR BEST RESPONSE TO MOST RECENT CHEMO | |
| CR, CCR | 2 (3%) |
| PR | 15 (25%) |
| SD | 23 (38%) |
| PD | 20 (33%) |
| DURATION (MONTHS) OF RESPONSE TO MOST RECENT CHEMO | |
| Median (range) | 3.4 (2-7) |

Note: 1 patient had missing LDH value at baseline.

As shown above, the median age of patients was 60 (range 38-82), the median time from diagnosis to protocol entry was 53 months (range: 9-334), and the median number of prior chemotherapy regimens was 4 (range 2-13).

Of the sixty one patients enrolled in the study, sixty patients received the dosimetric dose and 58 of 60 patients completed both the dosimetric dose and the therapeutic dose; 1 patient (004-018-001) received the dosimetric dose but expired from progressive disease prior to receiving the therapeutic dose, and 1 patient (004-015-005) received the dosimetric dose but experienced an infusion-related adverse experience during administration of the unlabeled Tositumomab portion of the therapeutic dose resulting in termination of treatment prior to administration of the radiolabeled portion of the therapeutic dose. The efficacy analysis was done on sixty patients. The application contains MIRROR panel assessed response assessments based on review conducted in November of 2001, and an additional confirmatory re-review in July 2002 of five patients. Investigator-assessed long-term response assessments continue to be conducted for the ongoing responders. Patients, who were censored in ongoing response at their last MIRROR Panel assessment, had their efficacy supplemented with the Investigator assessments conducted after the last MIRROR Panel review. This included two patients who were reported to have progressive disease 1–3 years following treatment and six patients who continue in ongoing complete response. These supplemented outcome data are referred to as the supplemented MIRROR Panel–assessments were also provided in this application.

The analyses of primary efficacy endpoint as defined in the protocol (comparison to the response to the last qualifying chemotherapy are given below. However, for reasons outlined in this review elsewhere, only the endpoints of response rate and duration are used for this reviewer’s recommendations regarding this application and the analysis provided is not considered to carry weight.

Patient-As-Own-Control: Duration of Response

| Assessment | Longer Duration | | P-Value ^a |
|---------------------------|---|----|----------------------|
| | On Last Qualifying Chemotherapy On Iodine I 131 Tositumomab | | |
| Supplemented MIRROR panel | 5 | 26 | <0.001 |
| MIRROR panel | 5 | 26 | <0.001 |

^a McNemars vs. 0.5

The following table provides response rate and duration of patients on the study.

Efficacy Outcomes in Bexxar Clinical Study RIT-II-004

| | (n=60) |
|---|---------------------------|
| Overall Response Rate 95% CI ^a | 47% (34%, 60%) |
| Response Duration (mos) Median 95% CI ^a Range | 12 (7, 47) 2 to 47 |
| Complete Response ^c Rate 95% CI ^a | 20% (11%, 32%) |
| Complete response ^c duration (mos) Median 95% CI ^a Range | 47 (47, NR) 9 to 47 |

^a CI = Confidence Interval

^b NR = Not reached, Median duration of follow up: Study 1 = 26 months; Study 2 = 30 months

^c Complete response rate = Pathologic and clinical complete responses

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Investigators continued to follow the eight patients with complete response in the study after the last independent review panel assessment. The updated duration of ongoing response as per investigators was reported to range from 42 to 85 months.

A brief description of the supportive studies with pertinent efficacy data is given below. All these studies were reviewed during the original application and contained in the previous review of that application.

Study CP-97-012

Clinical Study CP-97-012, which formed the basis for approval of Bexxar in chemotherapy and Rituximab refractory low grade and low grade transformed lymphomas and were also reviewed before was a multicenter, single-arm study of 40 patients whose disease had not responded to or had progressed after at least four doses of Rituximab therapy. The median age was 57 (range: 35–78); the median time from diagnosis to protocol entry was 50 months (range: 12–170); and the median number of prior chemotherapy regimens was 4 (range: 1–11). The efficacy outcome data from this study, as determined by an independent panel that reviewed patient records and radiologic studies, and which appear in the current label showed an overall response rate of 68% (95% CI 51% to 81%) with a median duration of response of 16 months (range 1+ to 38+ months). The complete response rate in that study was 33% with a 95% CI of 19% and 49%.

Study RIT-I-000

Study RIT-I-000 was a Phase 1/2 dose-escalation, single-arm, open-label, single-center study of the safety, pharmacokinetics, dosimetry, and efficacy of Bexxar for the treatment of patients with relapsed/refractory NHL (i.e. low-, intermediate-, high-grade and transformed low-grade) NHL. Fifty-nine patients were enrolled in the study.

Twenty-two patients in this study who were Rituximab-naïve and had follicular non-Hodgkin's lymphoma with or without transformation were evaluated for efficacy. For these 22 patients, the overall confirmed response rate was 64% (14/22; 95% CI of 41% to 83%) with a median duration of response of 16 months (95% CI 4.6 to 59 months; range of 2.6 to 93.6 months). Nine patients had a confirmed complete response with a median duration of response of 37 months (95% CI 13 months to infinity; range of 2.6 to 93.6 months).

Study RIT-II-001

Study RIT-II-001 was a single-arm, open-label, multicenter study of Bexxar in patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. The primary objective of this study was to demonstrate that each independent site could conduct whole-body dosimetry reproducibly and accurately. Additional objectives

were to evaluate the efficacy and safety Bexxar in a multicenter study prior to initiation of a pivotal trial. Forty-seven patients were enrolled at seven sites.

The overall confirmed response rate was 49% (23/47; 95% CI of 34% to 64%) with a median duration of response of 13 months (95% CI of 7.4 to 58 months; range of 1.4+ to 60+ months). Twelve patients (26%) had a confirmed complete response with a median response duration of 58 months (range of 10 to 60+ months).

Study RIT-II-002 & Crossover

Study RIT-II-002 was a randomized, open-label, multicenter study that included patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. Patients were required to be relapsed/refractory following 1-3 chemotherapy regimens that included an anthracycline, anthracenedione or alkylating agent. The study was designed to determine the incremental benefit of Bexxar to the unlabeled antibody (Tositumomab) and to examine safety and efficacy. Patients received the standard regimen of Tositumomab plus Bexxar (Bexxar), or the same regimen with an equal total dose of antibody, but without the radioconjugated antibody (Bexxar). Patients randomized to Tositumomab were allowed to cross over and receive Bexxar following disease progression. The primary endpoint of the study was the comparison of complete response rates between the study arms. Secondary endpoints included overall response rate, duration of overall and complete response, progression-free survival, and safety. Seventy-eight patients were enrolled. Forty-two patients were randomized to receive Bexxar and 36 patients were randomized to receive Tositumomab. Nineteen patients crossed over to receive Bexxar after progressing following Tositumomab.

For the sixty-one patients (42 +19) that received Bexxar, the overall confirmed response rate was 59% (36/61; 95% CI of 46% to 71%) with a median duration of response of 13 months (95% CI of 9.2 months to infinity; range of 1.7 to 57+ months). Twenty-two patients (36%) had a confirmed complete response with a response duration range from 4.6 to 57+ months (the median response duration was not attained).

6.1.6 Efficacy Conclusions

The overall response rates seen in the pivotal study (RIT-II-004) of 47% and response rate ranging from 49% to 64% among all the other studies exceed that which would be expected in chemotherapy refractory low grade or transformed follicular lymphoma. The long response duration as described in the preceding section and the high percentage of complete responses across the pivotal study and all the supportive studies suggest that the responses to Bexxar are likely to predict clinical benefit in terms of survival and/or symptom improvement in the chemotherapy refractory population regardless of whether they have received prior Rituximab therapy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Data regarding immediate adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule and had more rigorous early follow-up and laboratory measurements. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism. The data from expanded access programs were not considered in determining the acute toxicity of Bexxar because of the variability in the rigor of follow up of those patients and because adequate number of patients from more rigorously followed clinical studies were available.

The toxicity data for Bexxar were previously reviewed in detail during the review of the original application. Note that on 27 June 2003, Corixa received full approval to market Bexxar for patients who were refractory to chemotherapy as well as Rituximab. The safety data on clinical studies contained in that application were closed to accrual for a considerable time during that submission as shown in the following table:

| Study Number | Date Accrual Initiated | Date study closed to enrollment |
|---------------------|-------------------------------|--|
| RIT-II-004 | Nov 22, 1996 | March 6, 1998 |
| CP-97-012 | July 11, 1998 | Nov. 19, 1999 |
| RIT-II-002 | Sept. 18, 1996 | June 1, 2000 |
| RIT-I-000 | April 24, 1990 | Jan 17, 1996 |
| RIT-II-001 | Dec. 5, 1995 | Nov. 20, 1996 |

For the reasons cited above, for this supplemental application, only delayed toxicity effects are discussed and contain special focus on the incidence of myelodysplasia and or acute myeloid leukemia, other secondary non-hematologic malignancies, hypothyroidism, and immunogenicity. Two Post-marketing medwatch reports of fatal anaphylaxis after this submission was received are also discussed under post-marketing reports section. Incidence of hypothyroidism based on TSH elevation or history of taking thyroid medications is described under laboratory findings, while the rest are discussed under respective subheadings.

7.1.7 Laboratory Findings

Thyroid (TSH) Evaluation

The protocol-specified laboratory TSH schedule was Baseline, Month 6 and every 3 months up to year 2 (one year for RIT-II-001) for all the studies and additional week 7 and week 13 for the study RIT-I-000 and week 13 for the study RIT-II-002.

There were 947 patients (out of 995 patients in the Safety database) who had TSH measured at baseline. Seventy four (74) of 947 (8%) patients had an elevated TSH prior to the therapeutic dose, and an additional 37 (3%) patients had a history of thyroid medication. Thus 111 of 995 (11%) patients had a history of hypothyroidism prior to receiving their therapeutic dose. Of 873 patients who were euthyroid at entry, 592 (68%) had at least one post-treatment TSH value obtained. With a median observation period of 34.5 months, 70 out of 592 patients (12%) became hypothyroid as determined by elevated TSH and 83 patients (14%) had elevated TSH or started thyroid medication. The median time to elevated TSH for these 70 patients was 12.8 months (IQ range 6 – 26.7 months and range 1.8 to 76.3 months)

The cumulative incidences of hypothyroidism were 9.4% and 18.5% at 2 years and 5 years respectively using Percent Elevated TSH Censored at the Last available TSH Value or death for ISS Population n=995. These estimates do not account for competing risks and overestimate the percent of patients who develop an elevated TSH.

Of the 592 patients who had at least one post-treatment TSH value obtained, 137 patients belonged to the study group (ISE). With a median observation period of 46.6 months, 19 out of 137 patients (14%) became hypothyroid as determined by elevated TSH and 25 patients (18.4%) had elevated TSH or started thyroid medication. The median time to elevated TSH for these 19 patients was 12.2 months (IQ range 5.5 – 30.4 months and range 2.5 to 76.3 months). New events when taken into account either elevation of TSH or initiation of thyroid hormone treatment have been observed up to 90 months post-treatment.

The cumulative incidences of hypothyroidism were 11.1% and 19.3% at 2 years and 5 years respectively using Percent Elevated TSH Censored at the Last available TSH Value or death for ISE Population n=230. These estimates do not account for competing risks and overestimate the percent of patients who develop an elevated TSH. A summary for TSH is provided in Table 3.11 for the integrated efficacy population, the expanded access population and the combined population.

Summary for Hypothyroidism:

| Assessment | Population | | |
|--|-------------------|-----------------------------|------------------|
| | Efficacy N=230 | Expanded Access N=765 | Overall N=995 |
| No elevated TSH, no Rx at Baseline | 203 | 670 | 873 |
| No. that had at least one post tx TSH value obtained | 137 | 455 | 592 |
| Median follow-up TSH (Months) | 46 | 32.8 | 35 |
| No. with elevated TSH | 19 | 51 | 70 |
| Median time in months to elevation for elevated patients | 12.2 | 14.5 | 12.8 |
| No. with elevated TSH or started thyroid medication | 25 | 58 | 83 |
| Median months to elevation | 15.8 | 14.5 | 15.3 |
| Kaplan-Meier TSH Rate ^a | | | |
| 2-year rate | 11.1% | 9.0% | 9.4% |
| 5-year rate | 19.3% | 16.9% | 18.5% |

^a based on elevated TSH or started thyroid medication

7.1.10 Immunogenicity

For assessment of immunogenicity of Bexxar, data were analyzed separately for the 230 patients enrolled in clinical studies and 765 patients enrolled in the expanded access programs. Analysis was also carried out on the entire safety population of 995 patients.

There were six (6) patients who had no baseline assessment for HAMA leaving 989 out of 995 patients in the safety dataset who were assessed for HAMA at the baseline with 11 HAMA positive and 978 HAMA negative. Thus, one percent (11/989) of the chemotherapy-relapsed or refractory patients included in the clinical studies or the expanded access program had a positive serology for HAMA prior to treatment. Of the 978 patients who were seronegative for HAMA prior to treatment, 788 (81%) had at least one post-treatment HAMA value obtained (aeval=1).

Of the 788 patients who had at least one post-treatment HAMA value obtained, a total of 80 patients (10%) became seropositive for HAMA post-treatment. The median time for HAMA development was 172 days (95% CI 97 to 169 days, IQ range 91 to 271 days and range 5 days to 3400 days). 45 of 80 (56%) patients converting to HAMA positivity on or prior to Month 6 (183 days). Four patients converted to HAMA seropositivity after 18 months.

Of the 788 patients who had at least one post-treatment HAMA value obtained, 219 belonged to ISE (n=230). 23 out of 219 (10.5%) became seropositive for HAMA post-treatment. The median time for HAMA development was 189 days (95% CI – 48 to 198 days, IQ range 46 to 279 days and range 5 days to 3400 days). Eleven of 23 (48%) patients converting to HAMA positivity on or prior to Month 6 (183 days). One patient converted to HAMA seropositivity after 18 months. A summary for HAMA is provided in Table 3.12 for the integrated efficacy population, the expanded access population and the combined population.

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Summary of HAMA

| | Population | | |
|---|--------------|----------------------------|------------------|
| | ISE N=230 | Expanded Access N = 765 | Overall N=995 |
| # HAMA Negative at Baseline | 220 (96%) | 758 (99%) | 978 (98%) |
| # At least one post tx HAMA value obtained | 219 | 569 | 788 |
| Median months of follow-up for patients with ≥ 1 post tx value | 5.7 | 6.7 | 6.2 |
| # HAMA positive post treatment | 23 | 57 | 80 |
| Median months for HAMA + post treatment patients ^a | 6.2 | 5.3 | 5.7 |
| 6-month Kaplan-Meier Cumulative Incidence (HAMA+) Rate | 6.0% | 7.0% | 6.9% |
| 12-month Kaplan-Meier Cumulative Incidence (HAMA+) Rate | 17.4% | 12.1% | 13.3% |
| 18-month Kaplan-Meier Cumulative Incidence (HAMA+) Rate | 20.5% | 13.3% | 14.9% |

^a Median months for HAMA + post treatment patients is for patients who were positive post treatment.

