CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103948/0

MEDICAL REVIEW

BLA 99-0786: MEMO TO THE FILE

DATE: May 4, 2001

TO: Patricia Keegan, M.D.
Deputy Director
DCTDA, OTRR, CBER

FROM: Genevieve A. Schechter, M.D.
Clinical Reviewer - Oncol
Oncology, DCTDA, OTRR, CBER

Enclosed is the final review for BLA 99-0786 (STN 104948), Campath® (alemtuzumab) for the treatment of B-CLL in patients who have previously been treated with alkylating agents and are refractory to fludarabine. Included are an Introduction, Review of Study 211, Review of Study 009, and Review of Study 005, and Summary. Accelerated Approval is recommended for this BLA application. If you concur, please sign the last page of the review document.

COMPLETE REVIEW:
BLA 99-0786
(STN 103984)

Campath®
(Campath-1h, alemtuzumab)

INDICATION: For the treatment of B-CLL in patients who have been treated with alkylating agents and are refractory to fludarabine

May 4, 2001

COMPLETE REVIEW: BLA 99-0786

INDEX

INTRODUCTION

This document includes the reviews of the three trials (Study 211, Study 009, and Study 005) used to support the efficacy and safety of CAMPATH-1H in the treatment of patients with B-CLL who have received prior alkylator therapy and have failed fludarabine therapy, and a summary of the efficacy and safety data from these trials. Issues that have arisen during the review of this BLA include the definition of the progression after response for B-CLL for patients enrolled in these trials, the demonstration of patient benefit in single arm studies, and the safety of Campath with regard to hematological toxicities.

With regard to the definition of progression after response the following issues arose during the course of the review. In the original protocol dated January 27, 1998 time to progression was defined as time from initial treatment until first objective documentation of progressive disease. In Appendix G of the original study protocol the criteria used to define progressive disease (based on the NCI CLL WG Response Criteria published in a 1996 article by Cheson et al.) were listed. Appendix G was further revised and submitted as part of Protocol Amendment #1 dated March 13, 1998. In this revision the duration of response was added and was defined as that time period "measured from the time that the patient has exhibited the features of maximum response until evidence of progressive disease". The definition of progressive disease was expanded from the original version of the protocol in Amendment#1 to include the following:

- Lymphadenopathy: $\geq$ 50% increase in the sum of products of at least two lymph nodes on two consecutive determinations two weeks apart or new lymphadenopathy (at least one node must be $\geq$ 2 cm); or the appearance of new palpable lymph nodes;
- Hepatosplenomegaly: $\geq$ 50% increase in the size of the liver and / or spleen as determined by measurement below the respective costal margin or new hepatosplenomegaly;
- Lymphocytosis: $\geq$ 50% increase in absolute number of circulating lymphocytes to at least 5000/ul; or,
- Transformation to a more aggressive histology (e.g., Richter's syndrome or PLL with > 55% prolymphocytes)

The algorithm for progression defined in the statistical section of the original BLA submission entitled "Algorithm for Checking Progression" (Vol.3.31, pg. 222). The algorithm included the above criteria to define progression. This algorithm was used by the medical reviewer to assess progression and date of progression.

During several discussions with the sponsor conducted in March and April 2000, the sponsor indicated that the criteria used by the agency were too stringent and did not account for the waxing and waning of lymphocyte counts in patients with CLL. The sponsor sent a facsimile transmission dated April 14, 2000 that stated: *"An ANC > 5000/ul is frequently utilized as one of the criteria to establish a diagnosis of CLL, but there is no support in the literature, which we have been able to find that suggests that by itself, an ALC > 5000/ul either indicates clinically meaningful progression or constitutes an indication for treatment."* In the resubmission of August 18, 2000 the sponsor utilized

a new definition for disease progression after therapy which includes the following criteria:

- an increase by $\geq$ 50% or to at least 10,000/ul from the nadir ALC reached during Campath therapy;
- an increase by $\geq$ 50% in the sum of the areas of all nodes (the largest node must be at least 2 x 2 cm or $\geq$ 4 cm^2) from the smallest value reached during Campath therapy follows by consistent increases over time or the appearance of new nodes (the largest node must be at least 2 x 2 cm) followed by a consistent increase over time;
- an increase by $\geq$ 50% in the span of the liver or spleen below the corresponding costal margin (to at least 3 cm) from the smallest value reached during Campath therapy followed by a consistent increase over time or the appearance of new hepatosplenomegaly (>2 cm) followed by a consistent increase over time;
- transformation to more aggressive histology; or,
- development of autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenia (ITP) without other obvious cause.

The reviewer has continued to apply the criteria included in the 3/13/98 amended study protocol and the algorithm included in the original BLA submission, a definition of progression based on the 1996 NCI CLL working group criteria used to define disease progression either a priori or after response. Progression in the mind of the reviewer does not include the need for active (alternative) treatment but rather a clinically significant increase in activity of the malignant clone of B-cells. In this age of PCR it is possible that progression might be defined in an entirely different manner. Perhaps in some disease states with the advent of new technologies a better measure of therapeutic efficacy would be time to alternative therapy provided, of course, that clear guidelines for alternative treatment are defined prospectively.

A second issue that arose during the review of this BLA involved the demonstration of patient (clinical) benefit in these single arm studies. After several discussions with the sponsor, the data from the responders was reviewed to determine how patients benefited from therapy. The case report forms were reviewed for evidence of improvement in clinical symptomatology, improvement in organomegaly or adenopathy which due to its bulkiness may be uncomfortable, improvement in blood counts that could be correlated with a reduction / resolution of transfusion requirement, bleeding, or infection. Simple summaries of the benefits observed in responders included in this review. The reader can judge if this information is adequate to prove benefit to responders.

A third issue that arose during review was the severity of the hematological toxicity associated with Campath. In October, 1995 Burroughs-Wellcome stated in a letter to the agency that it had discontinued all development plans for CAMPATH-1H noting that 527 patients had been treated on phase I/II studies in lymphoma, myeloma, leukemia, rheumatoid arthritis, renal transplant, and compassionate use protocols. The letter states that: "The majority of adverse events have been administration-related and of short duration. These include acute hematological changes, characteristically a transient reduction in neutrophil and sometimes platelet counts, followed within hours of the infusion ending of transient neutropenia. Chronic hematological changes (neutropenia, thrombocytopenia, and anemia) have also been observed in approximately 40% of

patients with hematological malignancies. A few of these have been associated with well documented hypoplasis or aplasia." It should be noted that this letter was included with a revised SAE report for a case of bone marrow necrosis considered possibly related to Campath therapy in a patient with relapsed acute lymphoblastic leukemia. The reviewer has attempted to present as complete a picture as possible of the toxicity profile by presentation of detailed information about dose delays or interruptions, deaths, serious adverse events, information about hospitalizations, changes in hematological toxicity over the course of therapy, and changes in transfusion requirements. The clinical expertise of the members of the advisory committee will be particularly useful in placing the toxicity profile in proper context.

A word about the pharmacokinetics of CAMPATH-1H is in order. The estimated median $t_{1/2}$ for CAMPATH-1H 30 mg administered three times weekly intravenously is approximately 34 hours with a great degree of inter-patient variability. The tumor burden and the density of CD52 antigen on the cell surface contribute to the marked inter-patient variability noted in the pharmacokinetic studies. As the malignant lymphocytosis decline (with the nadir CLL count usually attained about week 4), the peak and trough levels of CAMPATH-1H begin to rise and after about two weeks reach a steady state. Over eight weeks of therapy CLL patients were noted to have a prolongation of the estimated median (and mean) $t_{1/2}$ from 26.9 hours to 85.4 hours (mean, median) at week eight, an increase in median (and mean) peak serum level from 0.59 μg/ml to a median peak level of 8.82 μg/ml (mean: 8.67 μg/ml), and an increase in the median trough level from 0.09 μg/ml (mean: 0.9 μg/ml) to a median trough level of 6.12 μg/ml (mean: 4.75 μg/ml). A proportional increase in AUC and C_{max} is noted with CAMPATH-1H doses up to 80 mg with a greater than proportional increased reported at doses higher than 80 mg. Increased toxicity, especially hematologic, is observed with doses greater than 80 mg. The increase in half-life and the serum drug concentration may contribute to the prolonged hematologic toxicity observed in some patients.

In the study reports information is included about differences between the sponsor and the reviewer in assessment of efficacy data as well as safety data. Hopefully the reader will not find this information extraneous or irrelevant to the review.

211 STUDY REPORT

Table of Contents

211 STUDY REPORT:

Title: A Phase II Study of Campath® in Patients with B-Cell Chronic Lymphocytic Leukemia Who Have Received an Alkylating Agent and Failed Fludarabine

Introduction:

Enrollment on this single arm phase II study began on March 31, 1998 and was completed on July 31, 1998. The study was conducted at twenty-two centers in the United States and Europe. Ninety-four patients were enrolled. Ninety-three patients are included in the efficacy and safety analyses. One patient who withdrew immediately after enrollment is not included in these analyses. The patient did not receive any Campath-1h therapy and no follow-up information is available for this patient. The original BLA submission (submitted on December 23, 1999) included patient information collected up to the cut-off date of January 31, 1999. The four-month safety update (submitted on March 15, 2000) contains follow-up information through October 15, 1999 for all patients enrolled on Study 211. After completion of the original review and receipt of the completed review letter, the sponsor updated the study database with a cut-off date of July 26, 2000. A revised study report was included in the submission of August 18, 2000 along with updated safety and efficacy information.

Brief Summary of Study Protocol:

(See Appendix 211A for a complete summary)

The primary objective of this single arm study was to determine the response rate and the confidence intervals around the response rate in patients with CLL who had failed alkylating agents ($\leq$ five regimens) and were refractory to fludarabine. Fludarabine refractoriness was defined as failure to achieve an objective response (CR or PR using the 1996 NCI Working Criteria), relapse within six months of achieving an objective response, or disease progression on fludarabine therapy. Secondary objectives included evaluation of the safety profile and determination of the clinical benefit of CAMPATH-1H therapy in this patient population.

Enrollment was restricted to patients who had histological evidence and /or flow cytometry evidence of CD5, CD 19 positive lymphocytes, WBC $\geq$ 5 x 10^9/L, age 18 or older, and a WHO PS $\leq$ 2. Enrollees were also required to have:

- RAI Stage II disease with evidence of
  - progressive marrow failure as manifested by the development of progressive marrow failure (worsening anemia and / or thrombocytopenia); or,
  - autoimmune thrombocytopenia or anemia; or,
  - massive or progressive splenomegaly; or,
  - progressive lymphocytosis with a > 50% increase within six months prior to study entry; or,

- lymphocyte count > 100,000 / μl; or,
- B-symptoms; or
- RAI Stage III, and RAI Stage IV disease.
- Creatinine and liver functions must be within two times the upper limits of normal. There were no specified lower limits for hematological inclusion criteria.

Exclusion criteria included HIV positivity, active infection, history of anaphylaxis to mouse monoclonal antibodies, prior therapy with Campath-1h, prior BM transplant, prior use of investigational agents within three –six weeks prior to Campath-1h therapy, pregnancy, lactation, or an active second malignancy.

Patients were treated with two-hour intravenous infusions of Campath-1h with a starting dose of 3 mg daily. The dose was increased to 10 mg daily, then 30 mg three times per week as tolerance developed to the infusion-related side effects of fever, chills, tremors (rigor), hypotension or bronchospasm. All patients were premedicated with diphenhydramine 50 mg PO and acetaminophen PO. In addition merperidine 50 – 75 mg was used as indicated for management of chills / rigor. Hydrocortisone was used for rash, urticaria and other allergic reaction that could not be controlled with antihistamines and acetaminophen.

Dose modifications / reductions were as follows:

- If the study drug was discontinued for more that seven days, Campath-1h was resumed at a dose of 3 mg and the dose escalated.
- For first occurrence of platelets < 25,000/mm^3 or ANC < 250 /mm^3 Campath-1h was discontinued and resumed at the 30 mg dose level. For a second recurrence Campath-1h was discontinued and resumed at 10 mg. If neutropenia or thrombocytopenia occurred a third time, Campath-1h was permanently discontinued.
- For infectious complications study drug was discontinued until resolution of the infection.
- For patients with a platelet count < 25,000 / μl or ANC < 250 / μl at entry dose a ≥ 50% reduction in the blood count for > 48 hours was used the guideline for discontinuation of Campath-1h therapy.
- Hematopoietic growth factors could be used during this trial at the investigator's discretion.

Trimethoprim / sulfamethoxozole DS one tablet BID 3 times / week and famciclovir 250 mg PO BID were to be prescribed starting eight days after initiation of therapy and continued until two months after completion of therapy as prophylaxis for opportunistic infections. Blood product support and gamma globulin support was allowed.

Evaluations for efficacy were to be performed every four weeks. Response groups were defined based on the NCI Working Group Criteria. NCI Common Toxicity Criteria were employed to grade toxicity. Follow-up after completion of therapy was monthly with evaluation of disease status every two months for the first six months post therapy. Six months after completion of study drug therapy, follow-up was lengthened to every three months until death or alternative therapy. Toxicities were followed until resolution.

DESCRIPTION OF THE STUDY POPULATION

Demographics:

The demographic characteristics for the study population are reported in the following table (Table 211- 1).

Table 211-1: Study Demographics

Demographic Characteristic	N = 93
Median Age (Range) in years	66 (32 – 86)
Gender Male (%) Female (%)	 73 (78.5%) 20 (21.5%)
Race Caucasian Black	 86 (92.5%) 7 (7.5%)
Rai Stage: 0 I II III IV	 0 (0.0%) 5 (5.4%) 16 (17.2%) 18 (19.4%) 53 (57.0%)

The enrollment of male study participants as compared to female study participants is greater than expected based on epidemiological information with regard to the incidence of CLL by gender. Enrollment of black study participants as compared to white study participants is lower than expected based on epidemiological studies of the incidence of CLL by race. The median age for study participants is similar to the reported median age for the diagnosis of CLL in the general population. Seventy-two (76.4%) of the study participants had advanced disease (Stage III / IV).

Patient Eligibility for Study

The Case Report Forms / Patient summaries were reviewed to determine if patients enrolled on study met the eligibility criteria for participation. Questions about eligibility were discussed with the sponsor in several telecons during April and May 2000. The

sponsor provided additional information to support eligibility. Problems encountered during review of eligibility of study participants are discussed in the following sections.

Type of Disease

From review of the CRFs, study reports, peripheral blood and bone marrow flow cytometry (and in one case the medical history) it was determined that eighty–six (92.5%) study participants had B-CLL. Seven study participants appear to have disease other than typical B-CLL.

- Three patients (23-070, 16-081, and 18-082) had mantle cell lymphoma by flow cytometry as noted by the sponsor in the 211 study report.
- Two patients had B-Cell lymphoma. Patient 6-027 had splenic cell lymphoma on pathology review by [redacted] although clinical presentation was consistent with CLL. Patient 6-044 had a B-cell malignancy with a flow cytometry pattern consistent with CLL. Review of the medical records revealed that this patient, a Jamacian by nationality, originally presented at age 27 with a cecal and pericolic lymphoid mass of the small cleaved cell type mass considered as small cell lymphoma. This patient was entered on study with Stage IV disease to undergo debulking prior to bone marrow transplant.
- Two other patients (5-057, 26-073) are considered to have "atypical" CLL based on flow cytometry. Patient 057's peripheral lymphocyte flow data included 91% CD19+, 86% CD20+, 96%CD5+, and 73% FMC7+ cells. Patient 073's peripheral lymphocyte flow cytometry included 96% CD19+, 93% CD20+, 33% CD5+, 96% CD23+, and 41% FMC7+ lymphocytes. No bone marrow evaluations or other clinical history was provided for review for these two "atypical CLL" patients.

Stage of Disease

Review of RAI stage assessments was considered important since treatment is not recommended for early stage CLL patients unless one of the following conditions is present[1]:

- any one of the following disease related conditions -
  - 10% or greater weight loss within the previous six months, or
  - extreme fatigue defined as ECOG $\geq$ 2 or inability to perform work or usual activities, or
  - fevers $\geq$ 100.5° for $\geq$ 2 weeks without evidence of infection or
  - night sweats without evidence of infection;
- evidence of progressive marrow failure as manifested by development of, or worsening of anemia or thrombocytopenia; or,
- autoimmune anemia and / or thrombocytopenia poorly responsive to corticosteroid therapy; or,
- massive ($\geq$ 6 cm. below the RCM) or progressive splenomegaly; or,

[1] Bruce D. Cheson et al. Blood 87 (12): 4990 –4997, 1996.

- massive nodal clusters (≥ 10 cm in longest diameter) or progressive lymphadenopathy; or
- progressive lymphocytosis with an increase of > 50% over a two month period of an anticipated doubling time < 6 months.

After review of disease stage in the revised study report (August, 2000) differences in staging classification were noted for patient 6-044 who had stage IV lymphoma not CLL, this patient is included in FDA'S analyses as "Stage IV" for purposes of this review.