7.1.11 Human Carcinogenicity

Human carcinogenicity from Bexxar was assessed separately for the more expected complication of myelodysplastic syndrome/Acute Leukemia and for solid tumors.

It should be noted that because of the high background incidence of secondary malignancies in this heavily pre-treated patient population the precise contribution of Bexxar in inducing second malignancies can not be determined. The incidences reported here do not take into account any of the competing risks.

Secondary Leukemia and Myelodysplastic Syndrome (MDS)

The major long-term safety concern associated with radioimmunotherapy is myelodysplasia (MDS) and associated acute leukemia. Patients treated with Bexxar were followed for the development of MDS/AML from study entry or until death or until the data cutoff. Information was collected semiannually. Table 3.10 provides a summary of the follow-up times, survival times and MDS/AML cases for the integrated efficacy population, the expanded access population and the combined population.

Summary of the follow-up times, survival times and MDS/AML cases

| | Population | | |
|---|----------------|--------------------------|---------------|
| | Efficacy n=230 | Expanded Access n=765 | Overall n=995 |
| Follow-up in Months | | | |
| Median | 38.9 | 27.5 | 29.1 |
| IQ | 29.5 – 71.8 | 12.2– 40.5 | 12.3 – 44.4 |
| Range | 8.2 – 128.4 | 0.1 – 65.3 | 0.1 – 128.4 |
| Survival in Months | | | |
| Median | 41.0 | 50.0 | 49.1 |
| IQ | 13.9 – 128.5 | 13.3 – Not reached | 13.8 – 128.5 |
| Range | 0.2 – 128.5+ | 0.1 – 65.3+ | 0.1 – 128.5+ |
| No. MDS/AML | 24 (10.4%) | 20 (2.6%) | 44 (4.4%) |
| Time to MDS^a (Months) | | | |
| Median | 34.2 | 30.6 | 31.1 |
| IQ | 21.1 – 56.4 | 10.8 – 34.4 | 19.4 – 39.9 |
| Range | 0.03 – 104.5 | 4.4 – 47.7 | 0.03 – 104.5 |
| Kaplan-Meier Incidence Rate of MDS/AML | | | |
| 2-year rate | 4.7% | 1.6% | 2.3% |
| 5-year rate | 15.1% | 5.9% | 9.9% |

^a Time to development of MDS for patients who developed MDS and/or acute leukemia

As per the statistical review, the cumulative incidences noted in the bottom-most row are based on Kaplan-Meier estimates. When using Kaplan-Meier estimates different overall cumulative incidences can be obtained depending on whether the overall cumulative incidences are based on integrating/averaging (using weights) the subgroup cumulative incidences or are based on pooling the data of the subgroups. For example, averaging the subgroup 5-year cumulative incidences of MDS/secondary leukemia using the subgroup sizes as weights gives an overall 5-year cumulative incidence of MDS/secondary leukemia of 8.0% $((0.151 \times 230 + 0.059 \times 765) / (230 + 765) = 8.0\%)$, yet when pooling the data from these subgroups the calculated 5-year cumulative incidence of MDS/secondary leukemia is 9.9%. Because Kaplan-Meier estimates need not satisfy certain distributive properties, these cumulative incidence estimates should be taken with caution.

NON-HEMATOLOGIC MALIGNANCIES

A total of 65 malignancies were reported by 54 patients and are summarized in the following table.

| Type of Malignancy | Number of Patients |
|--|--------------------|
| Total (Any Malignancy) | 54 (5%) |
| Skin Cancer | |
| Basal Cell Carcinoma | 13 (1%) |
| Squamous Cell Carcinoma | 9 (1%) |
| Melanoma | 3 (<1%) |
| NOS | 4 (<1%) |
| Lung Cancer | |
| NSCLC | 3 (<1%) |
| Small Cell Carcinoma | 1 (<1%) |
| Colorectal Cancer | |
| Colon | 4 (<1%) |
| Rectal (Squamous) | 3 (<1%) |
| Bladder Cancer | 4 (<1%) |
| Breast Cancer | 5 (1%) |
| Gastric Cancer | 2 (<1%) |
| Prostate Cancer | 1 (<1%) |
| Head and Neck Cancer | |
| Laryngeal | 1 (<1%) |
| Parotid | 1 (<1%) |
| Tongue | 2 (<1%) |
| Mucoepidermoid | 2 (<1%) |
| Renal Cancer | 1 (<1%) |
| Burkitt's Lymphoma | 1 (<1%) |
| Other (Site Unspecified) | |
| Squamous Cell Carcinoma | 3 (<1%) |
| Omental Carcinoma (Ovarian/Peritoneal) | 1 (<1%) |

Five percent of the patients experienced a second malignancy after drug administration. Approximately half of the malignancies were non-melanoma skin cancers, either basal cell, squamous cell, or unspecified.

7.1.17 Postmarketing Experience

Between the marketing approval by FDA on 27 June 2003 and the data cut-off date of 01 March 2004, 67 patients were treated with the Iodine I 131 Tositumomab therapeutic regimen in the commercial setting. Fivespontaneous reports of adverse events occurred in the postmarketing setting for Iodine I 131 Tositumomab and were included in the current submission. Three of these events were considered not serious and included leg pain, headache and fever and muscle aches and pain. Two that were considered serious included one report of anaphylaxis and one of nausea and vomiting.

Two additional reports of fatalities including one with clearcut anaphylaxis and another with at least a contribution from allergic reaction were reported to the medwatch after the data cut-off day and submission and hence not included in the submission and are described briefly below:

PH (manufacturer's control number TOS-000639) was a 65 year old male with diagnosis of follicular lymphoma since August 2000, treated with various chemotherapy regimens including, fludarbine, mitoxentrone and dexamethasone (FND), Rituximab, and several cycles of CHOP was found to have recurrent disease and was treated with dosimetric dose of Bexxar on July 9, 2004. On _____ patient reported rash and hives that were attributed to Lugol's iodine and the patient received Bexxar on _____ Patient developed fatal anaphylactic reaction following the antibody portion of the dose. Patient had history of allergy to Penicillin and had reactions following Rituximab. He also had a cardiac ejection fraction of 30% prior to treatment. Patient had a HAMA titer done posthumously on blood drawn on _____ hat showed a titer of 199 (reference range 0-188) ng/ml.

b(6)

MDD (manufacturer's control number TOS-000626) was a 77 year old female patient with Stage II cutaneous diffuse large B-cell lymphoma since September of 2001. She was initially treated with CHOP. Patient subsequently developed cardiomyopathy and congestive heart failure. IN April 2004, patient was found to have disease progression and received dosimetric dose of Bexxar on 19 May, 2004. Patient was admitted to hospital on _____ and found to have C. defficile toxin in the stool and treated for it. Her warfarin was held. On _____ patient developed rash over her chest. On _____ she was treated with unlabelled portion of Bexxar and developed hypotension, rash and bronchospasm. The infusion was stopped and then restarted and completed. On receiving the labeled portion her respiratory status worsened, she developed an embolism to the distal femoral artery. Approximately six hours after the labeled portion of Bexxar she developed hypotension, hypoxia and cardiac arrest and expired. A postmortem HAMA was negative.

b(6)

Based on above reports, fatal anaphylaxis was included in the BOXED warning of the revised label.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Secondary Malignancies: Myelodysplastic syndrome (MDS) and/or acute leukemia were reported in 10% (24/230) of patients enrolled in the clinical studies and 3% (20/765) of patients included in expanded access programs, with median follow-up of 39 and 27 months, respectively. Among the 44 reported cases, the median time to development of MDS/leukemia was 31 months following treatment; however, the cumulative rate continues to increase.

Additional non-hematological malignancies were also reported in 54 of the 995 patients enrolled in clinical studies or included in the expanded access program. Approximately half of these were non-melanomatous skin cancers. The remainder, which occurred in 2 or more patients, included colorectal cancer (7), head and neck cancer (6), breast cancer (5), lung cancer (4), bladder cancer (4), melanoma (3), and gastric cancer (2).

It should be noted that in this group of heavily pretreated patients, who had received cytotoxic chemotherapy the background incidence of secondary leukemia is high. The relative risk of developing secondary malignancies in patients receiving the BEXXAR therapeutic regimen over the background rate in this population cannot be determined, due to the absence of controlled studies.

Hypothyroidism:

Of the 230 patients in the clinical studies, with a median follow up period of 46 months, the incidence of hypothyroidism based on elevated TSH or initiation of thyroid replacement therapy in these patients was 18% with a median time to development of hypothyroidism of 16 months. Of the 765 patients in the expanded access programs, with less rigorous follow up, the incidence of hypothyroidism based on elevated TSH or initiation of thyroid replacement therapy in these 455 patients was 13% with a median time to development of hypothyroidism of 15 months.

Because of the radioiodine hypothyroidism is an expected and manageable toxicity..

Immunogenicity: Of the 230 patients in the clinical studies, 220 patients were seronegative for HAMA prior to treatment, and 219 had at least one post-treatment HAMA value obtained. With a median observation period of 6 months, a total of 23 patients (11%) became seropositive for HAMA post-treatment. The median time of HAMA development was 6 months. The cumulative incidences of HAMA seropositivity at 6 months, 12 months, and 18 months were 6%, 17% and 21% respectively. Of the 765 patients in the expanded access programs, 758 patients were seronegative for

HAMA prior to treatment, and 569 patients had at least one post-treatment HAMA value obtained. With a median observation period of 7 months, a total of 57 patients (10%) became seropositive for HAMA post-treatment. The median time of HAMA development was 5 months. The cumulative incidences of HAMA seropositivity at 6 months, 12 months, and 18 months were 7%, 12% and 13%, respectively.

In a study of 76 previously untreated patients with low-grade non-Hodgkin's lymphoma who received the BEXXAR therapeutic regimen, the incidence of conversion to HAMA seropositivity was 70%, with a median time to development of HAMA of 27 days.

Development of HAMA response is an integral aspect of the murine antibody therapy. The label contains adequate description of this adverse event. It should be noted that the data reflect the percentage of patients whose test results were considered positive for HAMA in an ELISA assay that detects antibodies to the Fc portion of IgG₁ murine immunoglobulin and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of HAMA in patients treated with the BEXXAR therapeutic regimen with the incidence of HAMA in patients treated with other products may be misleading.

Anaphylaxis:

Based on the post-marketing reports of fatal although few incidences (three) of anaphylactic reactions, discussed elsewhere in this review, this information is included in the boxed warning section of the label.

8 ADDITIONAL CLINICAL ISSUES:

Please see Dr. Mary Andrich's review regarding nuclear medicine aspects of the application.

9 OVERALL ASSESSMENT

9.1 Conclusions

The overall response rates seen in the pivotal study (RIT-II-004) of 47% and response rate ranging from 49% to 64% among all the other studies exceed that which would be expected in chemotherapy refractory low grade or transformed follicular lymphoma. The long response duration (median 12 months; range 2 to 47 months) and 20% complete responses across the pivotal study and similarly high response durations and complete response rates across all the supportive studies suggest that the

responses to Bexxar are likely to predict clinical benefit in the chemotherapy refractory population regardless of whether they have received prior Rituximab therapy.

The safety database is adequate to describe the safety of the Bexxar therapeutic regimen and the described risks are justified in the indicated patient population. Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Data from the expanded access program, which included 765 patients, were used to supplement the characterization of delayed adverse events of myelodysplastic/myeloproliferative syndromes, development of Human Anti-Mouse Antibodies (HAMA), and increase in TSH levels indicating clinical or subclinical hypothyroidism.

9.2 Recommendation on Regulatory Action

Currently, Bexxar is indicated for use in patients with low grade or transformed follicular Non-Hodgkin's lymphoma, whose disease is refractory or has relapsed following chemotherapy and Rituximab treatment. I recommend approval of this application to expand the indication of Bexxar to include patients who are refractory to chemotherapy alone and ~~not~~ not have received prior Rituximab therapy for their low grade or transformed follicular lymphoma. This recommendation of approval is under accelerated approval guidelines based on the surrogate end point of response rate. The response rates seen in the pivotal study and the supportive studies exceed that which would be expected in chemotherapy refractory low grade or transformed follicular lymphoma. The long response duration and the high percentage of complete responses in the pivotal study and all the supportive studies suggest that the responses to Bexxar are likely to predict clinical benefit in terms of survival and/or symptom improvement.

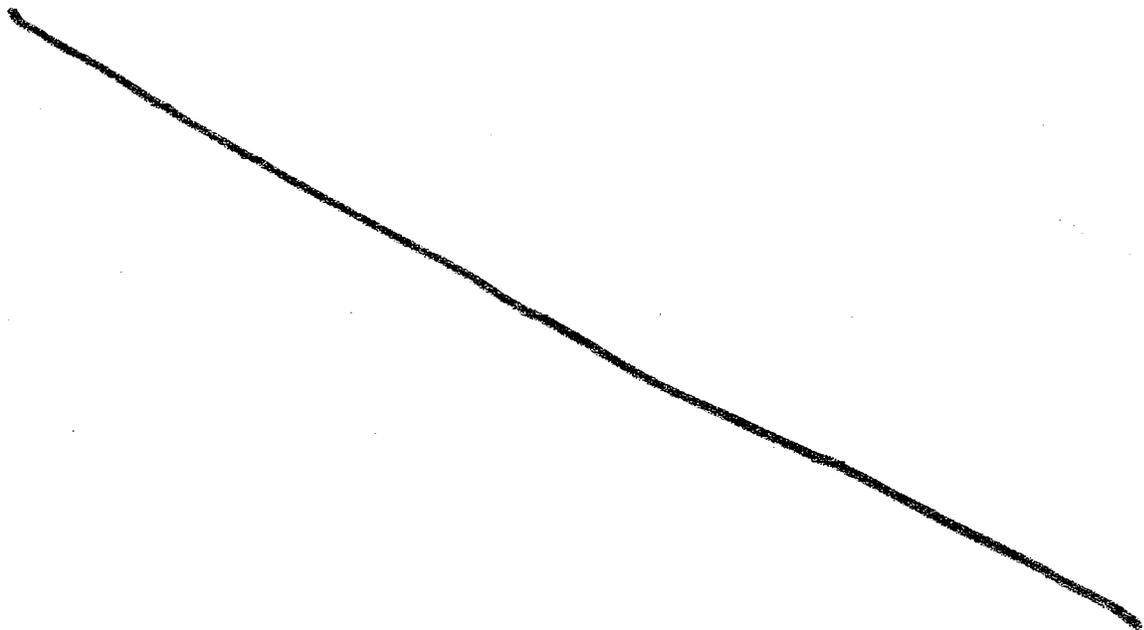
b(4)

9.3 Recommendation on Postmarketing Actions

No specific post-marketing recommendations related to this application are deemed necessary. The sponsor of the application already has a study CCBX001-049 under way to confirm and further define the clinical benefits of the BEXXAR therapeutic regimen compared to Rituximab. The protocol for Study CCBX001-049 was reviewed and finalized under Special Protocol Assessment with FDA on 30 September 2003. This is a multi-center, randomized Phase 3 comparison of Rituximab and BEXXAR in the treatment of patients with relapsed follicular non-Hodgkin's B-cell lymphoma. A total of 506 patients, approximately 253 per arm, will be enrolled at sites in the United States and Europe. As per the sponsor, the study was opened to enrollment in March 2004 and twelve U.S. and 5 European sites have been initiated or are completing IRB/EC approvals. It should be noted that this study was also part of the post-marketing

commitment of the full approval of Bexxar that was granted for chemotherapy and Rituximab refractory patients.

9.4 Labeling Review



b(4)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125011/S024

CLINICAL PHARMACOLOGY



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drugs Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

CLINICAL PHARMACOLOGY REVIEW

Date: December 1, 2004

From: Anil K. Rajpal, M.D., Clinical Pharmacology Reviewer *AR 12/1/04*

Through: Martin D. Green, Ph.D., Associate Director for Pharmacology and Toxicology, ODE VI *MDG 12/7/04*

and

Through: Patricia Keegan, M.D., Director, Division of Therapeutic Biologic Oncology Products, ODE VI *PKeegan 12/7/04*

Subject: Clinical Pharmacology Review of Biologics License Application STN 125011/24 for Iodine I131 Tositumomab (BEXXAR®) from Corixa Corporation.

To: Office / Division – ODE VI / DTBOP
Clinical Reviewer – Kaushik Shastri, M.D.

Please see the attached review.

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Appendix 1

b(4)

Studies Included in CCBX001-059

Page 1 of 2

| Study | | Enrollment | | | | | | Length of MDS/AML F/U |
|------------------------------------|---|-------------|-------------|--------------|--|--|---|-----------------------|
| Number | Design | Start | Last | Study Status | Patients Receiving Iodine I 131 Tosifu-momab | Integrated MDS Surveillance Population | Integrated Relapsed/Refractory NHL Population | |
| Follow in Study CCBX001-051 | | | | | | | | |
| RIT-I-000 | Single-center (University Michigan) Phase 1/2 Dose Escalation in Relapse/Refractory NHL including Retreatment | 24 Apr 1990 | 17 Jan 1996 | Complete | 59 | 27 | 22 | 10 yrs |
| RIT-II-001 | Multi-center Phase 2 in Low-grade/Transformed NHL | 05 Dec 1995 | 20 Nov 1996 | Complete | 47 | 47 | 47 | 10 yrs |
| RIT-II-002 | Multi-center Randomized Hot vs. Cold in Relapsed/Refractory Low-grade/Transformed NHL | 18 Sep 1996 | 07 Jan 2002 | Complete | 61 | 61 | 61 | 10 yrs |
| RIT-II-004 | Multi-center Phase 3 Pt-as-own-control in Refractory Low-grade/Transformed NHL | 22 Nov 1996 | 06 Mar 1998 | Complete | 60 | 60 | 60 | 10 yrs |
| CP-97-012 | Multi-center Phase 2 in Low-grade/Follicular NHL, Rituxan Failures | 17 Jul 1998 | 19 Nov 1999 | Complete | 40 | 40 | 40 | 10 yrs |
| Follow in Study CCBX001-052 | | | | | | | | |
| CP-97-011 | Multi-center Phase 2 UK in 1st/2nd Relapsed Low-grade/Transformed NHL | 02 Jul 1998 | 22 Feb 2001 | Complete | 41 | 41 | 41 | 10 yrs |
| CP-98-025 | Single-center (Cornell) Phase 2 Fludarabine (x3) + BEXXAR in Untreated Low-grade NHL | 18 Aug 1998 | 14 Jun 1999 | Complete | 35 | 35 | 0 | 10 yrs |

Appendix 2

Total Body Dosimetry of Iodine I¹³¹ Tositimumab (Study CCBX001-059)

(The tables below are taken from pages 104-106 of the CCBX001-059 Study Report)

| | RIT-I-000 | RIT-II-001 | RIT-II-002 | RIT-II-003 | RIT-II-004 | CP-97-011 | CP-97-012 |
|--|-----------------|--------------|---------------|--------------|--------------|--------------|--------------|
| | ARM A/Crossover | | | | | | |
| Number of Patients | 59 | 47 | 61 | 76 | 60 | 41 | 40 |
| Total Body Residence Time (h) | | | | | | | |
| N | 53 | 47 | 61 | 76 | 60 | 41 | 40 |
| Mean (SD) | 93.3 (16.52) | 93.4 (17.90) | 92.4 (18.01) | 91.8 (12.18) | 90.3 (18.29) | 90.8 (17.25) | 97.9 (14.29) |
| Median | 95.1 | 93.3 | 94.0 | 94.1 | 91.9 | 92.0 | 98.8 |
| Range | 41.7 - 127.9 | 64.2 - 145.6 | 42.0 - 128.0 | 59.4 - 122.0 | 40.0 - 123.0 | 50.0 - 121.0 | 53.0 - 121.0 |
| Total Body Effective Half-Life (h) [a] | | | | | | | |
| N | 53 | 47 | 61 | 76 | 60 | 41 | 40 |
| Mean (SD) | 64.7 (11.45) | 64.8 (12.41) | 64.0 (12.49) | 63.6 (8.44) | 62.6 (12.68) | 63.0 (11.96) | 67.8 (9.91) |
| Median | 65.9 | 64.7 | 65.2 | 65.2 | 63.7 | 63.8 | 68.4 |
| Range | 28.9 - 88.6 | 44.5 - 100.9 | 29.1 - 88.7 | 41.2 - 84.6 | 27.7 - 85.3 | 34.7 - 83.9 | 36.7 - 83.9 |
| | | | | | b(4) | | b(4) |
| | CP-98-018 | CP-98-020 | CP-98-025 | CP-98-028 | ██████████ | CP-99-036 | ██████████ |
| Number of Patients | 12 | 764 | 35 | 11 | ██████████ | 30 | ██████████ |
| Total Body Residence Time (h) | | | | | | | |
| N | 5 | 756 | 35 | 11 | ██████████ | 30 | ██████████ |
| Mean (SD) | 75.8 (8.90) | 96.9 (16.74) | 103.6 (12.10) | 77.6 (17.67) | ██████████ | 103.7 (8.55) | ██████████ |
| Median | 80.0 | 98.0 | 101.4 | 82.0 | ██████████ | 102.0 | ██████████ |
| Range | 65.0 - 86.0 | 43.2 - 166.0 | 75.0 - 126.0 | 51.5 - 106.0 | ██████████ | 93.0 - 126.0 | ██████████ |
| Total Body Effective Half-Life (h) [a] | | | | | | | |
| N | 5 | 756 | 35 | 11 | ██████████ | 30 | ██████████ |
| Mean (SD) | 52.5 (6.17) | 67.2 (11.60) | 71.8 (8.38) | 53.8 (12.25) | ██████████ | 71.9 (5.93) | ██████████ |
| Median | 55.5 | 67.9 | 70.3 | 56.8 | ██████████ | 70.7 | ██████████ |
| Range | 45.1 - 59.6 | 29.9 - 115.1 | 52.0 - 87.3 | 35.7 - 73.5 | ██████████ | 64.5 - 87.3 | ██████████ |

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125011/S024

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

BLA/Serial Number: STN 125011/24
Drug Name: Iodine I 131 Tositumomab (Bexxar)
Indication(s): Chemotherapy-refractory low-grade or transformed low-grade NHL
Applicant: Corixa Corporation
Date(s): Received on July 3, 2004
Review Priority: 6 month Priority PAS Efficacy Supplement

Biometrics Division: BTSS
Statistical Reviewers: Kallappa M. Koti, Ph.D.
Satish Misra, Ph. D.
Concurring Reviewers: Dr. Mark Rothmann (Team Leader)
Dr. Aloka Chakravarty (Staff Director)

Medical Division: DTBOP
Clinical Reviewer: Dr. Kaushikkumar Shastri
Project Manager: Dale Slavin

Keywords: Non-Hodgkin's Lymphoma; Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel; Generalized McNemar's test; Censored data; Median response time; Prentice-Wilcoxon paired test.

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1. EXECUTIVE SUMMARY

Corixa Corporation has requested accelerated approval for Iodine I 131 Tositumomab to expand the indication to patients with relapsed or refractory low-grade, follicular, or transformed CD20 positive Non-Hodgkin's Lymphoma (NHL) including patients with Rituximab-refractory NHL. This submission is a 6-month priority efficacy supplement.

1.1 Conclusions and Recommendations

Efficacy data provided in the SAS export data file RESPOUT (Study RIT-II-004) support the descriptive efficacy summaries in the labeling. However, the statistical methods used in the efficacy analyses leading to the reported conclusions are questionable (see section 1.3).

The results of study RIT-II-004 must be analyzed like a typical single-arm study.

1.2 Brief Overview of Clinical Studies

STUDY RIT-II-004:

Title: Multicenter, Pivotal Phase 3 Study of Bexxar therapeutic regimen (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.

Specific Aims and Objectives

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.

The sponsor recruited 60 chemotherapy refractory patients in study RIT-II-004. There were 23 females and 38 males. The median age was 60, the median time from diagnosis to protocol entry was 53 months, and the median number of prior chemotherapy regimes was 4.

The primary endpoint was a comparison, as assessed by an independent panel, of the number of patients with a longer duration of response (>30 days) following the BEXXAR therapeutic regimen to the number of patients with a longer duration of response following their last qualifying chemotherapy regimen. Twenty-six patients had a longer duration of response following the BEXXAR therapeutic regimen while only 5 had a longer duration of response on the last qualifying chemotherapy regimen. Secondary endpoints included response rate and duration of response.

The results from four previous studies have also been submitted. The designs and results from these trials are briefly provided in section 3.1.2 of this review.

1.3 Statistical Issues and Findings

For study RIT-II-004, the efficacy analyses on response rate using McNemar's test are invalid. The last qualifying chemotherapy (LQC) best response are controlled (not random), and since best response is a dichotomous endpoint, the conditional distribution for how a patient's best response on Bexxar relatively compares to their best response on LQC depends on whether that patient did or did not have a response on their LQC.

In order for the LQC best responses to have been random, either the patients would have entered the trial prior to receiving their last qualifying chemotherapy (and then later receive Bexxar, as in a cross-over design), or the patients were randomly selected (not volunteers). Neither scenario is the case here.

Putting aside that a cross-over design would have required a random order for a patient receiving "LQC" and Bexxar, let's compare study RIT-II-004 with a cross-over study where each patient receives their LQC then later in the study receives Bexxar. For this cross-over design the assumptions needed for McNemar's test are satisfied. However, study RIT-II-004 would get those patients from the cross-over study that would choose to later receive Bexxar – such patients are not randomly selected. Patients that had very good outcomes on their LQC would probably not need to later receive Bexxar. So, study RIT-II-004 would tend to have those patients from the cross-over study that had poorer outcomes on their LQC.

For paired continuous data, it may not be necessary for the "before" observation to be random. In the most basic model for a particular therapy, the change or difference ("after" minus "before") may still be modeled as a specific normal distribution (independent of the specific value of the "before" observation).

It is also not clear what hypothesis is intended to be tested here. The comparison involves response for different lines of therapy. Different baseline time points and baseline measurements are used for determining the respective response and duration of response for LQC and Bexxar.

For the paired response durations analogous comments apply for the paired Prentice-Wilcoxon test.

The results of study RIT-II-004 must be analyzed like a typical single-arm study.

2. INTRODUCTION

2.1 Overview

Study RIT-II-004 was a multicenter, single arm, open-label, pivotal phase 3 study of IODINE-131 Tositumomab (murine) radioimmunotherapy for chemotherapy-refractory low-grade B-cell Lymphomas and low-grade Lymphomas that have transformed to higher-grade histologies.

The Tositumomab (450 mg, 70 minutes) and Iodine I 131 Tositumomab (35 mg, 30 minutes) were administered by intravenous (IV) infusion.

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 on Iodine I 131 Tositumomab therapeutic regimen (Iodine I 131 Tositumomab) to the number of patients having a longer duration of response on their last qualifying chemotherapy regimen.

2.2 Data Sources

Sponsor submitted SAS export datasets DEMOG, HAMAOUT, MDSOUT, PTOUT, RESPOUT, and THYROUT were analyzed.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This section will describe the efficacy results for Bexxar from the relevant studies.

3.1.1 Study RIT-II-004

This section will describe the efficacy results for Bexxar for study RIT-II-004.

3.1.1.1 Study Design and Endpoints

Study RIT-II-004 was a multi-center, single arm, open-label, pivotal phase 3 study. There was no random assignment of patients to treatment arms. Each patient served as his/her own control. One of the main inclusion criteria was: "Patients must have been treated with at least two different regimens of qualifying chemotherapy on separate occasions and have progressed on, failed to achieve an objective response [complete response (CR), clinical complete response (CCR), or partial response (PR)] on, or relapsed / progressed within 6 months after completion of the last qualifying chemotherapy regimen. Patient must have objective evidence of progression or failure to respond. Patients receiving additional therapy (such as steroids or a non-qualifying chemotherapy) after their last qualifying chemotherapy must have failed to achieve an objective response (CR, CCR, or PR) or progressed within 6 months of completion of this therapy." See Appendix 1 for the definitions of CR, CCR, and PR. Only patients with adequate documentation

(radiographs and medical notes) pertaining to their last qualifying chemotherapy were enrolled in the study.

This study was designed to enroll 60 evaluable patients (i.e., patients who received at least part of the dosimetric dose). A total of 61 patients were enrolled in this study resulting in 60 evaluable patients; 1 patient withdrew consent prior to receiving study drug.

Tables 3.1 and 3.2 give the schedule of assessments that were carried out to evaluate efficacy.