Seventy-one (76.3%) study subjects had stage III / IV disease and were clearly eligible for study. For earlier stage disease (0-II) eligibility was carefully reviewed to determine if the patient met both the 211 Study Eligibility criteria and the NCIWG group criteria for treatment of CLL.[2] The protocol allowed enrollment of early stage patients based solely on lymphocyte count > 100,000/ul without a requirement for rapid doubling of the lymphocyte count or other evidence of active disease. The protocol allowed enrollment of patients with symptom of "fatigue" without the requirement for a concomitant ECOG PS ≥ 2. Problems encountered on review include the failure to document information about the degree of fever and the severity of night sweats in the CRFs, the failure to collect information about successive lymphocyte counts to demonstrate doubling of the lymphocytosis. As a result, after the initial review, FDA queried the sponsor re: the stage and / or reason for treatment for twenty-four patients, about one quarter of the study population. Table 211-2 presents a listing of the problems / changes with regard to staging and reason for treatment for the 'Stage 0-II' patients enrolled on study based on 8/2000 updated information from the sponsor.

Table 211-2:Problems with Staging and Justification for Treatment, Study 211

Original RAI Stage	Patient Number	Justification for Treatment	Comments with Regard to Change in RAI Stage with Review of Resubmission
Stage 0	002-0026	Hemolytic Anemia (S/P Splenectomy); Progressive lymphocytosis	Changed to RAI Stage II by sponsor
	006-0044	Intra-abdominal lymphoma; Considered Stage IV by FDA	Stage 0 RAI per sponsor
	011-0052	Considered Stage II by FDA (S/P Splenectomy for disease); Justification for treatment ALC – 217,000/ul	Changed to RAI Stage II by sponsor
Stage I	005-0035	Fatigue, night sweats	No change in stage
	001-0041	Stage IV on initial FDA review	Changed to Stage IV by sponsor
	003-0049	Stage II w Progressive lymphocytosis (S/P splenectomy for CLL in [redacted]	Changed to RAI Stage II by sponsor
	013-0054	Night sweats; Progressive lymphocytosis	No change in RAI Stage
	004-0055	Night sweats	No change in RAI Stage
	006-0093	Night sweats, weight loss; progressive lymphocytosis	No change in RAI Stage
	006-0094	No symptoms;	No change in RAI Stage

[2] Ibid.

[3] Ibid.

Original RAI Stage	Patient Number	Justification for Treatment	Comments with Regard to Change in RAI Stage with Review of Resubmission
		Lymphocytosis > 100,000/ul Platelet count ~ 106,000/ul	
Stage II	007-0003	Night sweats, weight loss; hepatomegaly – 12 cm.	No change in stage
	002-0010	Progressive lymphocytosis	No change in stage
	012-0011	ALC 161,500/ul	No change in stage
	005-0013	Fatigue gr. 2 with P.S. = 1; ALC – 155,000/ul	No change in stage
	006-0025	Massive organomegaly	No change in stage
	007-0029	Massive organomegaly	No change in stage
	008-0036	Fever > 38° C	No change in stage
	011-0047	Night sweats	No change in stage
	011-0048	Anemia – 8.0 gm%; RAI Stage III on FDA review	Changed to Stage III by sponsor
	003-0049	Progressive lymphocytosis	No change in Stage
	020-0074	Neutropenia; Progressive lymphocytosis	No change in stage
	024-0076	Progressive lymphocytosis	No change in stage
	017-0084	Night sweats with P.S. = 2	No change in stage
	004-0092	Massive organomegaly; Night sweats	No change in stage
	002-0098	Fever; Pleural effusions; P.S. = 2	No change in stage

Three patients (001-0041, 011-0048, 006-0094) included in the above table were noted to have platelet counts at enrollment of 102,000/ul, 106,000/ul, and 105,000/ul respectively without evidence of autoimmune phenomenon. Patient 001-0041 was restaged as Stage IV after review of the medical records. Patient 011-0048 was noted on review to have anemia of 8 gm% and restaged as Rai Stage III. Three patients who meet 211 Protocol Eligibility Criteria did not meet the NCIWG criteria for treatment. No documentation of doubling of the lymphocyte count with six months prior to entry or 50% increase in lymphocytosis within two months of study entry was noted for the following patients:

- 011-0052 eligible due to absolute lymphocyte count (ALC) = 217,200/ul;
- 012-0011 eligible due to absolute lymphocyte count (ALC) = 161,500/ul; and
- 005-0013 eligible due to ALC 155,000/ul with Grade 2 fatigue but an ECOG performance status =1.

In summary over 90% of the patients were eligible for therapy using the NCIWG criteria.

Refractoriness to Fludarabine

The proposed indication for Campath-1h is the treatment of advanced B-CLL in patients with a history of prior alkylator therapy who are refractory to fludarabine. The inclusion criterion defines fludarabine refractory as:

(1) failure to have an objective response (PR or CR) to fludarabine in the first or subsequent courses of therapy;

(2) relapse within six months of an objective response to fludarabine; or,

(3) disease progression while on fludarabine therapy.

All patients enrolled on this study were exposed to fludarabine. After initial review of the CRFs and line listings, twelve patients were identified who did not appear to meet the protocol definition of fludarabine refractory, This information was relayed to the sponsor. The sponsor provided further information as to fludarabine refractoriness for these twelve patients as noted in Table 211-3.

Table 211-3: Listing of Patients Whose Refractoriness to Fludarabine Was Questioned

Patient No.	Reason Patient Considered Not Fludarabine Refractory. *Sponsor's Reply in Italics.*
001-0041	PR response with relapse after ten months. No further fludarabine therapy due to fludarabine-related thrombocytopenia according to study monitor. *Patient could not tolerate fludarabine due to severe thrombocytopenia.*
003-0049	PR response with relapse fifteen months after completion of therapy. Retreated for five months with a partial response lasting 11 months. *Sponsor was able to provide information to show that patient more than doubled ALC within four months of completion of second cycle of fludarabine*
006-0027	PR response of "unknown duration" with date of relapse crossed out twice in the chart and final date for relapse is given as six months. New treatment was not initiated until almost 12 months after last dose of fludarabine using therapy dates in CRF. *Sponsor provided information to prove that PR after fludarabine lasted only about 5 months.*
006-0094*	PR response lasting 25 months; no retreatment. *Patient developed ITP after four cycles of fludarabine (completed 2/96). ITP considered related to CLL but possibly due to fludarabine per investigator. The patient had a PR lasting 25 months. Sponsor states that the patient was not retreated with fludarabine due to the ITP.*
007-0008*	PR response with a duration of 25 months; No retreatment. *No definitive proof that patient was refractory to fludarabine.*
008-0036	PR lasting six months. No retreatment. *Sponsor states that patient relapsed 6 months and three days after last dose of fludarabine.*
011-0009*	PR after fludarabine therapy lasting twenty-four months; No retreatment with fludarabine *Sponsor provided information that showed progression with doubling of lymphocyte count while on fludarabine with an ALC ~ 23,700 /ul < 6 months after last dose of fludarabine.*
011-0053	PR of 6 months duration after 14 months of fludarabine therapy using the dates reported in the CRF. *According to study monitor patient had rising lymphocyte counts raising question as to validity of the PR response. The patient had a transfusion requirement during the period of partial response. Further information from the sponsor indicated that patient relapsed within one month of last dose of fludarabine and had two courses of radiation for hypersplenism associated with disease.*
016-0080	Treated with fludarabine x 3 with PR reported to last 18, 8, and 6 months respectively. Last fludarabine dose in 12/97. Did not start Campath-1h until 8/3/98 a period of eight months. *Sponsor states that PR lasted < 6 months after last treatment.*
016-0081	PR after fludarabine therapy. Duration of "8"months crossed out and "5 " entered in CRF. By treatment dates patient did not start new therapy until 10 months after fludarabine therapy ended. No further therapy with fludarabine. *Sponsor provided information to show that after last dose of fludarabine on 6/13/97 ALC rose to 99000/ul on 11/18/97.*
023-0064	PR after fludarabine therapy lasting eight months. No retreatment with fludarabine. Next therapy for CLL (Campath-1h) initiated 17 months later. *Sponsor provided data to show that after last dose of fludarabine on 2/23/97 the ALC reached 6435/ul on 4/24/97.*
023-0072	PR twice following fludarabine therapy lasting 11 months and 8 months respectively *Sponsor provided information to indicate that patient was probably not a PR after second course as ALC after completion (1/97) of fludarabine therapy was 23,700/ul (2/25/97) with an increase to 128,000/ul on 5/22/97.*

* Treated with cladribine also.

As stated by the sponsor in the study report, three patients (006-0094, 007-0008, and 011-0009) were treated with cladribine and were designated as fludarabine refractory since cladribine is "an analog of fludarabine". (Patient 006-0094 progressed on cladribine, patient 007-0008 had stable disease, and patient 011-0009 had a PR lasting five and one-

half months after cladribine therapy.) Patient 001-0041 was found to be intolerant but not refractory to fludarabine. Two patients (011-0080, 008-0036) progressed at six months and three days after completion of fludarabine. In summary six patients did not meet the protocol specified definition of fludarabine-refractoriness.

Other Chemotherapy Regimens

Five patients (006-0033, 006-0044, 007-0012, 011-0009, and 026-0085) had been treated with six prior chemotherapy regimes and one patient (026-0073) received seven different chemotherapy regimens prior to enrollment exceeding the mandatory limit of five previous therapies. In violation of a study exclusion criterion one patient (006-0056) enrolled on study was treated with oral cyclophosphamide within three weeks of initiation of study drug therapy. One patient (004-0092), enrolled on study approximately two months after completion of a two month course of fludarabine with a stable disease response, had a WBC at enrollment reported as 1760/ul (ANC = 990/ul, and ALC = 500/ul). Need for further therapy for this patient was based on the presence of the B-symptom of night sweats and splenomegaly (7 cms).

Summary (Eligibility)

Seven patients enrolled on this study did not have B-CLL. Three patients had mantle cell lymphoma (23-070, 16-081, and 18-082); one (6-027) had splenic lymphoma, one (6-044) small cell lymphoma, and two (5-057, 26-073) "atypical B-CLL" possibly PLL. Three patients (11-052, 12-011, 5-013) did not meet the NCIWG criteria for therapy although these patients met study eligibility criteria. Patient 006-0044 did not meet the Rai staging criteria, although the patient had Stage IV disease (lymphoma) per [redacted] classification. Six patients (6-094, 7-008, 11-049, 1-041, 11-080, 8-036) do not meet the strict protocol definition of fludarabine refractoriness. In addition six patients (6-036, 6-044, 7-012, 11-009, 26-085, 26-073) had more than the proscribed number of chemotherapy courses prior to enrollment. One patient (6-056) was enrolled within three weeks of completion of cyclophosphamide therapy.

EFFICACY EVALUATION:

Patient Disposition

Patient disposition (i.e. completion of therapy / discontinuation for other reasons) for this study is as follows:

- 59 (63.4%) patients discontinued study because Campath-1h therapy was completed.
  - Two patients completed therapy > 12 weeks (> 38 infusions) with one response of PR and one SD response.
  - Thirty-four patients completed therapy in > 8 but $\leq$ 12 weeks (27 –35 infusions) with two CR, fifteen PR, twelve SD, and three PD responses included in this group. Two patients were not evaluable for response.

- Sixteen patients completed therapy in > four but ≤ 8 weeks (15 – 26 infusions) with five PR, ten with SD, one PD assessments reported.
- Seven patients completed therapy in ≤ four weeks (12 – 14 infusions) with one PR, two with SD, and three PD assessments reported in this group.

- Five (5.4%) patients (2-098, 18-071, 17-084, 18-082, 19-075) were discontinued for disease progression after fourteen, twenty-two, twenty-three infusions, twenty-six infusion, and thirty-two infusions respectively.
- Three (3.2%) patients died while on study
  - One death (5-045) was reported as due to progression.
  - Two deaths (1-040, 19-077) were due to Pseudomonas sepsis, related to study drug therapy.
- Twenty (21.5%) patients discontinued due to drug-related adverse events.
  - Six patients (6-033, 6-093, 7-006, 7-043, 11-053, 26-060) were discontinued due to serious / life-threatening infection.
  - One patient (6-022) was discontinued due to fever, neutropenia and anemia.
  - Five patients (1-002, 3-095, 6-016, 6-038, 7-007, 26-060) were discontinued for pancytopenia / myelosuppression.
  - One patient (6-031) was discontinued for declining neutrophil count in the face of Aspergillosis pulmonary infection.
  - Two patients (12-011, 27-002) were discontinued due to thrombocytopenia.
  - Three patients were discontinued for infusion related adverse events. Patient 13-096 was discontinued for acute bronchospasm; patient 6-094 for fevers and rigors due to infusions; and, patient 7-051 for infusion related coughing and rigors which aggravated lumbosacral back pain.
  - One patient (017-0084) was discontinued for extreme lethargy due to disease progression.
- Six (6.5%) patients refused to continue therapy.
  - Two (6-017, 6-019) discontinued due to weakness and fatigue.
  - One (6-020) discontinued due to side effects of therapy including rigor, rash, itching, tongue numbness as well as myelosuppression (gr. 4 neutropenia and gr. 3 thrombocytopenia).
  - One (7-029) discontinued giving personal preference as a reason after developing E. coli sepsis on therapy.
  - Two patients (2-010, 6-025) discontinued because no disease improvement was noted.
- One patient (1.1%) was discontinued by the clinical investigator for "immunosuppression" due to decreases in lymphocyte count during therapy, the investigator having failed to appreciated that a decline in lymphocyte counts is expected with Campath-1h therapy.

With regard to long term disposition, as of February 15, 2000, fifty-one (54.8%) patients had died. Two more deaths reported after the February 15, 2000 cut-off. Two patients were lost to follow-up prior to the cut-off date, 5-0039 on [redacted] with 18.7 months survival and 26-0060 on [redacted] with 9.9 months survival. Of the forty-two survivors reported as of February 15, 2000, thirty-five participants had begun

alternative therapy including the two patients who died after the cut-off date. Seven study participants were reported to have received no further therapy after Campath-1h treatment as of February 15, 2000 although progressive disease is noted in six by the FDA. (Four of the seven have progressed by the sponsor's assessment.)

Response Rate, Time to Response, and Duration of Response

The criteria for objective response (complete or partial response) used to assess response by the agency are based on the 1996 NCI Working Group Criteria. Complete response was defined as:

- the absence of constitutional symptoms, organomegaly, and lymphadenopathy
- with Hgb > 11 gm/dl, ANC $\geq$ 1500/μl, and platelets > 100,000/μl, and
- bone marrow without evidence of disease for a period of at least two months.

Partial response was defined as the following for a period of at least two months:

- a $\geq$ 50% decrease in lymphocytes from baseline and a 50% decrease in lymphadenopathy, hepatomegaly and / or lymphadenopathy for two months with at least one of the following:
- ANC $\geq$ 1500/ul or a 50% increase from prestudy baseline value;
- platelets $\geq$ 100,000 /ul or a 50% increase from baseline;
- Hgb $\geq$ 11 gm/dl or a 50% increase from baseline; CR with persistent nodules on confirmatory bone marrow; or
- CR with persistent anemia or thrombocytopenia

Time to response is the period from first dose of Campath-1h until the time of maximal response. Duration of response was defined as the time from maximal response to first evidence of progression. Due to a difference in the criteria used to define progression in responding patients, a difference in the duration of response as calculated by the FDA and the sponsor. Table 211-4 allows the reader to compare the response rates, time to response and duration of response as determined by the agency and the sponsor.

Table 211- 4: Comparison of the Response Data

Parameter	FDA (N = 93)	Sponsor (N = 93)
Response Category		
CR	2 (2.2%)	2 (2.2%)
PR	29 (31.2%)	29 (31.2%)
SD	43 (46.2%)	50 (53.8%)
PD	12 (12.9%)	8 (8.6%)
NE	7 (7.5%)	4 (4.3%)
Objective Responders	31 (33.3%)	31 (33.3%)
[95% Confidence Intervals]	[23.4%, 42.6%]	[24%, 44%]
Median Time to Response	1.6 months	1.5 months
[95% Confidence Intervals]	[1.1, 1.8 months]	[1.0, 1.7 months]
Median Duration of Response	6.9 months	8.7 months
[95% Confidence Intervals]	[4.6, 8.4 months]	[5.9, 11.5 months]

With regard to the number of objective responders, agreement is noted between the sponsor and the agency with the following reservation. Patient, 7-029 has a questionable PR after review. Patient 7-029, who had Stage II CLL with lymphadenopathy and

hepatomegaly, entered the study with a Hgb 14.2 gm%, Platelet count 264,000/ul, ALC 199,000/ul, and ANC 8650/ul. The patient was treated from 5/28/98 – 6/25/98. ALC was 570/ul on 6/25/98. Patient was assessed a PR on 7/2/98. On July 10, 1998 ALC was reported as 6,700/ul but decreased to 1100/ul then slowly rose. Follow-up in 8/98 revealed the absence of lymphadenopathy, hepatomegaly with the ALC reported as 4,000/ul. On September 2, 1998 ALC was 4200/ul without adenopathy or organomegaly. A bone marrow done on 9/4/98 showed an increase in lymphocyte infiltration (71%) as compared to a bone marrow on 6/25/98 (49% lymphocyte infiltration). On November 13, 1998 recurrence of hepatomegaly and adenopathy was documented with an ALC = 4800/ul reported at that time.

Two of the five patients with Stage I disease were responders, seven of sixteen patients with Stage II disease were responders, eight of the eighteen patients with Stage III disease were responders, and fourteen of the fifty-three patients with Stage IV disease at entry. Six of the seven responders with response duration $\geq$ 12 months had stage III or stage IV disease.

Differences in response assessments were observed for seven patients. The reason for the difference in assessment or the difference in the date assessed for response is presented in Table 211-5.

Table 211-5: Differences in Response Assessments

Patient No.	FDA Resp	Spon. Resp	FDA Response Date	Sponsor Response Date	FDA Progression Date	Reason for Difference in Response Assessment
001-0002	PD	SD	--	--	5/22/98	New hepatomegaly reported 5/22/98 Worsening performance status
005-0039	PR	PR	7/27/98	7/29/98	-	7/27/98 – Lymph nodes decreased by 50% and platelet count 142,000/ul
005-0045	PD	SD	--	--	7/22/98	Died from progressive disease on this date; At week 4 had 15 cm^2 increase in nodal size; Hgb drop > 2 gm%, drop in platelet count = 39,000/ul to 8000/ul
006-0020	NE	SD	--	--	6/19/98	Received only nine Campath-1h infusions and had no follow-up labs after week three
006-0024	PR	PR	6/23/98	6/8/98	---	Campath-1h therapy did not begin until 5/26/98; 4 week assessment done at 6/23/98
006-0032	PR	PR	7/29/98	7/31/98	---	7/29/98 –Platelet count and ANC adequate for partial response
006-0034	PD	SD			6/24/98	New splenomegaly wk. 4 confirmed at wk. 8
006-0044	NE	SD			1/5/99	No assessment of abdominal disease during study; no assessment nodal status at week 4
007-0091	PR	PR	9/30/98	9/9/98	--	9/30/98 Earliest date that 50% regression in splenomegaly and adenopathy and ANC > 1500/ul consistently seen
011-0014	PR	PR	10/16/94	6/4/98	---	10/16/94 First date liver decreased 50% with spleen decreased 50% on 6/29/98; non-palpable on 10/16/98
011-0048	PR	PR	8/3/98	8/14/98	---	8/3/98 Lymph nodes decreased 50% and

Patient No.	FDA Resp	Spon. Resp	FDA Response Date	Sponsor Response Date	FDA Progression Date	Reason for Difference in Response Assessment
						platelet ct > 100,000/ul
016-0078	NE	SD			1/28/99	New nodal sites reported at week 4 and week 8 not included at baseline; Overall decrease in nodal size but unable to assess response accurately
017-0084	PD	SD			10/8/98	Increase in liver size by 50%
019-0065	PR	PR	8/3/98	9/6/98	--	8/3/98 Lymph nodes decreased 50%; no week 8 (8/31/98) measurements (assume no change); Bld counts adequate when platelets > 100,000/ul on 9/8/98
027-0067	PR	PR	11/2/98	8/5/98	---	9/1/98 Two new nodes (each 2 x 2 cm); not present at wk 12 (10/6/98) assessment; Counts not adequate for PR until 11/2/98 when Hgb 11.7 gm%

The slight difference in the median time to response of < 0.1 month is noted when the FDA's and the sponsor's analyses are compared despite differences in the assessed date of response. A 2.4 month difference is observed in a comparison of the sponsor's and the agency's estimate of the median duration of response. The longer duration of response reported by the sponsor is due to the difference in the criteria used to judge progression after response. Differences in progression dates are present in the following section.

Progression Free Survival (Time to Progression)

Time to progression in defined by the sponsor as the date from the initial administration of Campath-1h to the first date of objective measurement of progression, to alternative therapy, or to death. This definition is considered to be the definition for "progression free or disease free survival" by the agency. In the original protocol dated January 27, 1998, time to progression was defined as time from initial treatment until first objective documentation of progressive disease. As noted in the introduction, the reviewer has continued to apply the definition stated in the amended study protocol and the algorithm based on this definition included in the original BLA submission. These definitions are based on the 1996 NCI CLL working group criteria used to define disease progression either a priori or after response. Table 211-6 provides information about median time to progression as determined by the sponsor and the agency.

Table 211-6: Time to Progression (Progression Free Survival) for All Patients and for Responders

Parameter	FDA (N = 93)	Sponsor (N = 93)
No. Progressed	92 (98.9%)	90 (96.8%)
No. Without Progression	1 (1.1%)	3 (3.2%)
Median Time to Progression (95% CI)	4.0 months (3.2, 4.7 months)	4.7 months (3.7, 5.8 months)
Objective Responders	**N = 31**	**N = 31**
No. Responders Progressed	30 (96.9%)	28 (90.3%)
No. Responders	1 (3.1%)	3 (9.7%)
Median Time to Progression (95% CI)	8.8 months (6.2, 10.2 months)	9.5 months (7.0, 13.2 months)

For the entire group a difference of less than one month in time to progression is noted between the sponsor's and the agency's values are compared. The median time to progression (TTP) for responders is slightly more that twice that of the entire study population as determined by the agency. The difference in time to progression for responders as determined by the agency and by the sponsor is about 0.7 months. Table 211-7 provides a listing of those patients where a difference from the sponsor was noted in the date of progression or in the assessment of disease progression. The reason for the difference in FDA assessment is also included. Partial responders are indicated underneath the patient number.

Table 211-7: Differences in Progression Information for Study 211

Pt. No.	FDA Date of Progression	Censor	Sponsor Date of Progression	Censor	Reason for Different Date
001-0002	5/22/98	0	7/1/98	0	5/22/99 New hepatomegaly (2 cm) on that date with worsening performance status; No further follow-up measurements until death
001-0041 (PR)	4/23/99	0	7/2/99	0	1/5/99 new node –2.25 cm^2; ALC – 700/ul 4/23/99 – two new nodes 5.0 cm^2; no ALC Investigator reports progression
002-0010	9/24/98	0	10/29/98	0	9/24/98 ALC – 5900/ul, plt. 47,000/ul (new thrombocytopenia) 10/29/98 ALC-10,700/ul
002-0026	8/17/98	0	10/18/99	0	8/17/98 – ALC 5400/ul 10/18/98 – New node 9.0 cm^2; ALC 5900/ul
002-0098	8/17/98	0	9/25/98	0	8/17/98-new mediastinal nodes (size not given) 9/21/98 Investigator assesses PD
003-0049 (PR)	11/9/98	0	1/12/99	0	11/9/98 – ALC 6800/ul 1/12/99 – ALC 24,000/ul
003-0095 (PR)	2/14/00	0	2/15/00	1	ALC-5800/ul; night sweats and thrombocytopenia since ——— (Medical record) 4/17/00 Sponsor date of progression
005-0013 (PR)	1/12/99	0	4/15/99	0	1/19/99 ALC – 10,100/ul 1/17/99 ALC – 10,900/ul 3/4/99 ALC – 12,900/ul 4/15/99 ALC – 10,800/ul
005-0018	9/10/98	0	10/8/98	0	9/10/98 ALC-6900/ul 10/8/98 ALC – 14,300/ul
005-0035 (PR)	11/30/98	0	1/10/00	0	11/30/98 ALC - 5800/ul 1/6/99 ALC - 5500/ul 2/10/99 ALC - 7200/ul 1/10/00 massive adenopathy; New hepatomegaly 12 cm (No F/U info between 2/10/99 and 1/10/00)
005-0039 (PR)	12/3/98	0	1/7/99	0	12/3/98 ALC 6200/ul 1/7/99 ALC 14,100/ul
005-0045	6/17/98	0	7/22/98	0	6/17/98 ALC reported as 120/ul on 6/15/98; on 6/17/98 ALC 323,800/ul; Pt. continued on Campath-1h. Had disease progression during entire course of therapy with worsening thrombocytopenia and Hgb drop from 9.0 gm% to 7.6 gms % despite transfusion until death on

Pt. No.	FDA Date of Progression	Censor	Sponsor Date of Progression	Censor	Reason for Different Date
005-0046	8/31/98	0	11/5/98	0	Baseline lymph node area – 35.9 cm^2 Week 4 – 9.08 cm^2 Week 8 – 3.4 cm^2 Week 12 (8/31/98)– 10.0 cm^2;(one node 2 X 3 cm); no further disease measurements 10/9/98 ALC 5700/ul 11/5/98 ALC 10,200/ul
006-0019	6/8/98	0	9/8/98	0	6/8/98 –New Rt. and Lt., Cervical nodes 1 x 1 cm ; Next measurement – 9/9/98 Rt. Cervical node –3 x 2 cm; 7/13/98 ALC – 6,600/ul; 8/3/98 ALC – 9200/ul; 9/8/98 ALC – 15,000/ul; new splenomegaly 6 cm
006-0023 (PR)	3/9/99	0	7/15/99	0	1/11/99 – new neck nodes reported; (no prior record of any adenopathy); nodes not measured; no further disease measurements after 1/11/99 1/11/99 ALC – 2000/ul 3/9/99 ALC – 7,100/ul 3/26/99 ALC – 6,200/ul 7/15/99 ALC – 11,400/ul
006-0025	8/25/98	0	9/28/98	0	At entry spleen 8 cm. At week 4 (6/15/98) spleen not palpable At week 8 (8/25/98) spleen 2 cm.; ALC – 4700/ul 11/4/98 spleen 3 cm (next measurement) 9/28/98 ALC-21,700/ul
006-0030	6/25/98	0	10/6/98	0	Increase in lt. neck node from 1 x 1 cm to 2 x 3 cm.; Node not measured from June 25 until Oct. 6
006-0033	9/7/98	0	9/18/98	0	9/7/99 Site of progression unclear
006-0034	6/24/98	0	9/9/98	0	6/24/98 - New splenomegaly, not measured which persisted at wk 8; site of progression on 9/9/98 unclear
006-0093	8/30/98	0	10/10/98	0	8/30/98 Transformation to PLL Death due to progression of PLL
006-0094	11/17/98	0	1/15/99	0	11/17/98 – ALC 5200/ul 1/15/99 – ALC 12,500/ul; recurrence of cervical nodes (2 x 1 cm. each)
007-0012	6/19/98	0	7/9/98	0	6/19/98 Independent reviewer date of progression; ALC – 5300/ul 6/29/98 New Rt. axillary node 1.5 x 1.5 cm.; 7/9/98 Investigator date of progression
007-0015	9/14/98	0	12/1/98	0	8/5/98 –reappearance of two nodes 1 x1 cm each; next node follow-up 12/1/98 9/14/98 ALC - 5000/ul 10/14/98 ALC - 9100/ul 11/30/98 ALC - 9200/ul 12/1/98 Reappearance of hepatomegaly 4 cm.
007-0021	6/16/98	0	9/1/98	0	6/16/98 – Two new nodes 2 x 1 cm and 2 x 2 cm.
007-0051	7/8/98	0	7/11/98	0	7/8/98 ALC – 5400/ul 7/11/98 ALC – 134,000/ul
007-0058	8/17/98	0	10/1/98	0	8/17/98 New hepatomegaly 2 cm.; increased to 4 cm on 10/1/98
008-0036	6/24/98	0	8/4/98	0	6/24/98 Investigator date of progression
011-0042 (CR)	11/17/99	0	2/15/00	1	11/17/99 ALC 6500/ul 4/27/00 Sponsor date

Pt. No.	FDA Date of Progression	Censor	Sponsor Date of Progression	Censor	Reason for Different Date
011-0050 (PR)	8/16/99	0	11/22/99	0	8/16/99 ALC - 5700/ul 11/22/99 ALC -11,900/ul
011-0052	11/23/98	0	2/23/99	0	9/28/98 ALC 5100/ul; not persistent 11/23/98 Two new nodes 1.5 cm^2; .25 cm^2 12/24/98 New node 4 cm^2 in area; (no further measurements nodes, liver, or spleen) 2/23/99 Investigator report of progression
012-0011 (PR)	9/9/98	0	12/10/98	0	9/9/98 ALC -6,700/ul 10/9/98 ALC - 9300/ul 11/3/98 ALC - 9600/ul 12/10/98 ALC - 11,900/ul
016-0079	1/11/99	0	1/11/99	0	10/7/98 Increase in lymph node area which did not persist; 1/11/99 Spleen size increased 12 cm; ALC- 7900/ul
016-0081	11/10/98	0	1/14/99	0	9/1/98 Two new lymph node areas 1 x 1 cm and 2 x 1cm which did not persist; 11/10/98 Transformation to more aggressive histology on biopsy 1/14/99 Recurrence of splenomegaly 2 cm. 5/20/99 ALC - 4000/ul; No further blood counts. Death due to CVA
017-0084	8/28/98	0	10/8/98	0	8/28/98 Increase in liver size from 2 to 3 cm; no further measurements; Assessed as PD Died due to PTE
018-0082	10/14/98	0	11/19/98	0	10/14/98 Date investigator assigned progression; Transformation to more aggressive histology
019-0075	9/11/99	0	9/21/00	0	9/11/99 Investigator date of progression
026-0060	11/11/98	0	1/14/99	0	11/11/98 – ALC 8400/ul; increase in nodal area; no follow-up of hepatosplenomegaly after week 4 until 3/99 1/14/99 ALC 16,2000/ul
027-0067 (PR)	3/31/99	0	4/27/99	0	3/31/99 Decrease in platelet ct. from 32,000/ul to 16,000/ul with ALC increase to 2400/ul 4/27/99 –Plt. Ct. 13,000/ul with ALC 3600/ul

Time to Treatment Failure

Treatment failure is defined by the agency as failure of study drug therapy due to disease progression, death, institution of alternative therapy, or discontinuation due to an adverse event or other reasons. Using the agency's definition time to treatment failure is calculated from the first day of therapy until the date of progression, death, discontinuation for adverse event or other reasons, or the initiation of alternative therapy. The definition of time to treatment failure, utilized by the sponsor, is slightly different. Time to treatment failure is defined as the date from the initial administration of Campath-1h to the date of the last dose for patients who failed to complete therapy or the time of disease progression or death for patients who completed therapy. Thirty-eight (40.9%) patients discontinued Campath-1h therapy for reasons other than completion of course of therapy. Reasons for discontinuations included: progression on therapy in five (5.4%) patients; death for three (3.2%) patients; adverse events in eighteen (19.3%)

patients; refusal to continue in six (6.5%) patients, and physician judgement of immunosuppression in one patient (1.1%). For this reason the time to treatment failure is shorter than the time to progression by about one month. Table 211-8 provides information on treatment failure.

Table 211-8: Treatment Failure Information

Parameter	FDA	Sponsor
No. of Treatment Failures **No. Censored**	92 (98.9%) 1 (1.1%)	91 (97.8%) 2 (2.2%)
Median Time to Treatment Failure **[95% Confidence Intervals]**	3.0 months [2.4, 4.3 months]	3.4 months [2.5, 2.7 months]
No. Responder Treatment Failures **No. Responders**	30 (96.8%) 1 (3.3%)	29 (93.5%) 2 (6.5%)
Median Time to TTF for Responders **[95% Confidence Intervals]**	8.1 months [5.9, 9.5 months]	8.9 months [6.2, 112.6 months]

Survival

Survival is measured in this study from the date of initiation of study drug therapy until the date of death. Median survival for this study is 15.9 months [95% CI: 11.8, + months] with forty-two (45.2%) patients alive (censored) for survival as of the cut-off date.

Summary of Efficacy Parameters

On review an objective response (CR + PR) is confirmed in 31 (33.3%) of the ninety-three study participants with a median duration of response of about 6.9 months (95% CI: 4.6, 8.3 months) with all but one patient considered to have progressed at the time of this review. Progression-free survival of 4.0 months [95% CI: 3.2, 4.7 months] is reported with ninety-two (98.9%) patients considered to have progressed. Median time to treatment failure is 3.0 months (95% CI: 2.4, 4.3 months) with ninety-two patients considered to have failed treatment as of February 15, 2000. Median survival is estimated at 15.9 months [95% CI: 11.8, + months] with forty-two (45.2%) patients alive as of February 15, 2000.