Table 3.1: RIT-II-004 Study Calendar

| REQUIRED STUDIES | Baseline | Day -1 | Day 0 | Day 2,3,4 | Day 5 | Day 6or 7 | Day 7 | Day 10* |
|----------------------|----------|--------|-------|-----------|-------|-----------|-------|---------|
| Dosimetric Dose | | | X | | | | | |
| RIT Dose | | | | | | | X | |
| Start SSKI | | X | | | | | | |
| PHYSICAL | X | | | | | | | |
| LABORATORY | X | | X | X | X | X | | X |
| NUCLEAR MED/SCANS | X | | X | X | | X | | X |
| TUMOR STAGING | X | | | | | | | |
| Response Evaluation | | | | | | | | |
| AES & CMS Evaluation | X | X | X | X | X | X | X | X |

* or Day of release

Table 3.1: RIT-II-004 Study Calendar (continued)

| REQUIRED STUDIES | Week 3 | Wks 4,5, 6 | Week 7 | Wks 8 & 9 | Week 13 | Week 19 | Week 25 | Follow-Up |
|----------------------|--------|------------|--------|-----------|---------|---------|---------|-----------|
| Dosimetric Dose | | | | | | | | |
| RIT Dose | | | | | | | | |
| Start SSKI | | | | | | | | |
| PHYSICAL | X | | X | | X | X | X | X |
| LABORATORY | X | X | X | X | X | X | X | X |
| NUCLEAR MED/SCANS | | | X | | X | X | X | X |
| TUMOR STAGING | | | X | | X | X | X | X |
| Response Evaluation | | | X | | X | X | X | X |
| AES & CMS Evaluation | X | | X | X | X | X | X | X |

Table 3.2: Protocol-Specified Response Assessments

| Study | Base-line | Week 6/7 | Week 12/13 | Week 19 | Month 6 | Continued assessment until LTFU* |
|------------|-----------|----------|------------|---------|---------|---|
| RIT-II-004 | X | X | X | X | X | Ever 3 months up to Year 2, then every 6 months |
| CP-97-012 | X | X | X | | X | Ever 6 months up to Year 2, then every 6 months |

* long-term follow-up

The primary efficacy endpoint of the study was the comparison, as assessed by the MIRROR Panel, of the number of patients having a longer duration of response on Iodine I 131 Tositumomab to the number of patients having a longer duration of response on their last qualifying chemotherapy regimen.

Secondary efficacy endpoint analyses were to establish response rates, complete response rates, time-to-progression, and survival established on this study. The comparison of the response rates, duration of response, and times to progression following Iodine I 131 Tositumomab with the response rate, durations of response, and times to progression following the last qualifying chemotherapy regimen were additional secondary endpoint analyses.

The sponsor's results on the secondary outcomes are summarized in Table 3.6.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

Thirty-six of 60 (60%) patients had low-grade NHL: small lymphocytic lymphoma (4), follicular small cleaved (21), and follicular mixed small. Table 3.3 contains the baseline disease and patient characteristics.

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Table 3.3: Baseline disease and patient characteristics

| | |
|---|-------------|
| Gender | |
| Male | 38 (63%) |
| Female | 22 (37%) |
| Age (years): median (range) | 60 (38-82) |
| Time (months) since diagnosis | |
| Median (range) | 53 (9-354) |
| Prognostic Indicators | |
| Stage III/IV disease | 59 (98%) |
| Grade | |
| Low Grade | 36 (60%) |
| Transformed Low Grade | 23 (38%) |
| Intermediate | 1 (2%) |
| Elevated LDH | 26/59 (44%) |
| Lymph node ≥ 5 cm | 42 (70%) |
| Bulky disease (>500 g) | 23 (38%) |
| Bone marrow involvement | 33 (56%) |
| B-symptoms | 15 (25%) |
| IPI | |
| 0-1 | 18/59 (31%) |
| 2 | 22/59 (37%) |
| 3 | 13/59 (10%) |
| 4-5 | 6/59 (10%) |
| Number of prior chemotherapies | |
| Median (range) | 4 (2-13) |
| Investigator Best Response to most recent chemo | |
| CR, CCR | 2 (3%) |
| PR | 15 (25%) |
| SD | 23 (38%) |
| PD | 20 (33%) |
| Duration (months) of response to most recent chemo | |
| Median (range) | 3.4 (2-7) |

A total of 61 patients with chemotherapy-refractory, low-grade or transformed low-grade NHL were enrolled at eight institutions in this Phase 3, multicenter study (11/22/1996-3/6/1998). Sixty of 61 patients received the dosimetric dose and 58 of 61 patients received both the dosimetric dose and the therapeutic dose; 1 patient withdrew consent prior to receiving the dosimetric or therapeutic dose (this patient was not included in any analysis).

Seven of 61 (11%) patients are ongoing; six patients continue to be followed in the study and one patient is being followed in the rollover study CCBX001-051. Fifty-four of 61 (89%) patients have been discontinued from the study: 49 for progressive disease, 2 for an unrelated medical condition, 1 for non-compliance, 1 for death unrelated to study drug, and 1 for withdrawal of consent. The median follow-up was 30.1 months (range: 0.5-86.5 months). Patients surviving as of the data cutoff date had a minimum follow-up of 59 months.

3.1.1.3 Statistical Methodologies

The primary endpoint was the comparison of the number of patients with longer duration of response following the prior chemotherapy was compared to the number of patients with longer duration of response following Iodine I 131 Tositumomab. The primary analysis was the generalized McNemar's test that is based on a 2x2 table:

Table 3.4: Outcomes for Generalized McNemar's Test

| | |
|--|---|
| No response to either therapy (A) | Longer response (>30 days) to LQC (B) |
| Longer response (>30 days) to Iodine I 131 Tositumomab (C) | Equal response to the two therapies (D) |

The two treatments would be equivalent only if the number of responders in Group C was equal to the number of responders in Group B; i.e. $C/(C + B) = 0.5$. The corresponding numbers from Study (RIT-II-004) as assessed by the MIRROR Panel are:

Table 3.5: Primary efficacy data

| | | RESPONSE TO BEXXAR | | Total |
|--------------|-----|--------------------|-----|-------|
| | | YES | NO | |
| LQC RESPONSE | YES | 0 | 5 | 5 |
| | NO | 26 | 28* | 54 |
| Total | | 26 | 33 | 59 |

* Equal response to the two therapies

The test statistic was the proportion of patients with nonequivalent durations of response who had a longer response on Iodine I 131 Tositumomab.

Basically, the sponsor compared the proportion 26/31 to 0.5 using a single sample z-test.

The sponsor also performed the O'Brien-Fleming matched pairs test for censored data. This test incorporates the ranks of the paired differences of the durations. A brief explanation is provided in Appendix 2. See section 1.3 for a summary on the validity of these analyses.

3.1.1.4 Results and Conclusions

Sponsor's efficacy results:

The primary endpoint was a comparison of the nonequivalent (>30 days different) duration of response cases between the last qualifying chemotherapy and Iodine I 131 Tositumomab.

The test statistic was the proportion of patients with nonequivalent durations of response who had a longer response on Iodine I 131 Tositumomab. If the response following Iodine I 131 Tositumomab was equivalent to the response following the prior qualifying chemotherapy, then one would expect the proportion of nonequivalent patients having a longer duration of response to be 0.5 for both groups. The literature suggested that the duration of response decreases on average by approximately 50% with each subsequent therapy (Gallagher et. al. (1986) J. Clinical Oncology 4: 1470-80 and Johnson et. al. (1995) J. Clinical Oncology 13: 140-7) and the probability of a response similarly decreases with each successive relapse.

One of 60 (2%) patients was excluded because the shorter of the two MIRROR Panel assessed durations of response was censored in an ongoing response. Based upon the MIRROR panel assessment, 28 of the remaining 59 (47%) patients had equivalent (≤ 30 days) durations of response to their last qualifying chemotherapy regimen and Iodine I 131 Tositumomab. Five of the remaining 31 (16%) patients had a longer duration of response on their last qualifying chemotherapy regimen (i.e., more than 30 days longer), whereas 26 of the remaining 31 (84%) patients had a longer duration of response following Iodine 131 Tositumomab ($p < 0.001$, for both matched pairs test with null hypothesis of 37.5% and 50% of nonequivalent durations of response being longer on Iodine I 131 Tositumomab).

Based upon the MIRROR panel review, a confirmed response (PR, CCR, or CR) was observed in 7 of 60 (12%) patients following their last qualifying chemotherapy regimen compared with 28 of 60 (47%) patients following Iodine I 131 Tositumomab ($P < 0.001$; McNemar's test). The median duration of response was 4.1 months (95% CI: 3.0-5.4 months) following the last qualifying chemotherapy and 11.7 months (95% CI: 6.9-27.0 months) following Iodine I 131 Tositumomab.

Overall the durations of response following Iodine I 131 Tositumomab were significantly longer than the paired duration of response following the last qualifying chemotherapy ($p < 0.001$; Prentice-Wilcoxon paired test).

One of 60 (2%) patients had a complete response (CR or CCR) following their last qualifying chemotherapy regimen compared to 12 of 60 (20%) patients following Iodine I 131 Tositumomab ($p < 0.001$; McNemar's test). The duration of response for the complete responder following the last qualifying chemotherapy was 4.8 months and the median duration of response for complete responders was not reached days (95% CI: 47.2 months to not reached) following Iodine I 131 Tositumomab.

There were 28 (47%) patients that had a confirmed objective response on Bexxar therapy (5CCR, 7 CR, and 16 PR). Table 3.6 contains the sponsor's descriptive summary of objective response in study RIT-II-004.

Table 3.6: Descriptive Summary of Supplemented MIRROR Panel-Assessed Efficacy Results*

| Study Number | Response | | Complete Response | |
|----------------------|-------------------------------|--|-------------------------------|--|
| | Response Rate | Median Duration of Response (range) (months) | Response Rate | Median Duration of Response (range) (months) |
| RIT-II-004 (N=60) | 28/60 (47%) (34%, 60%) | 12 (2 - 85+) | 12/60 (20%) (11%, 32%) | Not reached (9 - 85+) |

* This reviewer has verified the results in this table

For all responders the 95% CI for the median duration of response was 7 months to 27 months.

Forty-five of the sixty patients either progressed, died or both. The median time to progression/death was 4.4 months with a 95% CI from 3.3 months to 6.0 months.

3.1.2 Other studies

The results of four other studies were included by the sponsor in the integrated summary of efficacy.

3.1.2.1 Study CP-97-012

Study CP-97-012 was a single-arm, open-label, multicenter study of Bexxar in the treatment of patients with non-Hodgkins lymphoma for whom prior rituximab therapy failed. Patients had chemotherapy-relapsed or -refractory and Rituximab-relapsed or refractory NHL. The objectives of the study were to assess the safety, response rate and duration of response to Bexxar in patients for whom Rituximab had failed. Forty patients were enrolled and received Bexxar. Previous results from this study were included in earlier labeling.

The ages ranged from 35 to 78 years with a median age of 57 years. The times from diagnosis to protocol entry ranged from 11 months to 70 months with a median of 50 months. The number of prior chemotherapy regimens ranged from one to eleven with a median of four. The efficacy outcome data, as determined by an independent panel that reviewed patient records and radiologic studies are summarized in Table 3.7. The median duration of follow-up was 26 months. The overall response rate was 68% with a median duration of response of 16 months.

Table 3.7. Summary of the response rates and durations of response for the ITT population.

| Study Number | Response | | Complete Response | |
|---------------------|-------------------------------|--|-------------------------------|--|
| | Response Rate | Median Duration of Response (range) (months) | Response Rate | Median Duration of Response (range) (months) |
| CP-97-012 (N=40) | 27/40 (68%) (51%, 81%) | 16 (1+ - 38+) | 13/40 (33%) (19%, 49%) | Not reached (4 - 38+) |

For all responders the 95% CI for the median duration of response was 10 months to infinity.

Twenty-four patients had disease that did not respond to their last treatment with Rituximab, 11 patients had disease that responded to Rituximab for less than 6 months, and five patients had disease that responded to Rituximab, with a duration of response of 6 months or greater. We have that 35 patients (24 + 11) met the definition of "Rituximab refractory", defined as no response or a response of less than 6 months duration. For this subset of patients (n=35) the overall objective response rate was 63% (22/35; 95% CI of 45% to 79%) with a median duration of 25 months (range of 3.8+ months to 35+ months). The complete response in this subset of patients was 29% (10/35; 95% CI of 15% to 46%); the median duration of response was not attained (range of 4 to 38+ months).

3.1.2.2 Study RIT-I-000

Study RIT-I-000 was a Phase 1/2 dose-escalation, single-arm, open-label, single-center study of the safety, pharmacokinetics, dosimetry, and efficacy of Bexxar for the treatment of patients with relapsed/refractory NHL (i.e. low-, intermediate-, high-grade and transformed low-grade) NHL. Fifty-nine patients were enrolled in the study.

Twenty-two patients in this study who were Rituximab-naïve and had follicular non-Hodgkin's lymphoma with or without transformation were evaluated for efficacy. For these 22 patients, the overall confirmed response rate was 64% (14/22; 95% CI of 41% to 83%) with a median duration of response of 16 months (95% CI 4.6 to 59 months; range of 2.6 to 93.6 months). Nine patients had a confirmed complete response with a median duration of response of 37 months (95% CI 13 months to infinity; range of 2.6 to 93.6 months).

3.1.2.3 Study RIT-II-001

Study RIT-II-001 was a single-arm, open-label, multicenter study of Bexxar in patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. The primary objective of this study was to demonstrate that each independent site could conduct whole-body dosimetry reproducibly and accurately. Additional objectives were to evaluate the efficacy and safety Bexxar in a multicenter study prior to initiation of a pivotal trial. Forty-seven patients were enrolled at seven sites.

The overall confirmed response rate was 49% (23/47; 95% CI of 34% to 64%) with a median duration of response of 13 months (95% CI of 7.4 to 58 months; range of 1.4+ to 60+ months). Twelve patients (26%) had a confirmed complete response with a median response duration of 58 months (95% CI of 17 months to infinity; range of 10 to 60+ months).

3.1.2.4 Study RIT-II-002 & Crossover

Study RIT-II-002 was a randomized, open-label, multicenter study that included patients with chemotherapy-relapsed or refractory low-grade or transformed low-grade NHL. Patients were required to be relapsed/refractory following 1-3 chemotherapy regimens that included an anthracycline, anthracenedione or alkylating agent. The study was designed to determine the incremental benefit of Bexxar to the unlabeled antibody (Tositumomab) and to examine safety and efficacy. Patients received the standard regimen of Tositumomab plus Bexxar (Iodine I 131 Tositumomab), or the same regimen with an equal total dose of antibody, but without the radioconjugated antibody (Bexxar). Patients randomized to Tositumomab were allowed to cross over and receive Iodine I 131 Tositumomab following disease progression. The primary endpoint of the study was the comparison of complete response rates between the study arms. Secondary endpoints included overall response rate, duration of overall and complete response, progression-free survival, and safety. Seventy-eight patients were enrolled. Forty-two patients were randomized to receive Iodine I 131 Tositumomab and 36 patients were randomized to receive Tositumomab. Nineteen patients crossed over to receive Iodine I 131 Tositumomab after progressing following Tositumomab.