SAFETY INFORMATION

Drug Delivery

All ninety-three patients enrolled on this study received at least one dose of Campath-1h. Ninety-two (98.9%) reached the target dose of Campath-1h 30 mg. Eighty-four (90.3%) patients reached the 30 mg dose level within five days, four (4.3%) with ten days, while four (4.3%) patients required more than 10 days to reach the target 30 mg dose level. Two patients were not treated with an initial Campath-1h dose of 3-mg dose as directed by the protocol treatment plan. Patient 26-0060 was initially infused at Campath-1h 10 mg, followed by a second infusion of Campath-1h 10 mg, with dose escalation to 30 mg without any report of adverse events related to the increased initial dose. Patient 7-0058 was infused day 1 with Campath-1h 30 mg and developed gr. 3 vomiting, grade 4 dyspnea, and grade 4 nervousness requiring management with antihistamines, steroids,

epinephrine, and albuterol, and merperidine but not requiring hospitalization. On day 2 Campath-1h 3 mg was infused without incident. Subsequent dose escalation as per protocol occurred without further acute allergic reactions.

One patient (013-0028) was treated with Campath-1h at 30 mg for five doses, however the dose was permanently reduced to between 10 - 20 mg. The investigator reported the lower dose was all this patient could tolerate. This patient is reported to have developed gr. 1 abdominal pain, gr. 3 urticaria, fever, and neutropenia grade 3 / 4 requiring Neupogen while on therapy. Interestingly review of the medications in the CRF indicate that this patient received only acetaminophen and diphenhydramine as premedication. No systemic steroid therapy were administered for infusion related toxicities. Prior to and during study, patient was treated with Danazol possibly for the management of thrombocytopenia related to CLL, but no other steroid usage is reported.

Two patients received a portion of their Campath-1h therapy subcutaneously. Patient 18-0061 received 23 of 42 doses (after week 6) subcutaneously and patient 27-0062 received 22 of 32 doses subcutaneously. Information about the comparability of subcutaneous and intravenous Campath-1h from an efficacy, safety, or pharmacokinetic perspective is not available. The protocol had no provisions for subcutaneous therapy.

Treatment Delays

Two patients had "prolonged treatment delays" of approximately 3.5 months. Treatment in patient 11-0009 was discontinued after four weeks with grade 2 / 3 fever and recurrence of pleural effusion, with cytology positive for CLL cells. This patient resumed therapy 3.5 months later and had twelve doses of therapy, three at the 3mg dose level and nine at the 10 mg dose level when therapy was discontinued so that the patient could [redacted] The agency assessed this patient as progressive disease after the first course of therapy (an assessment the sponsor agreed with in the August resubmission).

A second patient 11-052 received Campath-1h therapy from June 6, 1998 until August 6, 1998. Therapy was interrupted for development of a grade 3 fever and chills. The CRF contains no safety report for this patient. Absolute lymphocyte count was reported as 300/ul on August 3, 1998. On September 28, 1998 the ALC was 5130/ul. The patient is considered to have progressed on this date by the reviewer. When therapy was instituted a second time on November 23, 1998, the patient had developed new adenopathy. Resumption of therapy in this patient is considered as second course of treatment for relapsed disease. These two participants are excluded from the following analysis of dose delays.

Information about the reason for missed doses was not captured on the treatment record in the CRF, nor was the event always captured in the adverse event reporting section of the case report form. Review of the information provided by the sponsor in the August resubmission indicated that twenty (21.5%) study participants missed one or more single doses (treatment delay < 5 days) of therapy with a total of thirty-one missed doses. Thirty (32.3%) study participants were reported to have thirty-seven dose delays greater than

seven days including seven patients who also missed single doses at another time during therapy. Table 211-9 summarized the reasons provided by the sponsor for the missed therapy.

Table 211- 9: Dose Delays during Study

Reason	Single Dose Omissions (< 5 Days) N = 31	Treatment Delays ≥ Seven Days N = 37
Hematologic	(15)	(20)
Anemia	2	-
Neutropenia	4	12
Thrombocytopenia	7	2
Anemia, Neutropenia	-	2
Anemia, Thrombocytopenia	-	1
Neutropenia, Thrombocytopenia	1	2
Pancytopenia	1	1
Infection or Suspected Infection	(1)	(13)
Fever	1	3
Febrile Neutropenia	-	2
Infection with Neutropenia	-	2
Infection, NOS	-	3
Bacterial Infection	-	2
Fungal Infection	-	1
Viral Infection	-	1
Other (Disease / Treatment Related)	(6)	(0)
Fatigue	2	-
Itching	1	-
Hemoptysis	1	-
Worsening Performance Status	1	-
Pleural Effusion	1	-
Other	(9)	(3)
Acute M. I.	-	1
Awaiting Response Assessment	-	2
Holiday	3	-
Unknown	6	-

In the twenty-four instances where hematological toxicity was reported as the reason for the dose delay (including the two instances of febrile neutropenia and two instances of infection with neutropenia) the average delay between doses was 16.8 days (range: 7 – 53 days) with a ≥ 14 day delay between doses reported in nine instances. For the ten instances of fever or infection without reported concomitant hematological toxicity, the average delay between doses was 22.5 days (range: 3 – 33 days) with delay between doses ≥ 14 days in seven instances.

Deaths on Study, Within Thirty Days of Study Therapy, and Late Deaths

Nine patients (9.7%) died on study or within 30 days of the last dose of Campath-1h therapy. A short description of the clinical course prior to death and the relationship to Campath-1h therapy are presented here:

- **Patient 001-0040** with Stage III disease died on study due to Pseudomonas sepsis with grade 4 granulocytopenia. At initiation of study drug therapy hematological profile included: Hgb 10.1 gm%, Plt. Ct. 99,000/ul, and ANC 10,100/ul, and ALC 29,780/ul. Campath-1h therapy was administered between July 1 and August 28, 1998. After the twelfth Campath-1h infusion the patient was for hospitalization for Gr. 4 dyspnea, hypovolemia with Gr. 3 hypotension, Gr. 2 anemia, Gr. 3 thrombocytopenia, and Gr. 4 neutropenia and treated with fluids, RBC transfusions, and

metaproterenol. The patient improved and was discharged the next day. Patient received four additional infusions of Campath-1h therapy from July 29 to August 5 before therapy was held for fourteen days secondary to gr. 4 neutropenia and thrombocytopenia. Two additional doses of Campath-1h were administered on August 19 and August 21. Patient was hospitalized on ~~~ with Pseudomonas pneumonia and died on ~~~ CBC on ~~~ included Hgb 9.1 gm%, Plt. Ct. 67,000/ul, ANC 300/ul, and ALC 100/ul. Death is considered due to Campath-1h therapy. ~~~

- **Patient 005-0045** with Stage IV disease began Campath-1h therapy on June 15, 1998 with Hgb 7.7 gm%, platelet count 26,000/ul, ANC 4800/ul, and ALC 438,000/ul. After the third infusion ~~~ worsening thrombocytopenia (platelet count 11,000/ul) was noted and the patient was hospitalized for treatment with prednisone and a five-day infusion of IV immunoglobulins for autoimmune thrombocytopenia considered secondary to disease or possibly related to Campath-1h therapy. Campath-1h infusions were continued during hospitalization. Thrombocytopenia improved with platelet count reported as 24,000/ul on ~~~ During therapy three units of RBCs were administered (one on June 24 and two on July 10). The last Campath-1h infusion was administered on July 17, 1998 with no improvement reported in adenopathy or splenomegaly (13 cm) although a decrease from the entry ALC of 438,000/ul to 50,000/ul was reported. On July 20 platelet count was 8000/ul with ANC 1100/ul and ALC 45,500/ul. On ~~~ patient was hospitalized with gr. 4 hypoglycemia, gr. 1 fever, and gr. 4 pain in a left axillary node and expired the same day. No blood counts are available. The investigator reported progressive disease based on the increased size in the painful Lt. axillary node. The cause of death is not clear to the reviewer and question is raised whether infection played a role in this patient's demise.
- **Patient 006-0016** with Stage IV disease died on study due to Cryptococcus neoformans pneumonia with Gr. 4 neutropenia. Death is considered related to Campath-1h therapy. At entry into study CBC is as follows: Hgb – 11.0 gm%, Platelets – 64,000/ul, ANC – 2760/ul and ALC – 1670/ul. This patient was first hospitalized on ~~~ after the fourth Campath-1h infusion with Gr. 3 hypotension, Gr. 4 neutropenia (ANC - 100/ul), Gr. 4 thrombocytopenia (Plt. Count - 4000/ul), and gr. 1 anemia (Hgb - 9.0 gm%). With antibiotics, three units RBCs, and one SD platelet transfusion patient recovered and was discharged on the fifth hospital day ~~~ The patient received eight additional infusions of Campath-1h. On June 19 therapy was discontinues for eleven days for Gr. 4 granulocytopenia and gr. 2 / 3 anemia. Campath-1h therapy was resumed on July 1, 1998 and five additional infusions were administered before therapy was discontinued permanently on July 10, 1998. On ~~~ the patient presented with Gr. 4 neutropenia (ANC = 475/ul), bilateral pulmonary infiltrates considered as gr. 4 pneumonia, gr. 2 fever, and grade 3 dyspnea. Sputum cultures and bronchial washing were positive for Cryptococcus. Absolute lymphocyte count was 0. Patient died from cardiac arrest on ~~~
- **Patient 006-0038** with Stage IV disease died within thirty days of Campath-1h therapy due to rhinocerebral Mucormycosis with pancytopenia. Death is considered secondary to Campath-1h therapy. On June 2, 1998 pretherapy CBC included: Hgb 6.9 gm%, Platelets 55,000/ul, ANC 4280/ul and ALC 7590/ul. Thirteen infusions of Campath-1h therapy were administered between ~~~ and ~~~ Therapy was interrupted between June 5 and June 10 for pancytopenia and June 11 to June 17 for worsening thrombocytopenia and neutropenia. Therapy was permanently discontinued after ~~~ due to pancytopenia. CBC from July 8 included Hgb 9.3 gm%, Platelet count 35,000/ul; ANC 300/ul and ALC 100/ul. On ~~~ patient was hospitalized with left humoral and left femoral fractures sustained in a fall. On ~~~ while hospitalized the patient was noted to be less responsive with loss of vision and bilateral ptosis. MRI revealed sinus involvement with Mucormycosis with probable cerebral invasion. The patient became unresponsive, hypoxic, hypotensive and died on ~~~. Last CBC reported prior to death included Hgb – 11.5 gm% (transfused), Platelets –93,000/ul, ANC – 1800/ul, and ALC 300/ul.
- **Patient 002-0098** with Stage II disease died within thirty days of the last dose of Campath-1h due to progressive disease. This patient received twenty-three infusions of Campath-1h therapy between July 31, 1998 and ~~~. On ~~~ the patient was hospitalized for Gr. 2 anemia and Gr. 3 fatigue secondary to bleeding gastric ulceration due to small cell lymphoma. Patient responded to three units packed RBCs and hydration and was discharged in ~~~ Campath-1h therapy was continued until ~~~ when disease progression was noted.

Alternative therapy initiated at that time was unsuccessful and patient died thirty days after the last dose of Campath-1h from progressive disease.

- **Patient 007-0001** with Stage IV disease (Hgb 8.0 gm%, ANC 1700/ul, ALC 47,000/ul, Plt. Ct.26,000/ul on study entry) died thirty days after the last dose of Campath-1h therapy. Therapy was initiated on April 1, 1998 and continued until ——— After the third infusion on patient was hospitalized for twenty-four hours for management of gr. 2 fluid overload and gr. 3 anemia (Hgb - 7.5 gm%). Patient was treated with furosemide and two units PRBCs. Campath-1h therapy was resumed. After the thirteenth Campath-1h infusion on ——— the patient was hospitalized for management of gr. 2 fever with gr. 3 / 4 neutropenia (ANC 500/ul). Cultures and chest x-ray were negative. Patient was treated with antibiotics, transfused two units RBCs and one unit platelets then discharged with ANC 500/ul on ——— No further Campath-1h was administered. Patient continued to have grade 4 neutropenia and grade 3 / 4 thrombocytopenia. On ——— the patient was admit with hypotension, gr. 4 fever, intermittent dizziness, nausea, vomiting, ongoing cough, and gr. 4 neutropenia (ANC 400/ul). A rise in ALC from 0/ul on May 7 to ALC 37,700/ul on May 18 is reported. Blood cultures were positive for Pseudomonas.. Patient expired on ——— due to sepsis with disease progression.
- **Patient 017-0084** with Stage II disease, whose course of therapy was complicated by Campath-1h induced autoimmune hemolytic anemia, died ——— after the last infusion of Campath-1h therapy on ——— secondary to pulmonary emboli. At autopsy a left calf DVT, massive abdominal lymphadenopathy, and bilateral pulmonary emboli were reported. CBC prior to study included a Hgb 13.1 gm%, Plt Ct. 311,000/ul, ANC 480/ul with ALC 19,520/ul. Patient received twenty-two infusions of Campath-1h therapy between August 3 and ——— with a disease progression reported at the conclusion of therapy. No serious adverse events were reported during Campath-1h therapy, however review of the CRF indicated that patient was treated for Staph. coagulase negative sepsis gr. 2 from ——— as well as gr. 2 mucocutaneous candidiasis. Last reported CBC on ——— included a Hgb 10.7 gm%. Plt. Ct. 161,000/ul, ANC 400/ul and ALC 1400/ul (increased from 0/ul on September 16,1998).
- **Patient 018-0071** with Stage IV disease (grade 3 thrombocytopenia with platelet count 17,000/ul at entry) died ——— after last Campath-1h infusion. Patient received twenty-six infusions of Campath-1h between July 16 and ——— Between July 27 and August 12 patient had rectal bleeding, melena, and epistaxis due to worsening of grade 4 thrombocytopenia (platelet count 2000/ul) due to ITP. Platelet count rose to 176,000/ul with intravenous gamma globulin then continued to fall until at discontinuation of Campath-1h therapy platelet count was 27,000/ul. Patient was noted to have progressive disease (increased adenopathy) on September 9, 1998 and begun on alternative therapy with mitoxantrone, etoposide, cyclophosphamide, vincristine, and bleomycin. On September 20, 1998 patient experienced a massive GI hemorrhage (gr. 4) complicated by gr. 4 thrombocytopenia and grade 4 neutropenia. Patient continued a downhill course and expired on ——— Death appears related to chemotherapy given after discontinuation of Campath-1h.
- **Patient 019-0077** with Stage III B-CLL died ——— after the last dose on Campath-1h therapy from Pseudomonas sepsis. Death is considered related to Campath-1h therapy. Campath-1h therapy was initiated on August 3, 1998 with the following hematologic values: Hgb –10.3 gm%; Platelet count – 209,000/ul, ANC – 2200/ul, and ALC –106,000/ul. The patient received twenty-three Campath-1h infusions with the last dose infused on ——— During therapy grade 2 Hemophilus influenzae bronchitis was reported. Response at discontinuation of therapy was reported as stable disease. On ——— patient was hospitalized for treatment of a gr. 4 Pseudomonas pneumonia and gr. 1 Moniliasis. ANC was reported as 6700/ul with ALC 100/ul. CD3+/CD4+ count dropped from 2179/ul at entry to 0/ul at time of onset of pneumonia. The patient developed respiratory failure with acute pulmonary edema and expired on ———

Of the nine deaths that occurred on study or within thirty days of study drug therapy, four deaths are considered to be secondary to Campath-1h therapy, four are due to disease progression, and in one case, the cause is not clear.

Nine deaths, that occurred at greater than 30 days but less than 180 days after discontinuation of Campath-1h therapy are reviewed here since these deaths, in the opinion of the FDA, are very likely related to study drug. Six other deaths are not discussed here as disease progression was clearly documented prior to death and any infectious complications reported prior to death were not related to previous Campath-1h therapy.

- **Patient 001-0002** with Stage IV B-CLL entered the study with a Hgb – 10.2 gm%, Plt. Ct. – 77,000/ul, ANC –1200/ul, and ALC –1680/ul. Patient received nine Campath-1h infusions between April 27 and May 13, 1998. Patient was removed from study due to worsening pancytopenia. On May 15,1998 Hgb was reported as 10 gm%, Plt. Ct. – 61,100/ul and ANC-300/ul. A bone marrow biopsy performed on ——— is reported as hypocellular with no neoplastic cells. No follow-up CBCs after June 2 are reported. Patient was enrolled in hospice and died on ——— from "inanition". There is no documentation of progression or of improvement in hematological parameters prior to death so this death is considered related to Campath-1h. ———
- **Patient 005-0046** with Stage IV B-CLL received thirty-six Campath-1h infusions between June 15 until September 4, 1998. Patient entered the study with Grade 3 neutropenia and during therapy had several episodes of grade 4 neutropenia. Disease progression is noted at the time therapy was discontinued with a 100% increase in lymph node area was reported. (Independent response panel assessment of the patient's response was stable disease.) Patient developed disseminated Aspergillosis involving the lungs and brain diagnosed on January 8 and expired on ——— from this infection. CD3+/CD4+ count was reported as 297/ul at study entry, fell to 0/ul during study, and was recovered to 302/ul at the time the Apergillosis infection was diagnosed. Immune suppression secondary to Campath-1h therapy is considered to have played a role in the development of this fatal infection although disease progression was documented at the time of death.
- **Patient 006-0017** entered on study with Stage III disease and the following hematological values: Hgb – 9.1 gm%; Plt. Ct. – 114,000/ul; ANC – 4,240/ul; and ALC –13,270/ul. The patient received eleven infusions of Campath-1h between May 18 and June 10, 1998. The patient was hospitalized on ——— with gr. 2 anorexia, gr. 2 vomiting, gr. 2 weight loss, gr. 3 dehydration, grade 1 anemia and gr. 4 granulocytopenia (ANC – 300/ul) and probable infection. The patient was treated with fluids, antibiotics, G-CSF, and four units PRBCs. Neutrophil counts rose to 1700/ul and G-CSF was discontinued on ——— Patient was discharged on ——— and refused further therapy due to weakness, fatigue, insomnia and fever. Patient was enrolled in hospice. On July 8, 1998 hematological values include Hgb 10 gm%, Plt. Ct.109,000/ul, ANC 160/ul, and ALC 790/ul. On August 4, 1998 Hgb was reported as 10.7 gm%, Plt. Ct. 120,000/ul, ANC 300/ul and ALC 1700/ul. Patient expired on ——— reportedly due to disease progression however last disease measurements on this patient on June 12, 1998 report complete resolution of adenopathy in three of four sites and an 85% reduction in the fourth site of involvement. No organomegaly was reported during study. No follow-up bone marrow was performed after the initial dry tap and the neutropenia and fever may due to Campath-1h therapy rather than disease progression.
- **Patient 006-0034** entered study with Stage IV CLL and received twenty-one Campath-1h infusions between June 1 and July 22, 1998. At initiation of therapy Hgb was reported as 9.2 gm%, Plt. Ct. 15,000/ul; ANC 700/ul; and ALC 8800/ul. Bone marrow at entry was reported as hypocellular with > 90% infiltration. During the study patient required two units PRBCs (no prestudy transfusion requirement), was continued on erythropoietin, and required G-CSF from ——— 2 and from ——— for grade 4 neutropenia. A gr. 3 herpetic oral lesion was reported during therapy, but no other serious adverse events were noted. Bone marrow done on ——— is reported as hypocellular with no evidence of neoplastic infiltration. On August 10 hematological values included Hgb 11.4 gm%, Plt. Count 10,000/ul, ANC 100/ul, and ALC 800/ul. Independent review board considered response as stable disease. PCP prophylaxis was discontinued on July 24, 1998. Patient was hospitalized on ——— with weakness, fatigue, and diarrhea. Chest x-ray showed Rt. upper lobe consolidation. On admission Hgb was 11.4 gm%, Plt. Ct. 16,000/ul, ALC 1890/ul, and ANC 690/ul. Patent was treated with Primaxin 1 gm q 8 hours. Patient developed decreased oxygen saturation, was intubated, and Vancomycin was added. Despite these measures the patient became hypotensive. Blood

pressure did not respond to pressors and the patient expired on ———— This death appears to be related to Campath-1h therapy due to the prolonged neutropenia post therapy.

- **Patient 006-0093** entered the study with Rai stage I disease with B symptoms. At entry Hgb was reported as 12.6 gm%, Platelet count 140,000/ul, ANC 2600/ul and ALC 2500/ul. The patient received sixteen Campath-1h infusions between July 27 and ———— and was assessed as stable disease by the review panel. At time of discontinuation of Campath-1h therapy lymphadenopathy had resolved. On ———— (four days after the last Campath-1h infusion) patient was hospitalized with Gr. 3 CMV infection with grade 3 fever of seven days duration, gr. 2 neutropenia (ANC-1200/ul), and gr. 2 anemia (Hgb 9.1 gm%) and grade 1 thrombocytopenia (platelets 95,000/ul). Patient was treated with acyclovir, gangcyclovir, imipenim, indomethacin, and G-CSF (development of grade 4 neutropenia). The CMV infection and fever resolved by September 5 and ANC rose to 2900/ul. On ———— patient was hospitalized for gr. 2 vomiting, gr. 3 asthenia, gr. 2 fever, and gr. 2 bilateral thigh pain. ANC was 2050/ul, ALC was 400/ul, platelets 113,000/ul and Hgb 9.1 gm% on admission. Liver biopsy showed granulamotous infiltration but no evidence of leukemic infiltrates. Cultures of the bone marrow and liver for AFB and fungi were reported as negative. No bone marrow histology is reported in the adverse narrative or CRF. The patient continued a downhill course and expired on ———— ALC was noted to decrease from 400/ul to 0/ul at time of death. The Patient narrative states that death as due to progressive disease and reports that patient developed aggressive PLL, however this can not be verified in the CRF or bone marrow reports. On review the cause of death appears infectious in nature and is considered related to Campath-1h therapy.
- **Patient 007-0029** entered study with RAI stage II disease and the following hematologic values: Hgb 14.2 gm%, platelets 264,000/ul, ALC 199,000/ul and ANC 8700/ul. Patient received fourteen infusions of Campath-1h between May 28 and June 25, 1998 and achieved a partial response. Patient refused to continue therapy for personal reasons. On ———— patient was hospitalized with E. coli sepsis, grade 3 associated with grade 3 hypotension and grade 2 fever. ANC was 5900/ul with ALC reported as 1100/ul. Patient responded to antibiotics. CMV antigenemia was noted and famcyclovir continued. Patient was discharged on ———— On ———— patient underwent herniorrhapy without complication. On ———— patient with hospitalized with a severe sinus infection and progressive disease. ANC was 6800/ul and ALC 6900/ul. CT scan showed acute / chronic sinusitis in the sphenoid, ethmoid, and frontal sinuses. Treatment included multiple antibiotics for the sinusitis and reinstitution of Campath-1h therapy. On January 2, 1999 patient experienced respiratory arrest during a CT of the brain. MRI on January 8 showed parasinusitis. On January 14, 1999 WBC rose to 239,000/ul. On ———— patient expired from multiorgan failure. Autopsy reviewed disseminated mucormyosis. Campath-1h is considered to have played a role in the sinusitis / fungal infection while progression is also apparent.
- **Patient 017-0083** entered the study with Stage IV CLL. On entry Hgb was 10.7 gm%, Plt. Count 82,000/ul, ANC 700/ul, and ALC 21,630/ul. Patient received thirty-eight infusions of Campath-1h between August 3 and October 23, 1998. Gr. 2 bronchitis and gr. 2 rigors were reported between August 3 to August 7. Grade 4 neutropenia was reported from August 7 until August 12 when WBC rose to 4100/ul with use of G-CSF. No other adverse events are reported during therapy. At discontinuation of Campath-1h therapy response was assessed as stable disease. No blood product support was utilized during therapy. On October 23 Hgb was reported as 12.2 gm%, Plt. Ct. 146,000/ul, ANC 1630/ul, and ALC 540/ul. On ———— patient was hospitalized for gr. 4 sepsis, NOS, treated with azetreonam, teicoplanin, acyclovir, and co-trimoxazole. The sepsis was associated with grade 4 neutropenia. On November 20 ANC was reported as 2000/ul and ALC 2200/ul. On ———— patient was discharged. On ———— patient was readmitted with gr. 4 pneumonia (causative agent not identified) with an ANC of 100/ul and ALC 1600/ul. Patient expired on ———— Neutropenia secondary to Campath-1h therapy is considered to have contributed to this patient's fatal infection.
- **Patient 023-0070**, with Rai Stage IV disease, was treated with twenty-one infusions of Campath-1h between July 15 and September 9, 1998. At entry on study CBC included Hgb 9.2 gm%, platelets 49,000/ul, WBC 473,800/ul and ANC 4700/ul. On ———— patient was hospitalized with gr. 2 fever and grade 3 oral and esophageal Candidiasis and depression. CBC on admission included ANC 1000/ul, ALC 400/ul, Hgb 8.3 gm% and platelet count 52,000/ul. Patient was treated with fluconazole, ceftriaxone, and omeprazole. Candidiasis and fever resolved on August 24. Grade 3 neutropenia continued until August 29 when ANC rose to 3400/ul. Patient was started on antidepressants after

psychological evaluation, Campath-1h therapy was resumed on August 31 and the patient was discharged on ——— On ——— patient was hospitalized for twenty-four hours with grade 2 diarrhea, grade 2 hypokalemia, and grade 2 fever with ANC 1000/ul. On September 14 ANC dropped to 150/ul. On ——— ' patient was hospitalized with a left femoral fracture (?pathological) considered non-operable. On September 29 grade 2 with grade 4 neutropenia (ANC 100/ul) was noted. Grade 2 oral and esophageal Candidiasis were reported on October 2. Treatment included fluconazole and amphotrecin. Patient was discharged on ——— Patient continued to have grade 3 neutropenia with ALC reported as 2100/ul. On ——— ? patient was hospitalized for grade 2, probable infection, grade 4 neutropenia with ALC 1100/ul. On ——— ' patient was hospitalized with grade 4 Pseudomonas sepsis, gr.4 neutropenia, and ALC 801/ul with a Hgb 8.4 gm% and platelet count 107,000/ul. Patient was treated with antibiotics and foscarnet. Patient expired from sepsis and grade 4 neutropenia on ——— with autopsy confirming Pseudomonas sepsis as the cause of death. No mention of progressive disease is included in the summary. Patient had resolution of splenomegaly during study and had no adenoapthy or hepatomegaly reported at entry or during study . No follow-up bone marrows were performed. This late death appears related to Campath-1h therapy.

- **Patient 027-0062** entered the study with Stage III CLL. Hematological values on entry include a Hgb 10.4 gm%, Plt. Ct. 161,000/ul, ANC 7700/ul, and ALC 211,900/ul. Patient received thirty-two Campath-1h infusions between June 22 and September 25, 1998. On July 10 and July 13 patient experienced gr. 3 rigors and gr. 3 abdominal pain. On ——— patient was hospitalized for management of gr. 2 abdominal pain, gr. 2 – 3 rigors, gr. 2 dizziness, gr. 3 fever, gr. 2 night sweats, gr. 2 diarrhea, sore throat, myalgias, gr. 2 anemia and grade 2 neutropenia. Admitting hematology includes Hgb 8.5 gm%, Plt. Ct. 156,000/ul, ANC –1200/ul, and ALC – 100/ul.) Patient was treated with IV antibiotic, four units of whole blood, and was continued on prophylaxis. No infectious agent was identified. Patient was discharged on ——— Campath-1h therapy, which was discontinued on July 18, was resumed on August 10, 1998. During the last six weeks of therapy patient complained of skin rash, itching of the palms and soles, indigestion, difficulty sleeping, anxiety and pain in the shoulders, chest and fingers. Campath-1h therapy was discontinued on September 25 with an assessment of partial response. On September 28 platelet count was reported as 6,000/ul and a purpurtic rash was noted. On October 5 mucosal bleeding in association with a platelet count of 11,000/ul was reported. On ——— patient was admitted with gr. 4 thrombocytopenia , gr. 4 hematuria, gastrointestinal bleeding, gr. 3 bullous skin eruptions, and stomatitis. Bone marrow showed increased megakaryocyte with no evidence of CLL. Positive Coombs test was reported on ——— Despite steroids, immune globulin, platelet transfusions, plasmapheresis, emergency splenectomy, and chemotherapy with vincristine and cyclophosphamide, the patient expired on ——— from Gi bleeding. This patient's death is considered to be due to autoimmune thrombocytopenia secondary to Campath-1h therapy.

Discontinuations

As noted previously nineteen (20.4%) study participants were withdrawn from therapy for adverse events, three (3.2%) died during study, and six (6.5%) refused to continue therapy. Table 211-10 includes a listing of patients who discontinued therapy, the patient's stage of disease, FDA assessment of disease response, a description of the reason for discontinuation of study therapy, and FDA assessment of relationship of the discontinuation to treatment with Campath-1h. If hematological toxicity is captured in an adverse event, it represents a new or worsening grade of toxicity from baseline.

Table 211-10: Discontinuations from Study

Pt. Number	RAI Stage	Response (FDA)	Reason	Relationship to Study Drug
001-0002	IV	PD	Pancytopenia	Definite
001-0040	IV	SD	Death: Pseudomonas sepsis with neutropenia	Definite

Pt. Number	RAI Stage	Response (FDA)	Reason	Relationship to Study Drug
002-0010	II	SD	Pt. Refusal: No disease improvement	None
003-0095	IV	PR	Pancytopenia; Systemic Candidiasis	Definite
005-0045	IV	PD	Death ? due to Progression	Possible
006-0016	IV	SD	Pancytopenia (Bone Marrow Hypoplasia)	Definite
006-0017	IV	SD	Patient Refusal: Anorexia, gr. 2; Fatigue, gr. 3; Dehydration, gr. 3; Granulocytopenia, gr. 4	Definite
006-0019	IV	SD	Patient Refusal: Fatigue, fever secondary to drug, Neutropenia, Grade 3	Definite
006-0020	III	NE	Patient Refusal : Rigors, chills, tongue numbness, rash, itching; Neutropenia, Gr.4; thrombocytopenia, Gr. 3 anemia, gr.	Definite
006-0022	III	SD	Fever, gr. ?; Neutropenia, gr. 4	Definite
006-0025	II	PD	Patient Refusal: Treatment not effective	None
006-0027	IV	PR	"Immunosuppression"	None
006-0031	IV	SD	Worsening Neutropenia (gr.2 – gr.4) Ongoing Presumed Aspergillus pneumonia	Definite
006-0033	IV	SD	CMV Infection; gr. 3 / 4 Neutropenia;	Definite
006-0038	IV	SD	Pancytopenia (gr. 4 neutropenia, gr. 3 thrombocytopenia, gr. 2 anemia transfused)	Definite
006-0093	I	NE	CMV Infection, gr. 3	Definite
006-0094	IV	SD	Gr. 2 Fever, Rigors (persistent, resolved with discontinuation of Campath-1h)	Definite
007-0006	IV	PR	PCP pneumonia (gr.4); Gr. 4 neutropenia Toruloposis glabrata infection (gr.4) ? RSV infection	Definite
007-0007	III	PR	Pancytopenia with Marrow Hypoplasia	Definite
007-0029	II	PR	Patient Refusal: Personal preference	None
007-0043	IV	SD	Genital Herpes, ?grade –worsened with therapy	Definite
007-0051	IV	NE	Lumbosacral Pain aggravated by Campath-1h Infusions	Definite
008-0036	II	SD	Neutropenia, Anemia, Fever	Definite
011-0053	IV	NE	Gr. 4 Staph. Pneumonia with pleural effusion, Gr. 4 Neutropenia, Gr. 3 Anemia, Gr. 4 Thrombocytopenia	Definite
012-0011	II	PR	Campath-1h related Autoimmune Thrombocytopenia, gr. 4	Definite
013-0096	IV	NE	Acute Bronchospasm	Definite
017-0084	II	PD	Lethargy	Disease related
019-0077	III	SD	Death: Gr. 4 Pseudomonas Sepsis Gr. 1 Oral Candidiasis	Definite
026-0060	III	SD	Gr. 1 Pneumonia (NOS) Gr. 4 Neutropenia, Gr. 3 anemia; Gr. 2 Thrombocytopenia	Definite
027-0062	IV	PR	Autoimmune Thrombocytopenia	Definite

Patient 6-016 was reported as a completer at 8 weeks of therapy in the Study Termination Record rather than a discontinuation due to adverse event. Review of the Patient Narrative indicates that therapy was discontinued because of a hypoplastic bone marrow. Patient, 8-036, reported as having disease progression in Study Termination Record, ceased to receive Campath-1h after the eleventh infusion. On the day of the next

scheduled infusion patient was hospitalized for new grade 3 anemia (Hgb 7.7 gm%), new grade 4 granulocytopenia (ANC 132/ul), and fever without evidence of infection. Patient was treated with antibiotics and G-CSF. Campath-1h therapy was discontinued. Improvement in ANC and anemia were noted after discontinuation of Campath-1h. Fever initially abated but returned. Dexamethasone was added with resolution of the fever. Patient was assessed as stable disease at conclusion of therapy, however disease progression was noted two weeks after Campath-1h infusions were discontinued.

Twenty-five (83%) of the thirty discontinuations were related to Campath-1h therapy. Hematologic toxicity was responsible for eight treatment discontinuations including five discontinuation due to pancytopenia. Serious infections or febrile neutropenia were responsible for seven treatment discontinuations and two deaths on study. Infusion related toxicities were responsible for discontinuations of study drug in six patients.

Serious Adverse Events and Hospitalization

Sixty-two (66.7%) study participants experienced one-hundred fifteen episodes of one or more adverse events on study or within 180 days of therapy. The following table includes a listing of all study discontinuations, hospitalizations, serious adverse events including fatal events reported in the patient narratives. Information on disease stage, objective response as assessed by the agency, the number of Campath-1h infusions, the number of days of hospitalization, the day that the event occurred relative to the initial dose of Campath-1h therapy, and agency's assessment of relationship to study drug are included in Table 211-11. This information is included to provide the reader with an idea of the scope and severity of adverse events. Information about outcome of the adverse event and continuation of therapy is included in some cases. If hematological toxicity is reported, the hematologic toxicity represents a new toxicity compared to baseline values or worsening as compared to baseline values. One serious adverse event episode reported at +227 days after completion of study drug therapy, is also included in the table since it was a reportable adverse event.