For the sixty-one patients (42 +19) that received Bexxar, the overall confirmed response rate was 59% (36/61; 95% CI of 46% to 71%) with a median duration of response of 13 months (95% CI of 9.2 months to infinity; range of 1.7 to 57+ months). Twenty-two patients (36%) had a confirmed complete response with a response duration range from 4.6 to 57+ months (the median response duration was not attained).

3.1.2.4 Collective summary of the results of the studies

Table 3.8 contains point estimates and two-sided 95% confidence intervals for response rates for these five studies.

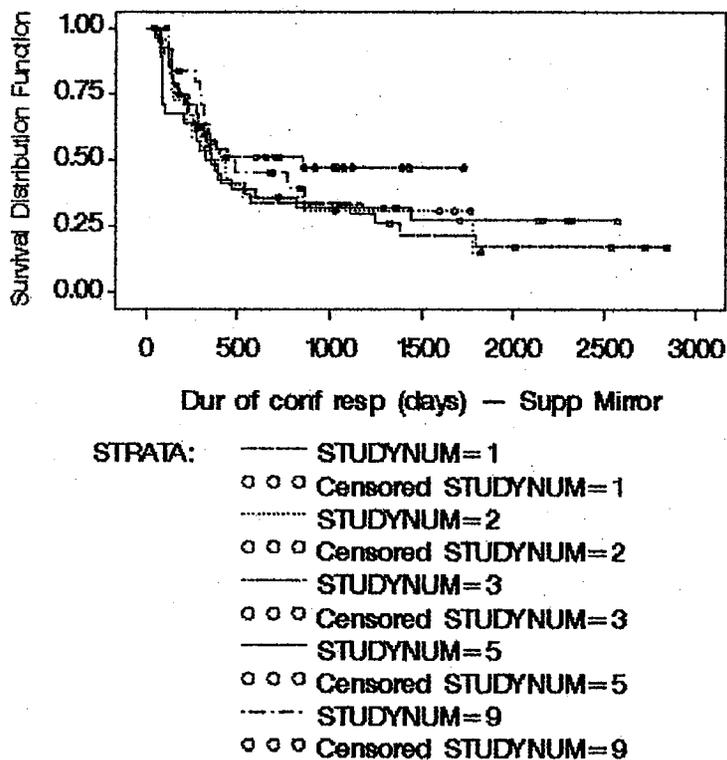
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Table 3.8: Secondary efficacy outcomes
 Summary of Investigator Updated MIRROR Panel-Assessed Efficacy Results

| Study Number | Response | | Complete Response | |
|----------------------|---------------|----------------|-------------------|----------------|
| | Response Rate | 95% C.I. | Response Rate | 95% C.I. |
| RIT-II-004 (N=60) | 28/60 (0.47) | (0.337, 0.600) | 12/60 (0.20) | (0.108, 0.323) |
| CP-97-012 (N=40) | 27/40 (0.675) | (0.509, 0.814) | 13/40 (0.325) | (0.186, 0.491) |
| RIT-II-002 (N=61) | 36/61 (0.59) | (0.457, 0.714) | 22/61 (0.361) | (0.242, 0.494) |
| RIT-I-000 (N=22) | 14/22 (0.636) | (0.407, 0.828) | 9/22 (0.409) | (0.207, 0.636) |
| RIT-II-001 (N=47) | 23/47 (0.489) | (0.341, 0.639) | 12/47 (0.255) | (0.139, 0.408) |

Kaplan-Meier duration of response curves for all studies are shown in Figure 1.

Figure 1: Duration of Response



STUDYNUM = 1, 2, 3, 5, and 9 respectively for studies RIT-I-000, RIT-II-001, RIT-002 & Crossover, RIT-II-004 and CP-97-012.

A corresponding summary that goes with Figure 1 is provided in Table 3.9. In all, 79 patients that responded relapsed. All five studies had a censored value for the largest duration of response. Therefore the estimates of the mean duration of response are biased and should taken with caution.

Table 3.9 Summary of Duration of Response

| STUDYNUM | N Failed | N Censored | Mean | | Std Error |
|---------------|----------|------------|---------|--------|-----------|
| 1: CP-97-012 | 11 | 3 | 756.786 | Biased | 199.065 |
| 2: RIT-I-000 | 16 | 7 | 757.117 | Biased | 156.94 |
| 3: RIT-II-001 | 17 | 19 | 304.652 | Biased | 21.6692 |
| 5: RIT-II-002 | 20 | 8 | 633.179 | Biased | 111.982 |
| 9: RIT-II-004 | 15 | 12 | 541.051 | Biased | 62.4546 |
| Combined | 79 | 49 | 825.315 | Biased | 68.5633 |

The median times (in months) to progression/death in studies RIT-I-000, RIT-II-001, RIT-002 & Crossover, RIT-II-004 and CP-97-012 (for those patients in the integrated summary of efficacy population) were respectively, 6.5, 5.9, 8.9, 4.4, and 12 months.

3.2 Evaluation of Safety

3.2.1 Overview:

The following is an integrated summary of safety endpoints:

Secondary Leukemia and Myelodysplastic Syndrome (MDS): There were 44 cases of MDS/secondary leukemia reported among 995 (4%) patients included in clinical studies and expanded access programs, with a median follow-up of 27 months. The overall incidence of MDS/secondary leukemia among the 230 patients included in the clinical studies, was 10% (24/230), with a median follow-up of 39 months and a median time to development of MDS if 34 months. The cumulative incidence of MDS/secondary leukemia in the 995 patient population was 2.3% at 2 years and 9.9% at 5 years.

Hypothyroidism: Eleven percent (111/995) of the patients included in the clinical studies or the expanded access programs had an elevated TSH level (8%) or a history of hypothyroidism (3%) prior to treatment. Of the 873 who were euthyroid at entry, 592 (68%) had at least one post-treatment TSH value obtained. With a median observation of 34.5 months, 70 out of 592 (12%) became hypothyroid as determined by elevated TSH. The cumulative incidences of hypothyroidism were 9.4% and 18.5% at 2 and 5 years, respectively.

Immunogenicity: One percent (11/989) of the chemo-therapy-relapsed or refractory patients included in the clinical studies or the expanded access program has a positive serology for HAMA prior to treatment and six patients had no baseline assessment for HAMA. Of the 978 patients who were seronegative for HAMA prior to treatment, 788 (81%) had at least one post-treatment HAMA value obtained.

Of the 788 patients who had at least one post-treatment HAMA value obtained, a total of 80 patients (10%) became seropositive for HAMA post-treatment. The median time for HAMA development was 172 days (95% CI – 97 to 169 days, IQ range 91 to 271 days and range 5 days to 3400 days). 45 of 80 (56%) patients converting to HAMA positivity on or prior to Month 6 (183 days). Four patients converted to HAMA seropositivity after 18 months.

Of the 788 patients who had at least one post-treatment HAMA value obtained, 219 belonged to ISE (n=230). 23 out of 219 (10.5%) became seropositive for HAMA post-treatment. The median time for HAMA development was 189 days (95% CI 48 to 198 days, IQ range 46 to 279 days and range 5 days to 3400 days).

3.2.2 Analyses of Safety Endpoints

Secondary Leukemia and Myelodysplastic Syndrome (MDS)

The major long-term safety concern associated with radioimmunotherapy is myelodysplasia (MDS) and associated acute leukemia. Patients treated with iodine I 131 tositumomab were followed for the development of MDS/AML from study entry or until death or until the data cutoff. Information was collected semiannually. Table 3.10 provides a summary of the follow-up times, survival times and MDS/AML cases for the integrated efficacy population, the expanded access population and the combined population.

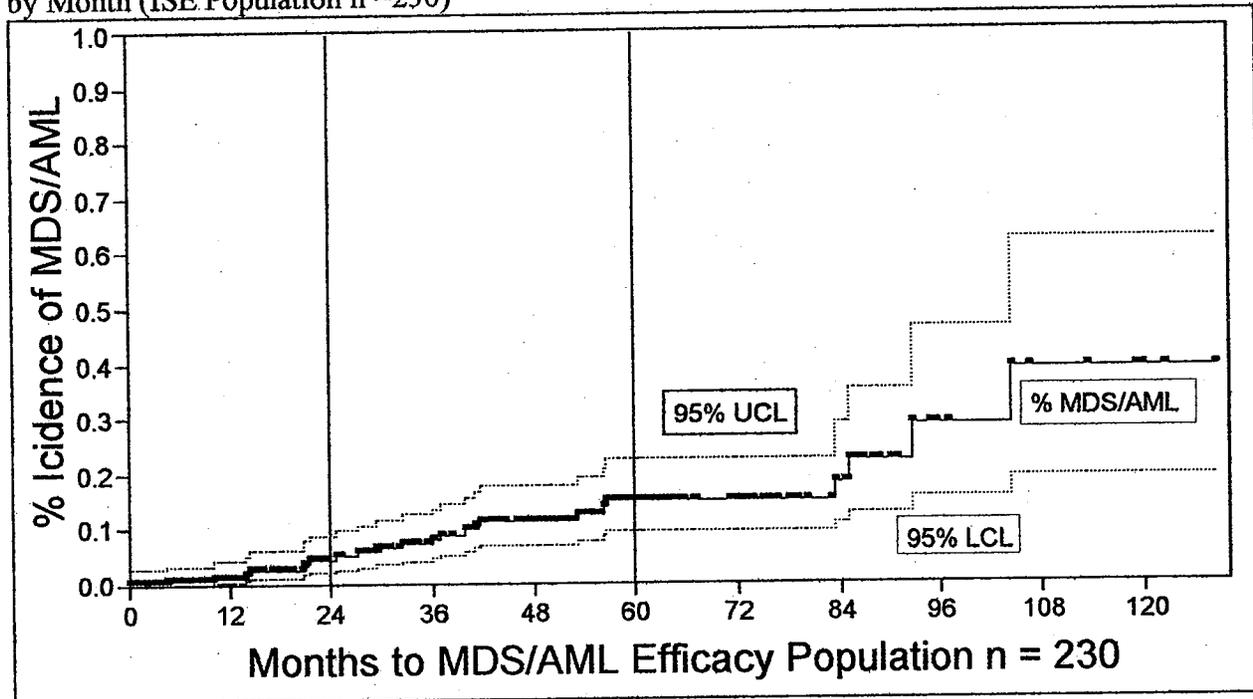
Table 3.10 Summary of the follow-up times, survival times and MDS/AML cases

| | Population | | |
|---|----------------|-----------------------|---------------|
| | Efficacy n=230 | Expanded Access n=765 | Overall n=995 |
| Follow-up in Months | | | |
| Median | 38.9 | 27.5 | 29.1 |
| IQ | 29.5 – 71.8 | 12.2– 40.5 | 12.3 – 44.4 |
| Range | 8.2 – 128.4 | 0.1 – 65.3 | 0.1 – 128.4 |
| Survival in Months | | | |
| Median | 41.0 | 50.0 | 49.1 |
| IQ | 13.9 – 128.5 | 13.3 – Not reached | 13.8 – 128.5 |
| Range | 0.2 – 128.5+ | 0.1 – 65.3+ | 0.1 – 128.5+ |
| No. MDS/AML | 24 (10.4%) | 20 (2.6%) | 44 (4.4%) |
| Time to MDS^a (Months) | | | |
| Median | 34.2 | 30.6 | 31.1 |
| IQ | 21.1 – 56.4 | 10.8 – 34.4 | 19.4 – 39.9 |
| Range | 0.03 – 104.5 | 4.4 – 47.7 | 0.03 – 104.5 |
| Kaplan-Meier Incidence Rate of MDS/AML | | | |
| 2-year rate | 4.7% | 1.6% | 2.3% |
| 5-year rate | 15.1% | 5.9% | 9.9% |

^a Time to development of MDS for patients who developed MDS and/or acute leukemia

Figures 2-4 provide Kaplan-Meier based curves of the cumulative incidence of MDS/AML for the integrated efficacy population, the expanded access population and the combined population, respectively.

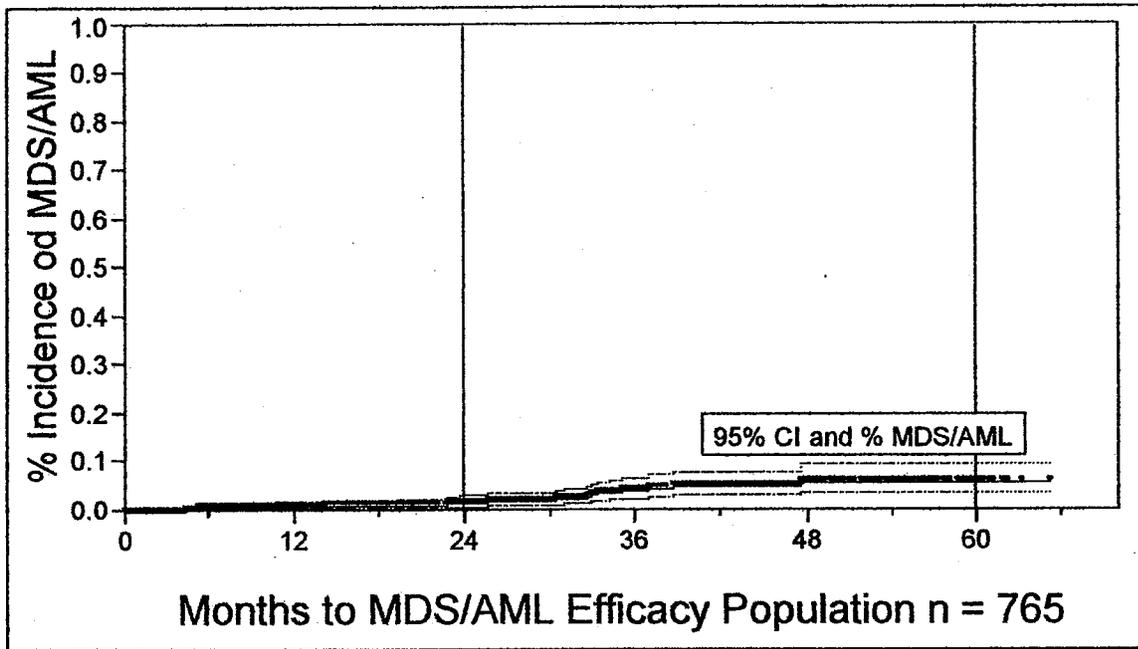
Figure 2: Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Month (ISE Population n =230)



For the integrated efficacy population, twenty-four of the 230 patients were known to have MDS/secondary leukemia. The cumulative incidence of MDS/secondary leukemia in the Efficacy patient population (n=230) was 4.7% at 2 years and 15.1% at 5 years.