Table 211-1I: Adverse Events and Hospitalizations on Study or within 180 Days Post Treatment (+ indicated number of days after Campath-1h discontinued)

Patient No.	Stage (Rsp)	No. Infusions	Reason for Adverse Event (Hospitalization)	Duration Hospital Stay	Relative Day Of Therapy	Relationship to Therapy
01-002	IV (NE)*	9	Pancytopenia (Marrow hypoplasia) (Rx. Discontinued); Death "Inanition"	-	16	Related
01-040	IV (SD)	18	Hypotension gr. 3; Hypovolemia, gr. 4; Dyspnea, gr. 4 (Infusion related) Anemia, gr. 2	1	28	Related
			Pseudomonas Sepsis, gr. 4 (Fatal) Neutropenia, gr. 4	1	52	Related
01-041	IV (PR)	37	Abdominal pain, gr. 3 Herpes Zoster, Disseminated, gr. 3, resolved	?	+59	Not Related Related
02-026	II (SD)	27	Confusion gr. 3; Fever, gr. 3; Hypoxia, gr. 2 (Drug related; cleared with steroids)	5	28	Related
02-098	II (PD)	23	Anemia, gr.2, Fatigue, gr. 3; Gi bleeding due to ulceration of	7	24	Not Related

Patient No.	Stage (Rsp)	No. Infusions	Reason for Adverse Event (Hospitalization)	Duration Hospital Stay	Relative Day Of Therapy	Relationship to Therapy
			lymphomatous gastric mass			
			Progressive Disease (Death)	27	+3	Not Related
03-095	IV (PR)	23	Pancytopenia (Rx. discontinued) Candida, Systemic, gr. 2	-	53	Related
04-092	II (PR)	37	Urticaria, gr. 3 (Infusion related)	1	4	Related
04-097	III (PR)	27	Pneumonia, gr. 3 (Gram +cocci)	3	+9	Related
			Pneumonia, gr. 3 (NOS)	7	+44	Related
5-013	II (PR)	28	Listeria Meningitis, gr. 3	7	+97	Related
			Staph. sepsis, gr. 3 (line infection)	13	+171	Related
05-039	III (PR)	25	Anemia, gr. 4; Fever, gr. 2; Neutropenia, gr. 3 / 4	3	35	Related
			Fever, gr. 2, Sinusitis, gr. 2; Dz. Progression	4	+160	Not related
05-045	IV (PD)	16	Thrombocytopenia, gr. 4	5	2	Probably
			Hypoglycemia, gr.4; Fever, gr. 1; Pain Lt. Axillary Node, gr.4 (Death)	3	+5 (35)	?
05-046	IV (SD)	37	Pneumonia, Aspergillus, gr. 4 (Fatal)	10	+123	Related
06-016	IV (SD)	20	Hypotension, gr. 3; Neutropenia, gr. 4 Thrombocytopenia, gr.4; Anemia, gr. 2	5	4	Related
			Pneumonia, Cryptococcus, gr. 4; Fever, gr. 2; Dyspnea, gr. 3; Neutropenia, gr. 4 (Fatal)	3	+17	Related
06-017	IV (SD)	11	Neutropenia, gr. 4; Fatigue, gr. 4; Dehydration, gr. 3, Anorexia, gr. 2; Vomiting, gr. 2 (Rx. Discontinued / Refused)	9	+5 (28)	Related
06-019	IV (SD)	18	Fatigue, gr. ?; Fever, gr. ? (Rx. Discontinued / Refused)	--	+3 (40)	Related
06-020	IV (NE)	10	Rigors, gr. 1, 2; Chills, gr. ?; Tongue numbness; Rash, Intermittent itching; Neutropenia, gr. 4; Thrombocytopenia, gr. 3 (Rx. Discontinued / Refused)	--	17	Related
06-022	III (SD)	15	E. Coli sepsis, gr. 3; Neutropenia, gr. 4 (Rx. Discontinued)	5	+2 (51)	Related
06-023	IV (PR)	20	Fever, gr. 2; Neutropenia, gr. 3 / 4; Thrombocytopenia, gr. 3	7	24	Related
06-025	II (PD)	25	Pneumonia, gr.4 (NOS); Neutropenia, gr. 2	5	27	Related
06-030	IV (PD)	36	Fever, gr.3, Neutropenia, gr. 3; Asthenia, gr. 2 Pneumonitis, gr. 3, NOS	3	52	Related
06-031	IV (SD)	30	Fever, gr. 3; Neutropenia, gr. 4; Asthenia, gr. 4; Pneumonia, gr. 3, probable Aspergillus Strep. oralis sepsis, gr. 1	24	35	Related
			Fever, gr. ?; Pleuritic Chest pain. Gr. 2 / 3 Neutropenia (Rx Discontinued)	--	+4 (109)	Related
06-032	IV (PD)	22	Fever, gr. 2; Bronchitis, gr. 2; Neutropenia, gr. 4; Anemia, gr. 3;	3	35	Related
			Fever, gr. 2; Nuetropenia, gr.4 (ANC 0/ul); Anemia, gr. 3	6	+7	Related
06-033	IV	15	Fever, gr. 2; Neutropenia, gr. 3;	10	+5	Related

Patient No.	Stage (Rsp)	No. Infusions	Reason for Adverse Event (Hospitalization)	Duration Hospital Stay	Relative Day Of Therapy	Relationship to Therapy
	(SD)		Anemia, gr. 3 (Rx. Discontinued)		(32)	
			CMV, gr. 3; Fever, gr. 2	32	+28	Related
			Fever (Plasma Cell Dyscrasia)	20	+36	Unrelated
06-034	IV (PD)	22	Pneumonia, NOS, gr. 4 (Fatal); Neutropenia, gr. 3; Thrombocytopenia, gr. 3	9	+45	Related
06-038	IV (SD)	13	Pancytopenia (Neutropenia, gr. 4; Thrombocytopenia, gr. 3, Anemia, gr. 2) (Rx. Discontinued)	--	30	Related
			Fractures, Lt. Humerus; Lt. Femur Mucormycosis, gr. 4 (Fatal); Neutropenia, gr. 4; Thrombocytopenia, gr. 3; Anemia, gr. 2	21	+9	Related
06-056	IV (SD)	22	Fever, gr. 2; Asthenia, gr. 2 Staph. aureus sepsis, gr. 3 (? Line infection) Staph. aureus endophthalmitis, gr. 2	9	2	Related
06-093	I (NE)	16	CMV infection, gr. 3; Fever, gr. 3; Neutropenia, gr. 2 / 3 (Rx Discontinued)	7	+4 (30)	Related
			Vomiting, gr. 2; Fever, gr. 3; Bilateral thigh pain, gr. 3; Hepatic Granuloma, NOS (Death)	24	+22	?
07-001	IV (SD)	14	Fluid overload, gr. 2 (preexisting); Anemia, gr. 3	1	2	Not related
			Fever, gr. 2; Neutropenia, gr. 3 / 4 CMV infection, gr. 2 (Rx. Discontinued)	4	26	Related
			Pseudomonas sepsis, gr. 4 (Fatal) Neutropenia, gr. 4	8	+22	Related
07-006	IV (PR)	24	PCP Pneumonia, gr. 4 RSV, Rhinovirus pneumonia, gr. 4 Torulopsis glabrata pneumonia, gr? (Rx Discontinued)	28	+1 (52)	Related
			Fever, gr. 2; Neutropenia, gr. 4; Anemia, gr. 2; Cough, gr. 2 (Probable Infection) Gout with Foot Drop	5	+91	Related Not Related
07-007	III (PR)	12	Rigors, gr. 2; Fever, gr. 2; Dyspnea, gr. 4 (Acute Infusion Reaction)	(1)	3	Related
			Thrombocytopenia, gr. 4 (Rx. Discontinuation)	--	23	Related
			Fever, gr. 2; Neutropenia, gr. 4 (ANC 0/ul); Thrombocytopenia, gr. 4; Anemia, gr. 3 (Hypoplastic Bone Marrow)	5	+15	Related
			Fever, gr. 2; Probable Infection Neutropenia , gr. ? treated with G-CSF and valacyclovir)	14	+76	Related
07-008	III (SD)	34	Dyspnea, gr. 4; Tachycardia, gr. 3; Acute MI Sepsis, gr. + cocci	10	1	Not related
			Phlebitis, gr. 3	19	36	Not related
			CMV infection, gr. 3	4	+7	Related
			Transformation to Richter's Syndrome; Chemotherapy; Phlebitis	17	+71	Not related
07-012	IV (SD)	12	Fever, gr. 2; Neutropenia, gr. 3 (resolved with G-CSF)	27	23	Related

Patient No.	Stage (Rsp)	No. Infusions	Reason for Adverse Event (Hospitalization)	Duration Hospital Stay	Relative Day Of Therapy	Relationship to Therapy
			Sepsis (Strep. α-hemolytic; Neisseria, Hemophilus), gr. 3; CMV, gr. 3 Pneumonia, Torulopsis, gr. 3			
07-015	IV (SD)	14	Pneumonia, gr. 4 (NOS) Neutropenia, gr. 4; Anemia, gr. 4; Thrombocytopenia, gr. 4 (Bone marrow hypoplasia)	23	+14	Related
07-021	IV (PD)	14	Fever, gr. 3; CMV Infection, gr. 2 Neutropenia, gr. 4; Thrombocytopenia, gr. 4; Anemia, gr. 3 Hyponatremia, gr. 4 Abnormal Gait, gr. 2	23	+8	Related Not related Not related
			Fever, gr. 3, Neutropenia, gr. 2; Thrombocytopenia, gr. 3	3	+23	Related
			Splenectomy for Thrombocytopenia, Transformation to Large Cell Lymphoma		+ 74	Not Related
07-029	II (PR)	14	Hypotension, gr. 3; Sepsis, E. coli, gr. 3; Fever, gr. 2	5	+45	Related
			Herniorraphy	1	+ 152	Not related
			Mucormycosis, disseminated, (Fatal) Sinusitis, (Dz. Progression)	21	+180	Related
07-043	IV (SD)	25	Fever. Gr. 3; Neutropenia, gr. 2 Stomatococcus sepsis, gr. 2	11	23	Related
			Herpes Simplex, (Genital) (Rx Discontinuation)	--	1 + (69)	Related
			Sepsis, E. Coli, Gr. 3	18	+42	Related
07-051	IV (NE)	3	Rigors, gr.2, Fever, gr. 2; Back Pain, gr.? (Rx. Discontinued)	--	3	Related
			Back Pain, gr. 3;	14	+3	Not Related
			Fever, neutropenia (Dz. Progression)	7	+92	Not related
07-058	IV (PD)	30	CMV infection, gr. 2; Neutropenia, gr. 2 Urinary tract Infection, gr. 2 Enterococcus Rigors, gr. 3 (Infusion related)	5	25	Related
07-091	IV (PR)	40	Perianal Abscess, gr. 3 / 4 Neutropenia, gr. 4 (ANC 200/ul)	2	+82	Related
			Perianal Abscess, gr. ?; I & D Fever, gr. ? Neutropenia, gr. 4 (ANC 20/ul)	6	+105	Related
08-036	II (SD)	11	Anemia, gr. 4 Neutropenia, gr. 4 Fever, gr. 3	8	+3	Related
11-009	III (PD)	26	Pleural effusion, gr. 3; Dyspnea, gr. 3 (Dz. Progression)	7	24	Not Related
11-014	III (PR)	38	Bronchitis, gr. 3, (NOS)	8	+105	?
11-050	IV (PR)	35	Cough, gr. 2 Fever, gr. 2, Neutropenia, gr. 2 / 3	3	69	Related
			Adenocarcinoma, Prostate, [Gleason 6]	-	+120	Not Related
			Herniorraphy	?	+170	Not Related
11-052	II (SD)	40	Pneumonia, RLL, NOS (No other information)	11	+24	? Related

Patient No.	Stage (Rsp)	No. Infusions	Reason for Adverse Event (Hospitalization)	Duration Hospital Stay	Relative Day Of Therapy	Relationship to Therapy
			Transformation, Large Cell Lymphoma			
11-053	IV NE)	4	Pneumonia, Staph., gr. 4 Fever, gr. 4 Probable Rt. Empyema Neutropenia, gr. 3 (Rx. Discontinued)	36	4	Related
			Acute spinal Fracture, Thrombocytopenia Dz. Progression	4	+63	Not related
			Sepsis, Fever, Meningitis (Death)	11	+84	Not related
12-011	II (PR)	24	Thrombocytopenia, Gr. 4 (Rx. Discontinued)	--	56	
			Thrombocytopenia, gr. 4, Autoimmune Campath-1h related	5	+10	Related
13-096	IV (NE)	2	Dyspnea, gr. 4; Bronchospasm, gr. 4 Dyspnea, gr. 4 despite premedication (Rx. Discontinued)	2	1	Related
			Sepsis, Gram +, gr. 4 Pneumonia, H. flu, Candida, Renal Insufficiency (Fatal)	15	+12	Not Related (Alternative Rx.)
16-078	IV (NE)	36	Pneumonia, gr. 4 (NOS) Hypoxia, gr. 2; Hypotension (Fatal) Pulmonary nodules – ? Progression	2	+143	?
17-083	IV (PD)	38	Sepsis, gr. 3, NOS Neutropenia, gr. 4	12	+21	Related
			Pneumonia, gr. 4, NOS Neutropenia, gr. 4 (Fatal)	1	+35	Related
17-084	II PD	22	Lethargy (Rx. Discontinued)	--	53	?
		22	Lethargy Neutropenia, gr. 3 / 4 (ongoing) ? Staph. Sepsis Pneumonia, Candida, gr. ? PTE (Fatal)	12	+3	? Contributory Not Related
18-061	IV (SD)	42	Fever, gr. 2; Neutropenia, gr. 4 (ANC 140/ul)	3	28	Related
			Hospice Care – Back pain	13	68	Not related
18-071	IV (SD)	26	Rectal Bleeding, Melena Thrombocytopenia, gr. 4 (IVIG therapy)	-	9	Related
			Fever, gr. 4 Neutropenia, gr. 4 Thrombocytopenia, gr. 4 Gi Bleeding, gr. 4 (Fatal) (Chemo – Dx. Progression)	18	+11	Not related
19-065	IV (PR)	15	Diarrhea, gr. 3; Gastroenteritis, gr. 3 Dehydration, gr. 3 Fever, gr. 2 Neutropenia, gr. 3 (ANC 546/ul)	3	+19	Related
			Gastroenteritis, Salmonella, gr. 3 Neutropenia, gr. 3	11	+118	Related
19-069	IV (PR)	35	Sepsis, Staph. coag -, gr. 2 (Line infection); Fever, gr. 2 Neutropenia, gr. 2	5	37	Related
			Fever, gr. 2 Pneumopathy, (NOS), gr. ? Bronchitis, gr. 2	6	+85	Related
			Pneumopathy (NOS, Bronch negative) Sepsis, Corynebacterium	13	+139	Related

Patient No.	Stage (Rsp)	No. Infusions	Reason for Adverse Event (Hospitalization)	Duration Hospital Stay	Relative Day Of Therapy	Relationship to Therapy
19-077	III (SD)	23	Pneumonia, Pseudomonas, gr. 4 (Fatal) Pulmonary edema Candida albicans, gr. 1	20	51	Related
22-068	IV (SD)	21	Bronchitis, NOS Neutropenia, gr. 3	?	+89	Related
			Pharnygitis, ? Candida with ulceration Dz. Progression	?	+175	?
23-070	IV (SD)	21	Candidiasis, gr. 3 (oral and esophageal) Neutropenia, gr. 2 / 3 Fever, gr. 2 Depression	14	35	Related Unknown
			Diarrhea, gr. 2 Hypokalemia, gr. 2 Fever, gr. 2 Neutropenia, gr. 2, 3 (Rx. Discontinued)	1	56	Related
			Fx. Lt. Femur, (?Pathological) Fever, gr. 2 Neutropenia, gr. 4 Candidiasis, gr. 2 (oral and esophageal)	12	+17	Related
			Fever, gr. 2 Neutropenia, gr. 4	1	+44	Related
			Sepsis, Pseudomonas, gr. 4 Neutropenia, gr. 4 (Fatal)	5	+71	Related
23-072	IV (SD)	24	Fever, Confusion, Pneumonia, Dz. Progression	5	+47	Not related
			Dyspnea, Fever, Asthenia Sepsis, Strep. Pneumonia	32	+71	Not related
			Dyspnea, Fever, Probable Infection (Death)	1	+154	Not related
26-060	III (SD)	14	Fever, Gr. 2 Neutropenia, gr. 4 Pneumonia, (NOS) gr. 1, ? Fungal (Rx. Discontinued)	30**	28	Related
26-073	III (SD)	18	Hemolysis, gr. 2 (8/10 – 11/9/98) Fever, gr. 2 Neutropenia, gr. 3 Pneumonia, gr. ? (Rx. Discontinued)	?21	21	Related
26-085	IV (SD)	29	Dx. Progression (Alternative Treatment) Sepsis, E. coli, Strep., gr. 4 (Fatal) Suprapatellar hematoma	8	+127	Not Related
27-062	III (PR)	32	Rigors, gr. 2; Flu-like Symptoms with giddiness; Abdominal Pain, gr. 2 Anemia, gr. 2 (Transfused 4 units RBCs); Neutropenia, gr. 2	10	31	Related
			Thrombocytopenia, gr. 4 (Rx Discontinued)	--	95	Related
			Thrombocytopenia, gr. 4 (Fatal); Retinal hemorrhage;Hematuria, gr. 4; Gi hemorrhage, gr. ?;Mouth blisters, gr. 3; Sepsis, gr. 2, gram + cocci	16	+21	Related
27-067	IV (PR)	37	Hepatosplenomegaly Thrombocytopenia, gr. 3 Fever, gr. 4 Sepsis, Enterococcus, Staph, coag.-, gr.4 Brainstem Hemorrhage Dz. Progression	?	+227	Not Related

* Reported as progression by the investigator

**Hospitalized for therapy; Duration of hospitalization due to pneumonia after Campath-1h discontinued

Eighty-four of the one hundred fifteen serious adverse events reported in Table 211-11 were judged by FDA as related to Campath-1h therapy. Ten events were related to infusion-related toxicities. Sixteen SAE were due to infection alone without evidence of myelosuppression. Thirty SAE were due to infections with neutropenia, with or without other evidence of myelosuppression. Sixteen SAE were due to fever with neutropenia (and in some instances other hematologic toxicity). Twelve SAE were due to hematological toxicity without concomitant fever or infection.