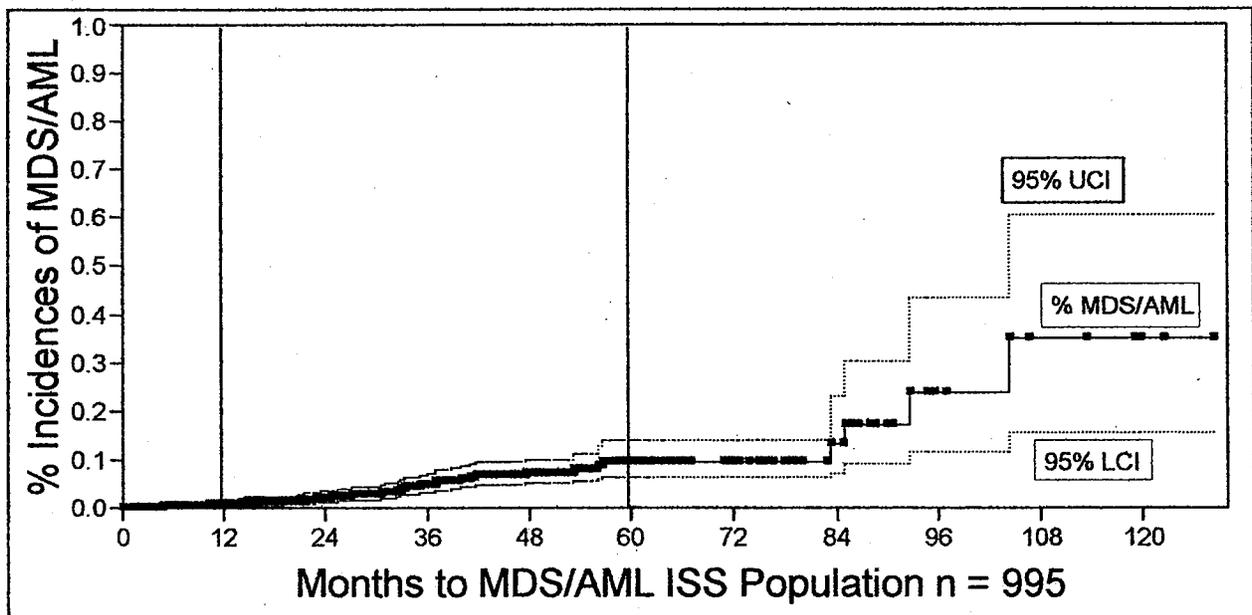
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Figure 3: Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Month (Expanded Access Population n =765)



For the expanded access population, twenty of the 765 patients were known to have MDS/secondary leukemia. The cumulative incidence of MDS/secondary leukemia in the Expanded Access patient population (n=765) was 1.6% at 2 years and 5.9% at 5 years.

Figure 4: Cumulative Incidence of MDS/AML in patients treated with Iodine I 131 tositumomab by Month (ISS Population (Safety Population) n =995)



For the overall population (integrated efficacy population plus the expanded access population), forty-four of the 995 patients were known to have MDS/secondary leukemia. The cumulative incidence of MDS/secondary leukemia among the overall population was 2.3% at 2 years and 9.9% at 5 years.

Because Kaplan-Meier estimates do not satisfy certain distributive properties $((0.151 \times 230 + 0.059 \times 765) / (230 + 765) = 8.0\%$ not 9.9%), in general, these cumulative incidence estimates should be taken with caution.

Thyroid (TSH) Evaluation

The protocol-specified laboratory TSH schedule was Baseline, Month 6 and every 3 months up to year 2 (one year for RIT-II-001) for all the studies and additional week 7 and week 13 for the study RIT-I-000 and week 13 for the study RIT-II-002.

There were 947 patients (out of 995 patients in the Safety database) who had TSH measured at baseline. Seventy four (74) of 947 (8%) patients had an elevated TSH prior to the therapeutic dose, and an additional 37 (3%) patients had a history of thyroid medication. Thus 111 of 995 (11%) patients had a history of hypothyroidism prior to receiving their therapeutic dose. Of 873 patients who were euthyroid at entry (elevbase=0), 592 (68%) had at least one post-treatment TSH value obtained (elevtx = 0 or 1). With a median observation period of 34.5 months, 70 out of 592 patients (12%) became hypothyroid as determined by elevated TSH (elevtx = 1) and 83 patients (14%) had elevated TSH or started thyroid medication. The median time to elevated TSH for these 70 patients was 12.8 months (IQ range 6 – 26.7 months and range 1.8 to 76.3 months)

The cumulative incidences of hypothyroidism were 9.4% and 18.5% at 2 years and 5 years respectively using Percent Elevated TSH Censored at the Last available TSH Value or death for ISS Population n=995. These estimates do not account for competing risks and overestimate the percent of patients who develop an elevated TSH.

Of the 592 patients who had at least one post-treatment TSH value obtained (elevtx = 0 or 1), 137 patients belonged to the study group (ISE). With a median observation period of 46.6 months, 19 out of 137 patients (14%) became hypothyroid as determined by elevated TSH (elevtx = 1) and 25 patients (18.4%) had elevated TSH or started thyroid medication (eventdyc). The median time to elevated TSH for these 19 patients was 12.2 months (IQ range 5.5 – 30.4 months and range 2.5 to 76.3 months).

The cumulative incidences of hypothyroidism were 11.1% and 19.3% at 2 years and 5 years respectively using Percent Elevated TSH Censored at the Last available TSH Value or death for ISE Population n=230. These estimates do not account for competing risks and overestimate the percent of patients who develop an elevated TSH. A summary for TSH is provided in Table 3.11 for the integrated efficacy population, the expanded access population and the combined population.

Table 3.11 Summary for TSH

| Assessment | Population | | |
|--|-------------------|-----------------------------|------------------|
| | Efficacy N=230 | Expanded Access N=765 | Overall N=995 |
| No elevated TSH, no Rx at Baseline | 203 | 670 | 873 |
| No. that had at least one post tx TSH value obtained | 137 | 455 | 592 |
| Median follow-up TSH (Months) | 46.6 | 32.8 | 35 |
| No. with elevated TSH | 19 | 51 | 70 |
| Median time in months to elevation for elevated patients | 12.2 | 14.5 | 12.8 |
| No. with elevated TSH or started thyroid medication | 25 | 58 | 83 |
| Median months to elevation | 15.8 | 14.5 | 15.3 |
| Kaplan-Meier TSH Rate ^a | | | |
| 2-year rate | 11.1% | 9.0% | 9.4% |
| 5-year rate | 19.3% | 16.9% | 18.5% |

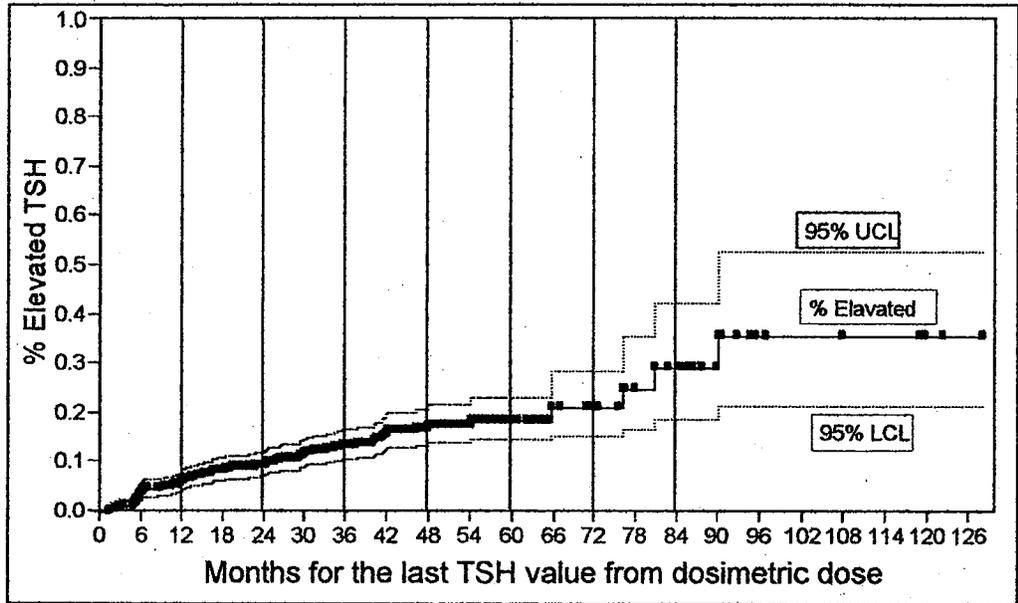
^a based on elevated TSH or started thyroid medication

Algorithm:

Once patients become hypothyroid, they continue to be hypothyroid. Therefore, the event was assumed to have occurred the first time a patient had elevated TSH or started thyroid medication. The remaining patients were assumed to have non-elevated TSH at their last day of TSH evaluation during the TSH follow-up, and are censored at individual patient's last evaluation day of TSH measurements.

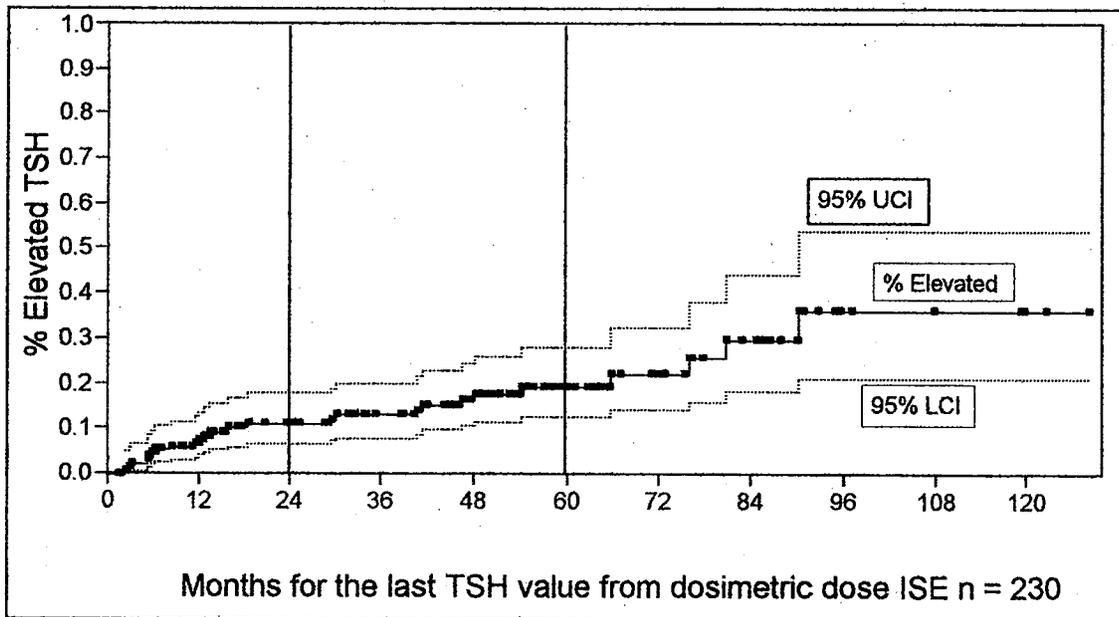
Figures 5-7 provide Kaplan-Meier based curves of the cumulative percent with elevated TSH, for those patients with at least one post-treatment TSH value obtained, for the combined population, the integrated efficacy population, and the expanded access population, respectively.

Figure 5. Percent Elevated TSH Censored at the Last available TSH Value or death ISS Overall Population n=592



For this subgroup of the integrated safety population, 83 of the 592 patients were known to have elevated TSH or started thyroid medication. The cumulative incidences of hypothyroidism were 9.4% and 18.5% at 2 years and 5 years respectively.

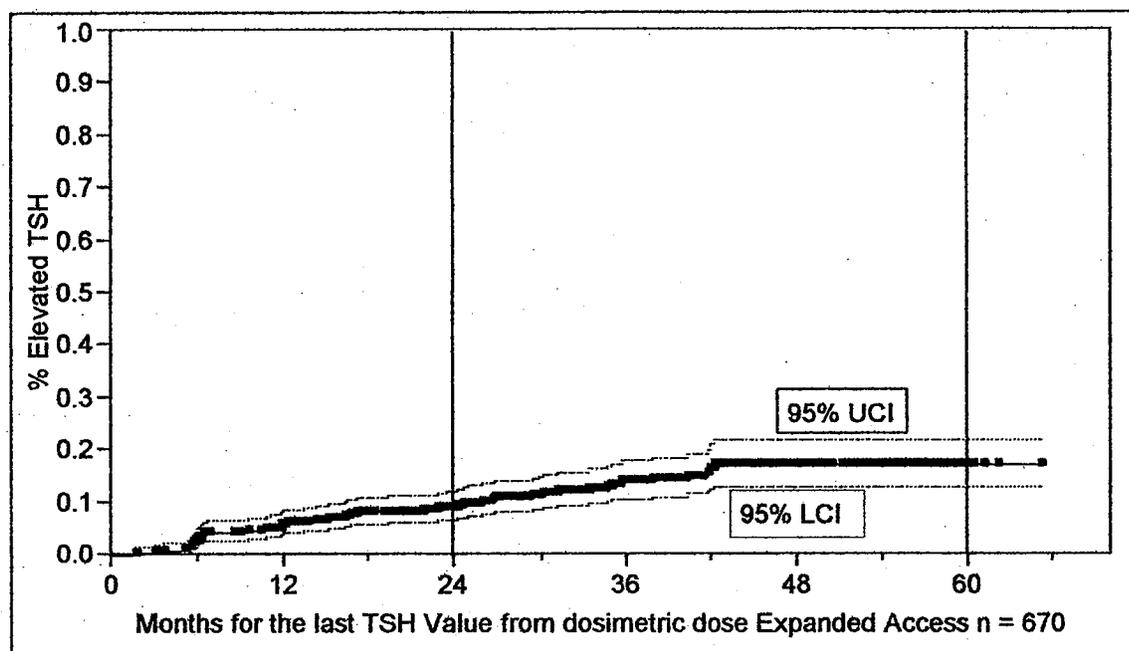
Figure 6. Percent elevated TSH censored at the last available TSH value or death for the integrated efficacy population n=137*



* This graph includes data from those 137 of the 230 patients in the integrated efficacy population who had at least one post treatment TSH value obtained.

For this subgroup of the integrated efficacy population, 25 of the 137 patients were known to have elevated TSH or started thyroid medication. The cumulative incidences of hypothyroidism were 11.1% and 19.3% at 2 years and 5 years respectively.

Figure 7. Percent elevated TSH censored at the last available TSH value or death for the expanded access population n=455*



* This graph includes data from those 455 of the 670 patients in the expanded access population who had at least one post treatment TSH value obtained.

For this subgroup of the expanded access patient population, 58 of the 455 patients were known to have elevated TSH or started thyroid medication. The cumulative incidences of hypothyroidism were 9.0% and 16.9% at 2 years and 5 years respectively.