Second Malignancies

Eight patients were noted to have developed a second malignancy or progressed to a more aggressive histology while on study:

- Patient 06-033 had Campath-1h therapy discontinued when a plasma cell dyscrasia was reported on bone marrow.
- Patient 02-098 was found to have small cell lymphoma involving the gastric wall with GI bleeding while on therapy. Campath-1h therapy was continued despite the biopsy report, until pulmonary progression was noted.
- Patient 07-008 had biopsy proven transformation to Richter's syndrome.
- Patient 19-005 has biopsy proven transformation to Richter's syndrome.
- Patient 07-021 had transformation to large cell lymphoma reported seventy-four days after the last dose of Campath-1h therapy.
- Patient 16-081 had transformation to large cell lymphoma reported thirty days after the last Campath-1h dose.
- Patient 11-050 was found to have a prosthetic nodule during therapy. Adenocarcinoma of the prostate [Gleason Stage 6] was found on evaluation three months after discontinuation of Campath-1h therapy.
- Patient 6-093 is reported to have developed PLL on study while receiving antiviral treatment for a CMV infection (see Deaths on Study section). The patient died months later from progressive disease.

Adverse Event Profile

All ninety-three (100%) participants experienced at least one adverse event on study with sixty-two (66.7%) experiencing at least one grade 3 / 4 event. Drug related adverse events were reported in all ninety-three patients with fifty-four (58.1%) participants experiencing at least one grade 3 / 4 adverse event related to Campath-1h therapy. Table 211-12 lists the sponsor's compilation of all participant's adverse events and all participants' drug-related adverse events that were reported in more than 5% of the Study 211 population. Also included in the Table is a listing of the number of patients who experienced a grade 3 / 4 adverse event even if with an incidence < 5%. Note that a patient may have experienced the same adverse event more than once. In that case the worse grade for the adverse event is reported. Note that a patient may have experienced more than one type of adverse event reported in a particular category.

Table 211-12: All Adverse Events and All Drug Related Adverse Events by Patient (N=93) in > 5% of Study Population and All Gr. 3 / 4 NCI CTC Adverse Events on Study

TYPE OF ADVERSE EVENT BY BODY SYSTEM	ALL ADVERSE EVENTS			DRUG-RELATED ADVERSE EVENTS		
	All N (%)	Gr. 3 N (%)	Gr. 4 N (%)	All N (%)	Gr. 3 N (%)	Gr. 4 N (%)
Body as a Whole						
Anorexia	17 (18.3)	2 (2.2)	1 (1.1)	9 (9.7)	--	--
Asthenia	15 (16.1)	5 (5.4)	1 (1.1)	8 (8.6)	--	--
Back Pain	10 (10.8)	3 (3.2)	0	4 (4.3)	2 (2.2)	-
Chest Pain	8 (8.6)	1 (1.1)	-	8 (8.6)	1 (1.1)	
Edema, Peripheral edema,	15 (16.1)	(1.1)	-	3 (3.2)	-	-
Fatigue	30 (32.3)	4 (4.3)	2 (2.2)	20 (21.5)	2 (2.2)	1 (1.1)
Fever	79 (84.9)	16 (17.2)	3 (3.2)	77 (82.8)	12 (12.9)	-
Influenza-Like Symptom	5 (5.4)	-	-	4 (4.3)	-	-
Malaise	9 (6.5)	1 (1.1)	-	1 (1.1)		
Neutropenic Fever	7 (7.5)	2 (2.2)	-	7 (7.5)	2 (2.2)	-
Pain	15 (16.1)	-	1 (1.1)	4 (4.3)	-	-
Rigors	84 (90.3)	13 (14.0)	-	83 (89.2)	11 (11.8)	-
Temperature Change Sensation	6 (6.5)	-	-	6 (6.5)	-	-
Cardiovascular						
Hypertension	14 (15.1.)	3 (3.2)	-	11 (11.8)	2 (2.2)	-
Hypotension	16 (17.2).	2 (2.2)	-	14 (15.1)	1 (1.1)	-
Tachycardia (with AF, SVT)	11 (11.8)	4 (4.3)	-	7 (7.5)	4 (4.3)	-
Acute MI	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Cardiac Arrest	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Central & Peripheral Nervous System						
Dizziness	13 (14.0)	1 (1.1)	-	3 (3.2)	-	-
Headache	18 (19.4)	-	-	12 (12.9)	-	-
Parathesias	6 (6.5)	-	-	4 (4.3)	-	-
Tremor	8 (8.6)	-	-	7 (7.5)	-	-
Gastrointestinal						
Abdominal Pain	11 (11.8)	1 (1.1)	-	4 (4.3)	1 (1.1)	-
Constipation	9 (9.7)	-	-	1 (1.1)	-	-
Diarrhea	24 (25.8)	1 (1.1)	-	12 (12.9)	1 (1.1)	-
Dyspepsia	12 (12.9)	-	-	3 (3.2)	-	-
Nausea	49 (52.7)	-	-	44 (47.3)	-	-
Vomiting	35 (37.6)	1 (1.1)	-	31 (33.3)	1 (1.1)	-
Stomatitis, Ulcerative Stomatitis, Mucositis	8 (8.6)	-	-	3 (3.2)	-	-
Metabolic & Nutritional						
Dehydration	4 (4.3)	3 (3.2)	-	3 (3.2)	3 (3.2)	-
Fluid Overload	1 (1.1)	1 (1.1)	-	-		
Hyperglycemia	1 (1.1)	-	1 (1.1)	-		
Hypoglycemia	1 (1.1)	1 (1.1)	-			
Hyponatremia	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Wt Decrease	10 (10.8)	-	-	6 (6.5)	-	-
Musculoskeletal						
Arthropathy	2 (2.2)	1 (1.1)	-	-	-	-
Bone Fracture	2 (2.2)	-	-	-	-	-
Myalgia	8 (8.6)	-	-	4 (4.3)	-	-

TYPE OF ADVERSE EVENT BY BODY SYSTEM	ALL ADVERSE EVENTS			DRUG-RELATED ADVERSE EVENTS		
	All N (%)	Gr. 3 N (%)	Gr. 4 N (%)	All N (%)	Gr. 3 N (%)	Gr. 4 N (%)
Platelet, Bleeding & Clotting Disorders						
PTE	1 (1.1)	-	1 (1.1)	-		
Epistaxis	7 (7.5)	2 (2.2)	-	1 (1.1)	-	-
Purpura	10 (10.8)	-	-	2 (2.2)	-	-
Thrombocytopenia	6 (6.5)	1 (1.1)	5 (5.4)	5 (5.4)	1 (1.1)	4 (4.3)
Psychiatric Disordes						
Abnormal Thinking	1 (1.1)	1 (1.1)	-	1 (1.1)	-	1 (1.1)
Anxiety	5 (5.4)	-	-	4 (4.3)	-	-
Depression	8 (8.6)	-	-	2 (2.2)	-	-
Hallucinations	1 (1.1)	-	1 (1.1)	-		
Insomnia	5 (5.4)	1 (1.1)	-	2 (2.2)	-	-
Somnolence	5 (5.4)	1 (1.1)	-	2 (2.2)	-	-
RBC Disorders						
Anemia	7 (7.5)	3 (3.2)	2 (2.2)	4 (4.3)	2 (2.2)	2 (2.2)
AIHA	1 (1.1)	-	-			
Resistance Mechanism Disorder						
CMV Infection	7 (7.5)	4 (4.3)	-	7 (7.5)	4 (4.3)	-
Herpes Simplex	6 (6.5)	1 (1.1)	-	5 (5.4)	1 (1.1)	-
Infections	2 (2.2)	-	-	2 (2.2)	-	-
Infection Bacterial	2 (2.2)	-	-	2 (2.2)	-	-
Infections, Fungal	2 (2.2)	-	-	2 (2.2)	-	-
Moniliasis	10 (10.8)	1 (1.1)	-	10 (10.8)	1 (1.1)	-
PCP Pneumonia	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Sepsis	14 (15.1)	4 (4.3)	5 (3.4)	14 (15.1)	4 (4.3)	5 (5.4)
Respiratory System Disorders						
Bronchospasm	13 (14.0)	2 (2.2)	1 (1.1)	9 (9.7)	2 (2.2)	1 (1.1)
Coughing	25 (26.9)	3 (3.2)	-	3 (3.2)	1	-
Dyspnea	26 (28.0)	5 (5.4)	6 (6.5)	16 (17.2)	3 (3.2)	4 (4.3)
Hypoxia	3 (3.2)	1 (1.1)	1 (1.1)	2 (2.2)	-	1 (1.1)
Pharyngitis	8 (8.6)	-	-	1 (1.1)	-	-
Pleural Effusion	4 (4.3)	2 (2.2)	2 (2.2)	1 (1.1)	-	-
Pneumonia, Pneumonitis	15 (16.1)	5 (5.4)	8 (8.6)	15 (16.1)	5 (5.4)	8 (8.6)
Pulm. Congestion/ Edema	6 (6.5)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Rhinitis	6 (6.5)	-	-	-	-	-
Sinusitis	3 (3.2)	-	1 (1.1)	2 (2.2)	-	1 (1.1)
Skin and Appendage Disorders						
Bullous Eruptions	1 (1.1)	1 (1.1)	-	1 (1.1)	1 (1.1)	-
Pruritis	17 (18.3)	-	-	13 (14.0)	-	-
Rash (with Maculopapular)	32 (34.4)	-	-	26 (28.0)	-	-
Rash, Erythematous	6 (6.5)	1 (1.1)	-	2 (2.2)	1 (1.1)	-
Urticaria	23 (24.7)	4 (4.3)	-	20 (21.5)	4 (4.3)	-
Increased Sweating	16 (17.2)	-	-	13 (14.0)	-	-
Urinary System						
Hematuria	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Vascular Disorder						
Phlebitis	(4.3)	1 (1.1)	-	1 (1.1)	-	-
WBC & RES Disorders						
Bone Marrow Aplasia	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Pancytopenia (Marrow Depression)	7 (7.5)	1 (1.1)	2 (2.2)	6 (6.5)	1 (1.1)	2 (2.2)

TYPE OF ADVERSE EVENT BY BODY SYSTEM	ALL ADVERSE EVENTS			DRUG-RELATED ADVERSE EVENTS		
	All N (%)	Gr. 3 N (%)	Gr. 4 N (%)	All N (%)	Gr. 3 N (%)	Gr. 4 N (%)
Granulocytopenia	10 (10.8)	2 (2.2)	6 (6.5)	10 (10.8)	2 (2.2)	6 (6.5)
Haptoglobin Decrease	1 (1.1)	1 (1.1)	-	1 (1.1)	1 (1.1)	-
Leukopenia	1 (1.1)	-	1 (1.1)	1 (1.1)	-	1 (1.1)
Lymphadenopathy	2 (2.2)	-	1 (1.1)	-	-	-

Information about adverse events occurring at greater than 30 days after completion of Campath-1h therapy is available for eighty-four (90.3%) study participants (Nine participants died on study or within thirty days of completion of Campath-1h therapy). All late serious adverse events reported at greater than 30 days were related to study drug. Table 211- 13 provides a list of drug-related adverse events that were reported in more than 5% of the study participants or were of grade 3 / 4 severity. With one exception (fatigue) these adverse events are infectious in nature.

Table 211-13: Post Study Drug Related Adverse Events (N = 84) in > 5% Study Population or Gr. 3 /4 Severity

Type of Adverse Event	No. (%) Patients	Patients (%) Grade 3 Event	Patients (%) Grade 4 Event	Patients (%) Grade Unknown
Fatigue	1 (1.2)	1 (1.2)	-	-
Meningimus	1 (1.2)	1 (1.2)	-	-
Meningitis	1 (1.2)	1 (1.2)	-	-
Gastroenterisitis	1 (1.2)	1 (1.2)	-	-
Herpes Zoster	4 (4.8)	-	1 (1.2)	-
Infection, NOS	3 (3.6)	-	1 (1.2)	-
Infection (Fungal)	1 (1.2)	-	1 (1.2)	
Moniliasis	3 (3.6)	-	-	1 (1.2)
Sepsis	9 (10.7)	5 (6.0)	4 (4.8)	-
Bronchitis	7 (8.3)	2 (2.4)	-	1 (1.2)
Pneumonia, Pneumonitis	10 (11.9)	4 (4.8)	6 (71.4)	-
Sinusitis	6 (7.1)	-	1 (1.2)	-
URI	5 (6.0)	-	-	1 (1.2)

As noted from review of the about tables, the majority of adverse events can be divided into infusion-related toxicities, infections, and hematological toxicities.

Infusion Related Adverse Events

All patients were premedicated with acetaminophen and diphenhydramine or another antihistamine. Thirty-eight (40.9%) of the study population required steroids on more than five occasions to control infusion related toxicities. Participants also received antiemetics usually ondanstetron to control nausea and merperidine to control rigors. Antiemetic use is reported in forty- three (42.6%) patients enrolled on study. Use of narcotic analgesics is reported in fifty-seven (61.3%) of the study participants.

Infusion related adverse events include the following:

- rigors reported in eighty-three (89.2%) participants with grade 3 rigors reported in 11 (11.8%) participants;
- tremors of grade 1/ 2 severity reported in seven (7.5%) participants;
- fever related to drug infusion reported in seventy-six (81.7%) participants with grade 3 fever in twelve (12.9%) participants;
- nausea reported in forty-four (47.3%) participants with no reports of grade 3 /4 nausea;
- vomiting related to study drug reported in thirty-one (33.3%) participants with grade 3 vomiting in one (1.1%) participant;
- rash reported in twenty-eight (28%) participants with a grade 3 erythematous rash in one (1.1%) participant;
- urticaria reported in twenty (21.5%) participants with grade 3 urticaria reported in four (4.3%) participants;
- pruritis of grade 1 / 2 severity reported in thirteen (14.0%) participants;
- dyspnea reported in 16 (17.2%) participants with grade 3 dyspnea in three (3.2%) and grade 4 dyspnea in four (4.3%) participants;
- bronchospasm reported in nine (9.7%) participants with grade 3 bronchospasm in two (2.2%) and grade 4 bronchospasm in one (1.1%) participant;
- hypoxia reported in two (2.2%) participants with gr. 4 hypoxia reported in one (1.1%) participant;
- hypotension reported in fourteen (15.1%) participants with grade 3 hypotension reported in one (1.1%) participant;
- increased sweating of grade 1 / 2 severity reported in thirteen (14.0%) participants;
- back / chest pain reported in twelve (12.9%) participants with grade 3 back / chest pain in three (3.3%) participants;
- headache of grade 1 / 2 severity reported in twelve (12.9%) participants;
- hypertension reported in eleven (11.8%) participants with grade 3 hypertension reported in two (2.2%) patients;
- tachycardia (including atrial fib) reported in seven (7.5%) patients with grade 3 tachyarrhythmia in four (4.3%) participants;
- temperature change sensation (grade 1 / 2) reported in six (6.5%) participants; and,
- peripheral edema (grade 1 / 2) reported in three (3.2%) participants.