Immunogenicity:

There were six (6) patients who had no baseline assessment for HAMA leaving 989 out of 995 patients in the safety dataset who were assessed for HAMA at the baseline with 11 HAMA positive and 978 HAMA negative. Thus, one percent (11/989) of the chemotherapy-relapsed or refractory patients included in the clinical studies or the expanded access program had a positive serology for HAMA prior to treatment. Of the 978 patients who were seronegative for HAMA prior to treatment, 788 (81%) had at least one post-treatment HAMA value obtained (aeval=1).

Of the 788 patients who had at least one post-treatment HAMA value obtained, a total of 80 patients (10%) became seropositive for HAMA post-treatment. The median time for HAMA development was 172 days (95% CI 97 to 169 days, IQ range 91 to 271 days and range 5 days to

3400 days). 45 of 80 (56%) patients converting to HAMA positivity on or prior to Month 6 (183 days). Four patients converted to HAMA seropositivity after 18 months.

Of the 788 patients who had at least one post-treatment HAMA value obtained, 219 belonged to ISE (n=230). 23 out of 219 (10.5%) became seropositive for HAMA post-treatment. The median time for HAMA development was 189 days (95% CI – 48 to 198 days, IQ range 46 to 279 days and range 5 days to 3400 days). Eleven of 23 (48%) patients converting to HAMA positivity on or prior to Month 6 (183 days). One patient converted to HAMA seropositivity after 18 months. A summary for HAMA is provided in Table 3.12 for the integrated efficacy population, the expanded access population and the combined population.

Table 3.12 Summary of HAMA

| | Population | | |
|---|--------------|----------------------------|------------------|
| | ISE N=230 | Expanded Access N = 765 | Overall N=995 |
| # HAMA Negative at Baseline | 220 (96%) | 758 (99%) | 978 (98%) |
| # At least one post tx HAMA value obtained | 219 | 569 | 788 |
| Median months of follow-up for patients with ≥ 1 post tx value | 5.7 | 6.7 | 6.2 |
| # HAMA positive post treatment | 23 | 57 | 80 |
| Median months for HAMA + post treatment patients ^a | 6.2 | 5.3 | 5.7 |
| 6-month Kaplan-Meier Cumulative Incidence (HAMA+) Rate | 6.0% | 7.0% | 6.9% |
| 12-month Kaplan-Meier Cumulative Incidence (HAMA+) Rate | 17.4% | 12.1% | 13.3% |
| 18-month Kaplan-Meier Cumulative Incidence (HAMA+) Rate | 20.5% | 13.3% | 14.9% |

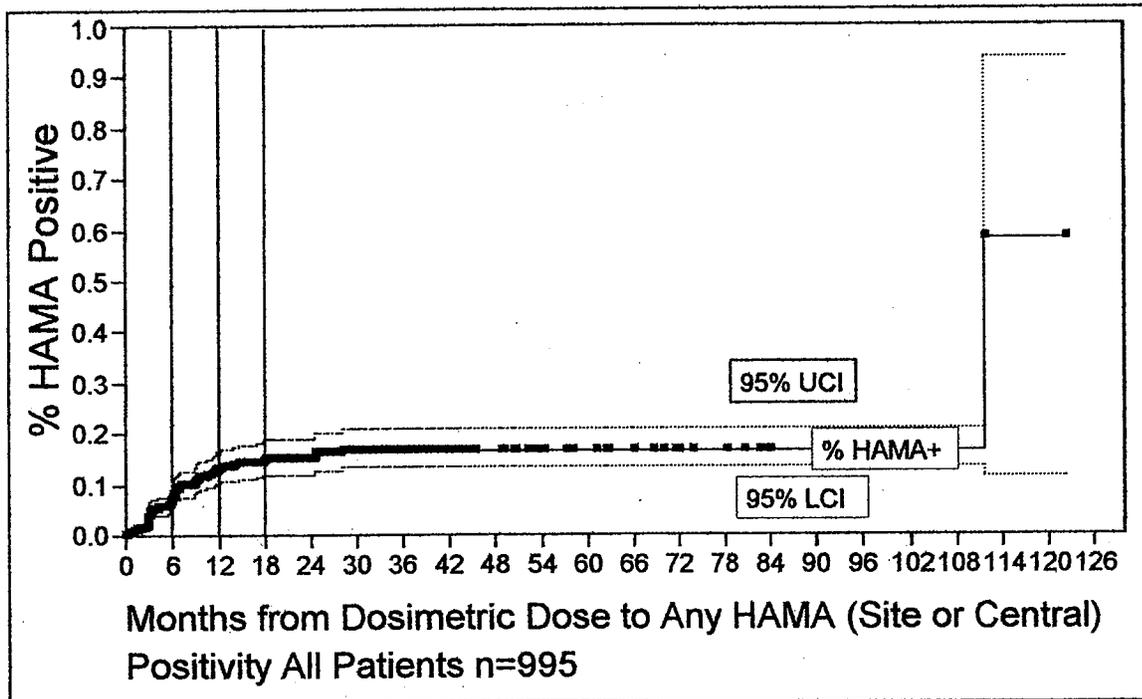
^a Median months for HAMA + post treatment patients is for patients who were positive post treatment.

Figures 8-10 provide Kaplan-Meier based curves of the cumulative incidence for conversion to HAMA positivity, for those patients with at least one post-treatment HAMA value obtained, for the combined population, the integrated efficacy population, and the expanded access population, respectively.

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Figure 8. The cumulative incidence for conversion to HAMA positivity for the integrated safety population

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) – n = 788 evaluable (at least one HAMA follow-up) patients out of 995 patients in the integrated safety Population *



* This graph includes data from those 788 of the 995 patients in the integrated safety population who were known to have a conversion to HAMA positivity.

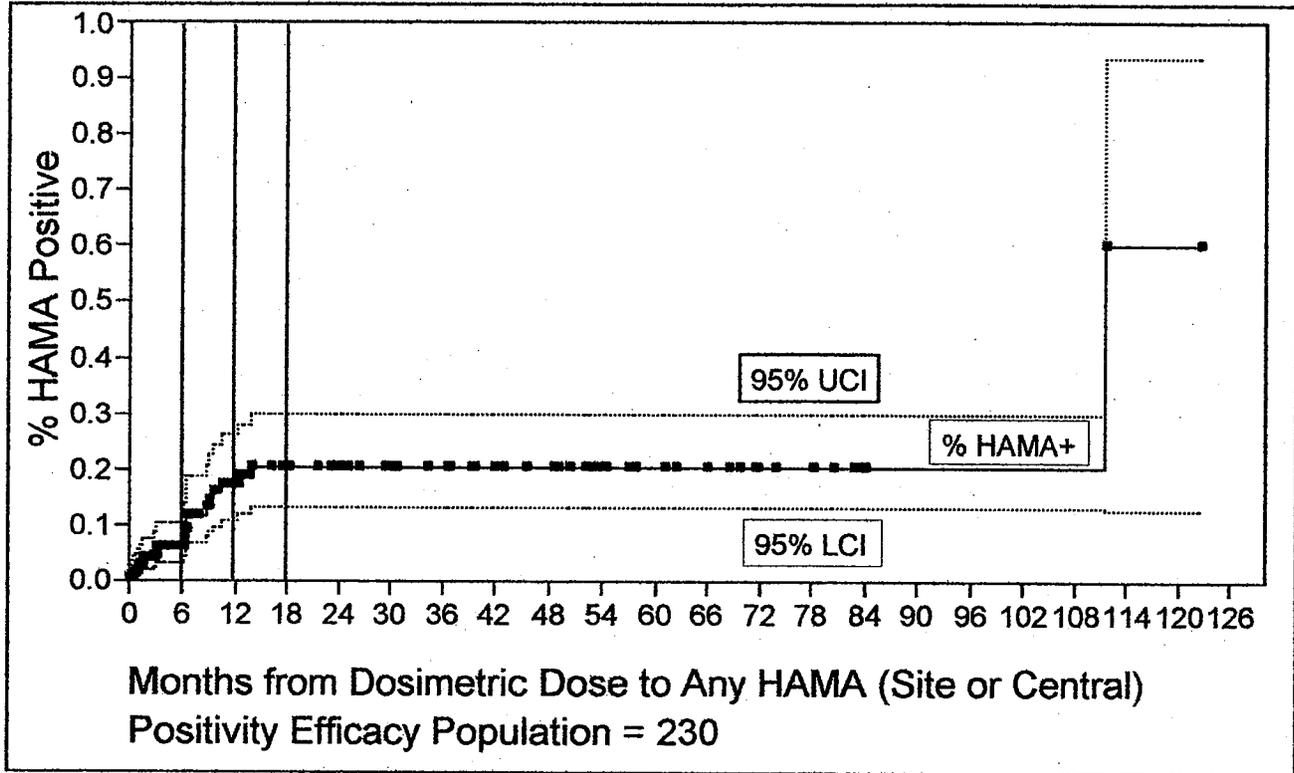
One patient converted to HAMA positive on Study Month 111.8 . Previous HAMA negative was on Study Month 84.1. The HAMA curve increase at month 111 is based on one longest lasting patients who had a HAMA reaction in months 111.

For this subgroup of the overall population, 80 of the 788 patients were known to have a conversion to HAMA positivity. For these 80 patients, the median time to HAMA positivity converting to HAMA positivity was 5.7 months (95% CI: 3.2 -6.2 months, Range: 0.2–111.8 months, IQ range 3.0 to 8.9 months). Forty-five of 80 (56%) patients converting to HAMA positivity on or prior to Month 6 (183 days).

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Figure 9. The cumulative incidence for conversion to HAMA positivity for the integrated efficacy population*

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) - n = 219 evaluable (at least one HAMA follow-up) patients out of 230 patients in the integrated efficacy population)



* This graph includes data from those 219 of the 230 patients in the integrated efficacy population who were known to have a conversion to HAMA positivity.

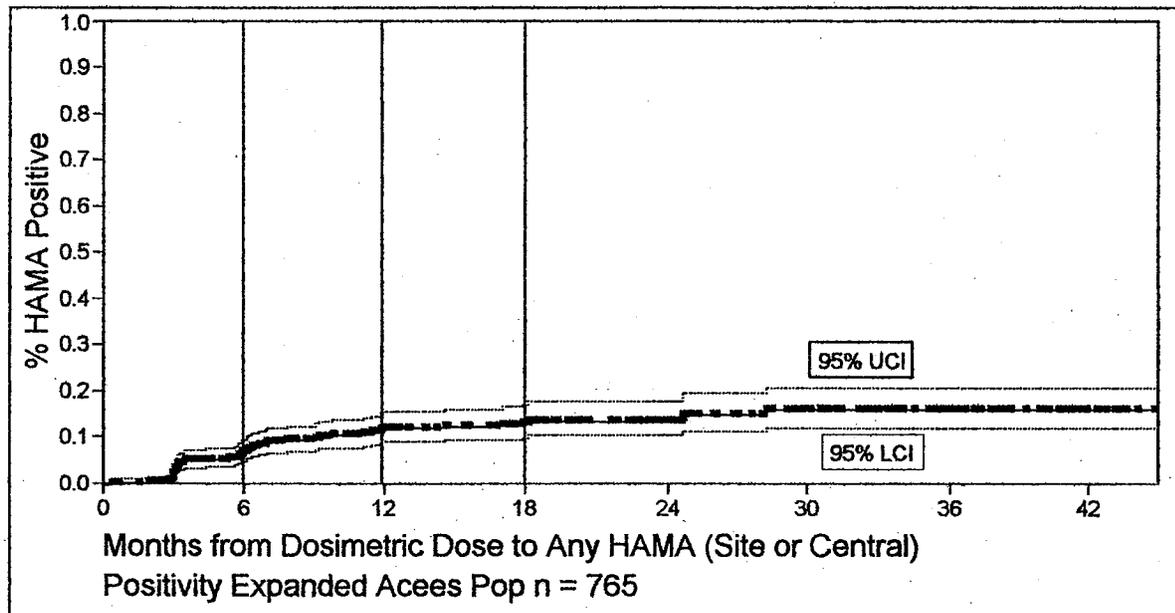
One patient converted to HAMA positive on Study Month 111.8. Previous HAMA negative was on Study Month 84.1. The HAMA curve increase at month 111 is based on one longest lasting patients who had a HAMA reaction in months 111.

For this subgroup of the integrated efficacy population, 23 of the 219 patients were known to have a conversion to HAMA positivity. For these 23 patients, the median time to HAMA positivity converting to HAMA positivity was 189 days (95% CI 48 to 198 days, IQ range 46 to 279 days and range 5 days to 3400 days).

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Figure 10. The cumulative incidence for conversion to HAMA positivity for the expanded access population*

Any HAMA positive (Site or Central) by Months Censored at the Last available HAMA Value (Cumulative) – n = 569 evaluable (at least one HAMA follow-up) patients out of 765 patients in the expanded access population)



* This graph includes data from those 569 of the 765 patients in the integrated efficacy population who were known to have a conversion to HAMA positivity.

For this subgroup of the expanded access population, 57 of the 569 patients were known to have a conversion to HAMA positivity.

See the clinical reviewer's review for further safety analyses.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Because of the small sample size, no analyses by gender, race and age were performed.

4.2 Other Special/Subgroup Populations

There are no subgroup analyses.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For study RIT-II-004, the efficacy analyses on response rate using McNemar's test are invalid. The last qualifying chemotherapy (LQC) best response are controlled (not random), and since best response is a dichotomous endpoint, the conditional distribution for how a patient's best response on Bexxar relatively compares to their best response on LQC depends on whether that patient did or did not have a response on their LQC.

In order for the LQC best responses to have been random, either the patients would have entered the trial prior to receiving their last qualifying chemotherapy (and then later receive Bexxar, as in a cross-over design), or the patients were randomly selected (not volunteers). Neither scenario is the case here.

Putting aside that a cross-over design would have required a random order for a patient receiving "LQC" and Bexxar, let's compare study RIT-II-004 with a cross-over study where each patient receives their LQC then later in the study receives Bexxar. For this cross-over design the assumptions needed for McNemar's test are satisfied. However, study RIT-II-004 would get those patients from the cross-over study that would choose to later receive Bexxar – such patients are not randomly selected. Patients that had very good outcomes on their LQC would probably not need to later receive Bexxar. So, study RIT-II-004 would tend to have those patients from the cross-over study that had poorer outcomes on their LQC.

For paired continuous data, it may not be necessary for the "before" observation to be random. In the most basic model for a particular therapy, the change or difference ("after" minus "before") may still be modeled as a specific normal distribution (independent of the specific value of the "before" observation).

It is also not clear what hypothesis is intended to be tested here. The comparison involves response for different lines of therapy. Different baseline time points and baseline measurements are used for determining the respective response and duration of response for LQC and Bexxar.

For the paired response durations analogous comments apply for the paired Prentice-Wilcoxon test.

5.2 Conclusions and Recommendations

Efficacy data provided in the SAS export data file RESPOUT (Study RIT-II-004) support the contents of the sponsor's study report.

The results of study RIT-II-004 must be analyzed like a typical single-arm study.

6. APPENDICES

6.1 Efficacy definitions

Complete response (CR): Complete resolution of all disease-related radiological abnormalities and disappearance of all signs and symptoms related to the disease.

Partial response (PR): $\geq 50\%$ reductions in the sum of the products of the longest perpendicular diameters of all measurable lesions with no new lesions.

Clinical complete response (CCR): Complete resolution of all disease-related symptoms except residual foci, thought to be residual scar tissue, are present. Generally, an unchanging lesion ≤ 2 cm diameter by radiographic evaluation or ≤ 1 cm diameter by physical examination can be considered scar tissue.

Confirmed response: Responses that were confirmed by two separate response evaluations at least 4 weeks apart. Only confirmed responses are reported for Iodine I 131 Tositumomab treated patients in this ISE.

Time to progression: The time from the start of treatment (i.e., dosimetric dose of Iodine I 131 Tositumomab) to the first documented progression. Accordingly, MIRROR Panel data were used to determine time to progression, which was defined as the time from the start of treatment to the first documented progression.

Duration of response: The time from the first documentation of response to the first documented progression for all patients with confirmed CR, CCR, or PR. Only durations of response for confirmed responders are reported for Iodine I 131 Tositumomab treated patients in this ISE.

6.2 Paired Prentice-Wilcoxon test for duration of response

Reference: O'Brien and Fleming (1987). A paired Prentice-Wilcoxon test for censored paired data. *Biometrics* 43, 169-180.

Denote the survival and censoring times associated with each pair by $\{ (S_x, C_x), (S_y, C_y) \}$.

Define $C = \min(C_x, C_y)$ to be a common censoring time for both pair members, ignoring any additional follow-up occurring beyond that point.

Rank all the observation times from smallest to largest, and let $n(j)$ denote the number of persons in the pooled sample with observation times greater than or equal to the j th distinct ordered observed death time, $t_j, j = 1, 2, \dots, D$. Assume that there are no ties in times of observed deaths. To compute the Prentice-Wilcoxon scores, define

$$s_i = \prod_{j=1}^i n(j)/[n(j)+1], \quad i = 1, \dots, D.$$

The score assigned to the individual having the observed death is given by $1 - 2s_i$. Individuals who are censored at the time of the i th death up to the $(i+1)$ st death are assigned a score of $1 - s_i$. Compute the scores (k_{xi}, k_{yi}) and define $\Delta_l = k_{xl} - k_{yl}$ for the l th pair, $l = 1, 2, \dots, n$.

Under the null hypothesis $H_0 : S_x = S_y$, $\sum_1^n \Delta_l$ has mean zero and variance $\sum_1^n \Delta_l^2$, and

$$Z_n \equiv \sum_1^n \Delta_l / \left(\sum_1^n \Delta_l^2 \right)^{1/2} \xrightarrow{D} Z,$$

where Z has a standard normal distribution.

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SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewers:
Date: November 19, 2004

Dr. Kallappa Koti

Dr. Satish Misra

Statistical Team Leader:

Dr. Mark Rothmann

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HFD-109 / Dr. Dale Slavin
HFD-107 / Dr. Kaushikkumar Shastri
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HFD-711 / Dr. Satish Misra
HFD-711 / Dr. Mark Rothmann
HFD-711 / Dr. Aloka Chakravarty
HFD-700 / Dr. Charles Anello
HFD-700 / Dr. Robert O'Neill

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125011/S024

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 21, 2004

FROM: Patricia Keegan, M.D. 
Division Director
Division of Biological Therapeutic Oncology Products

SUBJECT: Recommendation for Approval Action on BLA STN 125011.24

TO: STN 125011.24

Introduction:

This efficacy supplement is submitted in support of a request for accelerated approval of the Bexxar Therapeutic Regimen to expand the indication to patients with relapsed or refractory low-grade, follicular, or transformed CD20 positive Non-Hodgkin's Lymphoma (NHL) who have not received prior Rituximab.

The BEXXAR therapeutic regimen is a multi-step, multi-modality regimen that is indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma (NHL) with or without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. It is intended as a single course of treatment, administered in two discrete steps: the dosimetric and therapeutic steps. Each step consists of a sequential infusion of Tositumomab followed by Iodine I-131 Tositumomab. The dosimetric step consists of Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes, followed by Iodine I-131 Tositumomab (containing 5.0 mCi I-131 and 35 mg tositumomab) intravenously in 30 ml 0.9% Sodium Chloride over 20 minutes. The therapeutic step is administered 7-14 days after the dosimetric step and consists of Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes followed by Iodine I-131 Tositumomab containing the activity of Iodine-131 that is calculated to deliver 75cGy total body irradiation and 35 mg Tositumomab, administered intravenously over 20 minutes.

Regulatory History:

The Bexxar therapeutic regimen was approved on June 27, 2003 for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma (NHL) with or without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. The approval was based upon the results of a single arm study in 40 patients whose disease had progressed following a median of four prior chemotherapy regimens and who had received prior Rituximab. In this study, treatment with the Bexxar

therapeutic regimen resulted in a high rate of objective tumor responses (overall response rate of 68%) that were very durable (median duration 16 months). 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. The effects of Bexxar on overall survival and progression-free survival have not been established.

b(4)

_____ The ODAC advised the Agency to grant approval based on these data.

b(4)

Marketing approval for the Zevalin therapeutic regimen was granted on February 19, 2002. Marketing approval was granted for two indications, the first under the regular approval (21 CFR 601 Subpart A) regulations and the second, under the accelerated approval (21 CFR 601 Subpart E) regulations.

b(4)

b(4)

Efficacy (See primary reviews by Drs. Kaushik Shastri and Kallapa Koti)

This efficacy supplement is supported by evidence of a high rate of durable objective tumor responses observed in a multicenter, single arm trial (Study RIT-II-004). The study population consisted of 60 patients with low grade or follicular non-Hodgkin's

lymphoma, including a minority with pathologic transformation to a higher grade histology, whose disease refractory to combination chemotherapy but who had not received Rituximab. Eighty percent of the study population had received three or more prior chemotherapy regimens and all patients had experienced either no response or progressed within 6 months of their last qualifying (dose-intensive combination) chemotherapy. In this study, treatment with the Bexxar regimen yielded an overall response rate of 47%, median response duration of 12 months (range 2-47 months) and a complete response rate of 20%. The results are consistent with the responses observed in 4 other studies of the Bexxar therapeutic regimen in a similar population. The primary differences between this study and the primary efficacy study supporting the original approval were the extent of prior chemotherapy treatment, which was greater in this study (median 4 prior regimens vs. 2) and prior exposure to Rituximab (none in this study vs. refractory to Rituximab in the study supporting original approval). The high rate of durable responses in this study indicate that even in patients who have not received Rituximab, treatment with Bexxar is likely to provide a clinical benefit in terms of durable responses resulting in a prolonged treatment-free interval.

Rituximab, which is also indicated for this population, has also demonstrated durable objective responses (48% overall response rate, median duration of response 11 months, 6% complete response rate) in a study of 166 patients who had relapsed following or were refractory to prior chemotherapy

b(4) This is a multi-center, randomized, Phase 3 study comparing Rituximab and Bexxar in the treatment of patients with relapsed follicular non-Hodgkin's B-cell lymphoma. A total of 506 patients, approximately 253 per arm, will be enrolled at sites in the United States and Europe. As per the applicant, the study was opened to enrollment in March 2004 and twelve U.S. and 5 European sites have been initiated or are completing IRB/EC approvals. This study is also an agreed-upon post-marketing commitment obtained at the time of initial approval of Bexxar for the treatment of patients with chemotherapy and Rituximab refractory low grade and follicular NHL.

DSI Review

Clinical study site inspections were not conducted in the review of this supplement. Clinical study site inspections were conducted as a part of the original application (STN 125011.0) and included sites participating in Protocol RIT-II-004, the primary study supporting this supplement.

Safety (See primary reviews by Drs. Kaushik Shastri and Satish Misra)

The data regarding safety is very similar to the data provided at the time of the original approval; that is safety data derived five clinical trials using the recommended dose and schedule of Bexxar, in which 230 patients with non-Hodgkin's lymphoma were enrolled, supplemented by serious and targeted adverse events obtained from the expanded access program, which enrolled 765 patients. The major difference in the safety information between the original application and this supplement is the additional follow-up for targeted adverse events in the clinical trial and expanded access population with regard to the following targeted adverse events: second malignancies including secondary

leukemia, myelodysplastic syndrome, immune response to Bexxar as measured by Human Anti-Mouse Antibodies (HAMA), and clinical or subclinical hypothyroidism as detected by increases in thyroid-stimulating hormone (TSH) levels. Because the primary difference in safety information was based on the extended follow-up for targeted adverse events, there is little new safety information in the supplement and labeling with regard to adverse events remains largely unchanged. With greater length of observation, there are additional events leading to small increases in rates of the targeted toxicities. Updated cumulative incidence rates for these events were included in the revised labeling. Of these events, the most concerning from a safety viewpoint is the potential increase in second cancers and myelodysplasia. Given the uncontrolled nature of the data and the high background rate in this population exposed to both topoisomerase II and alkylating agents (both classes of drugs with leukemogenic potential) it remains difficult to isolate the extent to which treatment with the Bexxar therapeutic regimen. The updated information provided small increases in cumulative incidence, which is expected with the additional period of observation, is presented below.

Based on updated information, the cumulative incidences of myelodysplastic syndrome (MDS) and/or acute leukemia were 10% (24/230) among patients enrolled in the clinical studies and 3% (20/765) among patients treated in the expanded access programs, with median durations of follow-up of 39 and 27 months, respectively. Among the 44 reported cases, the median time to development of MDS/leukemia was 31 months following treatment. Non-hematological malignancies were also reported in 54 of the 995 patients enrolled in clinical studies or included in the expanded access program. Approximately half of these were non-melanomatous skin cancers; the remaining cases included a variety of solid tumors cancers encompassing many primary disease sites.

Nuclear Medicine Review (See primary review by Dr. Mary Andrich)

A number of editorial changes were proposed to the Dosage and Administration section of the labeling, specifically with regard to Preparation of the Dose and Image Acquisition and Interpretation. These modifications were reviewed by Dr. Mary Andrich, in consultation with Dr. George Mills, Director of the Division of Medical Imaging and were deemed acceptable for inclusion in labeling. 

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Clinical Pharmacology (See primary review by Dr. Anil Rajpal)

Changes to Clinical Pharmacology section were based on data reviewed by Dr. Rajpal. 


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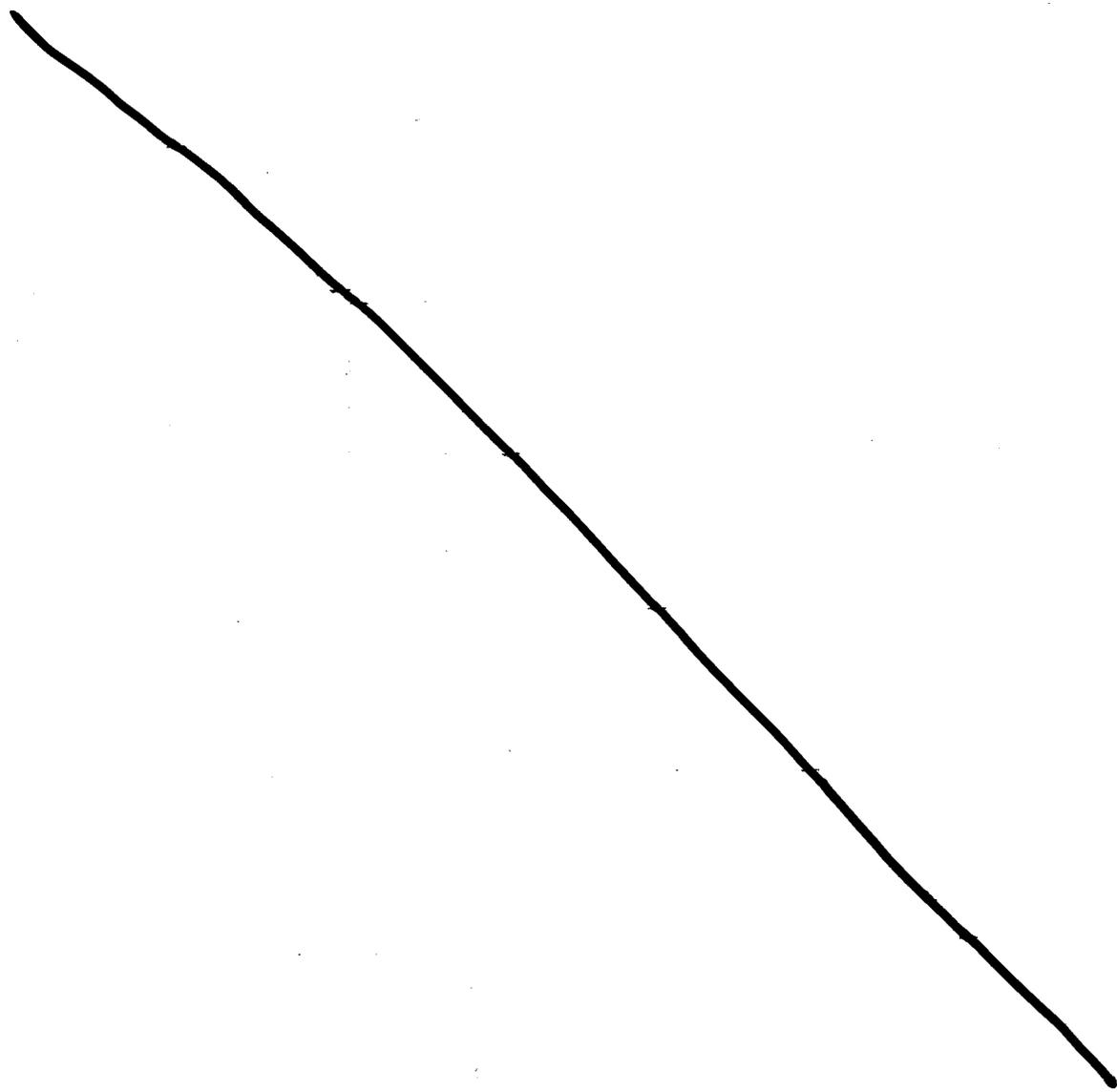
Pharmacology/Toxicology:

No information relevant to pharmacology or toxicology were submitted nor required for review of this efficacy supplement.

CMC

No information relevant to chemistry, manufacturing, or controls (CMC) were submitted nor required for review of this efficacy supplement. The product used in conduct of Protocol RIT-II-004 was the same as that used in studies supporting the original approval of the Bexxar therapeutic regimen.

Labeling Review:



b(4)

Recommendation:

All review team members have recommended approval of this efficacy supplement. I concur with the review team and also recommend approval.