Other less common adverse events include influenza-like symptoms (4.3%), myalgias (4.3%), feelings of anxiety (4.3%), parathesias (4.3%) and local (infusion site) reactions ($\leq$ grade 2) reported in three (3.2%) patients.

The sponsor has attempted to claim that tolerance for the infusion related adverse events develops with continuation of treatment. The sponsor provided analyses of incidence of rigors, fever, nausea, vomiting, and hypotension over the weeks of study in participants receiving systemic steroids as premedication on five or more occasions as compared to study participants who did not receive systemic steroids.

In the first week of study the rigors were reported 80% of steroid treated patients compared to 81% in the steroid free group. In the second week the number of patients

experiencing rigors had decreased to 33.3% in both groups. The number of patients reporting rigors and the number of events reported continued to decline each week with fewer events reported in the steroid free group as a rule. However, meperidine was used in a significant number of study participants to control rigors associated with Campath-1h infusion. Since patients who received continuing meperidine therapy for management of rigors are not excluded from this analysis, the role of tolerance in the decline in the incidence of rigors over the course of study can not determined.

Fever was reported in 60.5% of the steroid treated group as compared to 70.5% of the patients in the non-steroid treated group in the first week of therapy despite use of acetaminophen therapy. By the second week of study, the percentage of patients in the steroid group reporting this toxicity has decreased to 27.8%, while in the steroid free group the number was 29.4%. The number of events and the number of patients experiencing events remain in the 20 – 30% range until the seventh week of therapy when less than 20% of patients in either group were reported to have fever. It is possible that patient develop tolerance however continued use of antipyretics post-treatment may have influenced the occurrence of fever.

During the first week of treatment, nausea was reported in 42.1% of the steroid treated patients and in 40% of the non-steroid treated patients. By the second week of treatment this toxicity was reported 13.9% of the steroid treated group and in 11.8 % of the non-steroid treated group. The incidence of nausea was similar in both groups after the fourth week of therapy and was less than 10% in both groups. Vomiting was reported in 11.8% of the steroid treated patients and 29.1% of the non-steroid treated patients in the first week, in 5.6% and 13.7% respectively in the second week, 2.7% and 11.5% respectively in the third week. The incidence of vomiting continued to decline for the remaining weeks of study with an overall incidence of less than 5%. Patients who received antiemetic treatment chronically during Campath-1h therapy are included in patient group reported above. Continued antiemetic therapy rather than development of tolerance may have played a significant role in the decline in the incidence of nausea and vomiting. Use of steroids does not appear to influence the incidence of nausea and vomiting.

Hypotension was reported in 15.8% of the steroid treated patients compared to 7.3% of the non-steroid treated group during the first week. The incidence of hypotension in the steroid treated group dropped to 2.8% compared to 7.8% in those patients not treated with steroids in the second week. In the third week the incidence was 2.9% in the steriod treated group as compared to 1.9% in the untreated group. No reports of hypotension related to infusion were reported after week seven. While it is possible that tolerance may play a role in the prevention of infusion related hypotension, the numbers are too small to draw any conclusions. Steroids appear to ameliorate this toxicity.

As noted in the Table of Hospitalizations and Serious Adverse Events (Table 211-11) six patients (06-017, 06-019, 06-020, 06-094, 07-051, 013-096) discontinued therapy or were discontinued from therapy due to infusion related side effects. Four patients (01-040, 02-026, 07-007, 27-062) had serious infusion related adverse events. Tolerance to the infusion related side effects may develop over the course of Campath-1h therapy,

however the use of steroids, antiemetics, meperidine, and antipyretics contribute significantly to the reduction in infusion related toxicities. From the data presented in the application, claims with regard to tolerance can not be substantiated.

Infections during Study

Prophylaxis

Use of trimethoprim-sulfamethazole and an antiviral agent (usually famcyclovir) were required on study and for two months or more after completion of therapy to prevent infectious complications due to suppression of CD3+ / CD4+ cells secondary to Campath-1h therapy. Two patients (11-053, 13-096), who were discontinued from study after one and three infusions respectively, were not prophylaxed. Eighty (86%) study participants received both PCP and antiviral prophylaxis for the duration of Campath-1h therapy. (Patients who received pentamidine or dapsone in place of trimethoprim-sulfamethazole are considered as having received PCP prophylaxis.) Twelve patients did not have adequate prophylaxis during Campath-1h therapy. Two patients (7-001, 7-006) did not receive any PCP prophylaxis. Patient 7-006 developed PCP pneumonia. Two patients (6-093, 13-028) did not receive any antiviral prophylaxis. Patient 6-093 developed a CMV infection. In addition seven patients had trimethoprim-sulfamethazole prophylaxis discontinued prior to the completion of Campath-1h therapy usually for allergic manifestations and one patient, 6-033, had antiviral prophylaxis discontinued after two weeks on study developed grade 3 CMV infection.

Post study sixty-one (65.6%) patients were continued on PCP and antiviral prophylaxis for $\geq$ thirty days after discontinuation of Campath-1h. Several patients were continued for more than six months. Thirteen patients were not prophylaxed post study for either PCP or viral infections. Seven patients, noted above, did not continued PCP prophylaxis but did continue antiviral prophylaxis. Five patients did not continue antiviral prophylaxis but did continue PCP prophylaxis. One patient (7-007) who was did not receive antiviral prophylaxis post therapy developed an infection with neutropenia post study that was reported to respond to famcyclovir therapy.

Infections and Neutropenia

In reviewing information about infections that occurred during the course of Campath-1h therapy or in the six months following therapy, difficulties arose in attempting to determine the total number of infections and the relationship to study drug therapy. Problems that occurred included the simultaneous occurrence of two or more infections in the same patient, changes in the degree of neutropenia due to the delayed effect of Campath-1h on hematopoeisis, or assignment of more than one NCI grade or COSTART descriptive term to the same infection. A listing of infections reported by the sponsor in Data Listing # 14.2.3.2 was reconciled with information in the hospitalization and adverse event table noted in a previous section. From review of this information it was determined that sixty-two patients experienced one hundred forty-two infections of all grades. One hundred twenty-nine infections were considered related to Campath-1h

therapy. The degree of neutropenia during infections was determined from CRF / Hematology listing and reported in Table 211-14 along with information about number and types of infections reported on or post study.

Table 211-14: Drug Related Infections on Therapy or Post Therapy (≤ 180 Days)* with Information about Degree of Neutropenic Toxicity During Infection

Type of Infection	Total No. Infections N = 129	Gr. 1 N=17	Gr. 2 N= 60	Gr. 3 N = 31	Gr. 4 N = 21	Total Infections with Gr. 3 / 4 Neutropenia (N = 65)
BACTERIAL	47					(25)
Sepsis	18	1	2 (2)	9 (2)	6 (6)	(10)
Pneumonia	16	-	3 (1)	6 (4)	7 (4)	(9)
Gastroenteritis	2	-	-	2 (2)	-	(2)
Endoophthalamitis	1	-	1	-	-	-
Meningitis (Listeria)	1	-	-	1	-	-
Urinary Tract Infection	3	1 (1)	2	-	-	(1)
Infusion Site Related	2	1 (1)	1 (1)	-	-	(2)
Dental Abscess	2	-	2 (2)	-	-	(2)
Perianal Abscess	2	-	1 (1)	-	1 (1)	(2)
FUNGAL INFECTIONS	27					(12)
Candida, Systemic	1	-	1 (1)	-	-	(1)
Candida, Pneumonia	1	-	1 (1)	-	-	(1)
Candida, Oral / Esophageal	14	4 (1)	9 (4)	1	-	(5)
Torulopsis, Pneumonia	2	-	-	1	1	-
Fungal Ulcer, Stomatitis	1	-	1 (1)	-	-	(1)
Mucurmycocsis	2	-	-	-	2	-
Aspegillosis	4	-	1	1 (1)	2 (1)	(2)
Cryptococcal Pneumonia	1	-	-	-	1 (1)	(1)
Oncomycosis	1	1 (1)	-	-	-	(1)
VIRAL INFECTIONS	23					(14)
CMV Infection	9	-	5 (3)	4 (2)	-	(9)
Rhinovirus, RSV	1	-	-	1 (1)	-	(1)
Herpes Zoster / Varicella	3	-	2	1	-	-
Herpes Simplex, Oral, Genital	8	3	2 (2)	3 (2)	-	(4)
PROTOZOAN	1					
PCP	1	-	-	-	1	-
OTHER INFECTIONS	33					(15)
Fever, Infection, NOS	5	-	5 (3)	-	-	(3)
Influenza Symptoms	4	1	3 (3)	-	-	(3)
URI / Bronchitis	16	1	14 (3)	1	-	(3)
Sinusitis	6	3 (3)	3 (1)	-	-	(4)
Pharnygitis	1	1 (1)	-	-	-	(1)
Diarrhea	1	-	1 (1)	-	-	(1)

Two infections occurred at > 180 days but were related to study drug.

In 50% of the Campath-1h-related infectious episodes, Grade 3 / 4 neutropenia was involved. Ten infections reported in above table were fatal. Four deaths were due to Pseudomonas sepsis, three with gr. 4 neutropenia. Two deaths were due to mucormycosis. One death from mucormycosis was reported in a patient with bone marrow hypoplasia and one death reported in a patient with prolonged Grade 3 / 4 neutropenia. One death was due to Aspergillus, and one due to Cryptococcal pneumonia (in a patient with Grade 4 neutropenia). Two deaths were due to neutropenia sepsis (no organism identified).

Forty-seven (35.9%) of the infections considered Campath-1h related are regarded as opportunistic in nature. The following infections are considered as serious opportunistic infections:

- one Grade 3 oral / esophageal infection; one episode of Candida pneumonia; and one episode of systemic Candidiasis;
- nine reports of CMV in seven patients with four Grade 3 infections (one Grade 3 infection occurring in a patient who did not receive antiviral prophylaxis)
- Three Grade 3 episodes of Herpes simplex in three patients;
- four episodes of Aspergillus in four patients with three Grade 3 events;
- three cases of Zoster/Varicella in three patients with one of Grade 3 severity;
- two episodes of mucormycosis (fatal) in two patients;
- two reports of Torulopsis glabrata pneumonia in two patients; and
- one report of Listeria meningitis Gr. 2, one report of PCP pneumonia, Gr. 4, in a patient who failed to take PCP prophylaxis, and one report of fatal Cryptococcal pneumonia, Gr. 4.

In summary twenty-seven (29.0%) study participants had serious opportunistic infections during or after Campath-1h therapy.

Hematologic Toxicity

Pancytopenia

Nine (8.6%) study participants were reported by the sponsor to have pancytopenia as an adverse event. These patients are reviewed here.

- Patient, 6-027 had Gr.1 –2 anemia and Gr. 1 – 2 neutropenia on study. Platelet counts improved over the course of study and follow-up. The reviewer does not consider this patient as pancytopenic.
- Patient 1-002 who had nine Campath-1h infusions prior to discontinuation for pancytopenia had no evidence of marrow recovery at the time of her demise.
- Patient 6-016, who had twenty infusion prior to discontinuation, did not have recovery of myeloid or erythroid toxicity at the time of death from Cryptococcal penumonia.
- Patient 6-038, who had thirteen infusions, died from cerebral Mucormycosis without documented marrow recovery.
- Patient 6-023 was discontinued after twenty Campath-1h infusions. Patient had erythrotoxicity for four months post therapy despite continued use of EPO. The patient had continued neutropenia and thrombocytopenia with recovery to baseline in both blood elements after three and one half months.
- Patient 6-032 developed marrow suppression after fifteen Campath-1h infusions. This patient required EPO, G-CSF, RBCs, and platelet transfusions. Recover in peripheral blood was documented approximately four months after discontinuation of study drug.
- Patient 7-007, reported to have bone marrow aplasia, had received twelve infusions of Campath-1h. Recovery of hemoglobin and platelet counts to baseline values is noted after six months, but neutrophil counts > 2000/ul were not consistently reported until

ten months after onset of neutropenia. This patient was hospitalized for five days for an infection of unknown etiology that responded to valacyclovir.

- Patient 11-052, who received thirty-five Campath-1h infusions, had erythroid toxicity for two months before recovery to baseline, platelet toxicity for four months before recovery, and prolonged neutropenia gr. 3 / 4 with recovery to baseline after nine months. This patient had one episode of grade 2 fever and grade 2 cough with grade 2 / 3 nuetropenia requiring five days of hospitalization.

Autoimmune Complications

Five patients appear to have autoimmune complications related to Campath-1h.

- Patient 27-062, previously described, died from autoimmune thrombocytopenia secondary to Campath-1h therapy.
- Patient 12-011 had Campath-1h therapy discontinued after 24 infusions due to thrombocytopenia. The patient was hospitalized ten days later for five days for treatment of autoimmune thrombocytopenia secondary to Campath-1h. Despite aggressive measures the patient expired due to complications of thrombocytopenia.
- Patient 18-071 developed rectal bleeding with grade IV thrombocytopenia on the ninth day of study. The patient received IV IG as an outpatient with marked improvement in platelet counts. Campath-1h therapy was continued for an additional four weeks until grade 4 thrombocytopenia recurred. The patient was begun on alternative therapy for disease progression and died from gastrointestinal bleeding with persistent thrombocytopenia. It is unclear whether the thrombocytopenia was due solely to disease progression or if Campath-1h therapy continued after IVIG treatment may have contributed.
- Patient 26-073 developed grade 2 hemolysis and fever while on Campath-1h therapy. Therapy was discontinued three weeks after hemolysis was reported. The hemolysis resolved about three months after onset. The hemolysis was demonstrated to be secondary to Campath-1h therapy.

Blood Product Usage

Blood product usage on and post study (until progression) is discussed here. Information on transfusion history for the month prior to study is also included. Reporting of RBC transfusion are used to designate not only RBC transfusions but also whole blood transfusions. [An excessive number of "whole blood transfusions were reported, and question is raised as to the possibility of a reporting error.] Seventy-five (80.6%) patients enrolled on this study had no history of transfusions in the month prior to study. Of these seventy-five patients:

- Twenty-five patients completed therapy without transfusion.
- Twenty-seven patients, with no prior transfusion history, required RBC transfusions during therapy.
  - Fifteen required five or fewer RBC transfusions.
  - Ten required between six to ten transfusions.
  - Two patients received thirteen and fourteen units each.
- Twenty patients required transfusion with both RBCs and platelets.

    - Eight patients received less than five units of RBCs, nine between six and ten units, three patients twelve, fifteen, and eighteen units respectively.
    - Platelets were transfused once in ten patients, twice in three patients, thrice in four patients, four times in two patients, six times in one patient, and fifteen times in one patient.
- Three patients receive platelets only: 11-009 on one occasion; 11-050 on two occasions; and, 12-001 on eight occasions.

Eighteen patients had a transfusion history for RBCs and / or platelet transfusions in the month prior to study. Or these eighteen patients, nine patients were reported to have received only RBC transfusions in the month prior to study while nine had received both blood products.

- One patient required no transfusions on study.
- Two patients did not have an increase in the number of RBC transfusions on study.
- One patient was noted to have an increase in transfusions compared to the month prior to study.
- Five patients had an increase in RBC transfusions and in addition required platelets during or post therapy.
- Eight patients entered study with a history of platelet and RBC transfusions in the month prior to study.
    - Five patients had an increase in transfusion requirements.
    - Three patients had no change in the number of transfusions as compared to the month prior to study.
- One patient who received platelet transfusions prior to study was treated with IV gamma globulin and received no platelet transfusions on study. This patient but did require three units RBCs during study.

Sixty-seven (72.0%) study participants required transfusion of RBCs and / or platelets on or post study. New transfusion requirement noted in fifty patients. Sixty-two patients required more than 456 units of RBCs / whole blood. Six patients (7-043, 11-004,16-081, 18-0710, 26-085, and 27-067) required transfusion with a total of 119 units (range: 18 – 26 units) and excluded from the following analysis. For the other fifty-six patients who had RBC transfusions, the average number of RBC transfusions was 6 units, the median was 6 units (range: 2 –14). The median time on study for this group of fifty-four patients was 8 weeks (range: <1 – 14 weeks).

Thirty-five (38%) patients were infused with platelets hundred sixty-seven or more times on or post study. (Since both single donor and multiple units were used, the number of occasions on which platelets were infused is reported.) Patient 18-071 received platelets on fifteen occasions, patient 26-085 was transfused on eighteen occasions, and patient 27-067 was transfused on thirty-two occasions. These three patients are excluded from the following analysis. The remaining thirty-two patients experienced platelet transfusions and average of 2.9 times with a median of 3 times (range: 1 – 10 times). Median time on study for these thirty-two patients was seven weeks with a range from < 1 – 12 weeks. For comparison the median time on study for the twenty-five patients who were never transfused was eight weeks (range: 1 –14 weeks). Gamma globulin use was reported in twenty-one (22.6%) participants during study.

Hemoglobin Toxicity

Over the period of Campath-1h treatment and for the thirty days after completion of treatment seventy-seven (83%) patients developed some degree of hematological toxicity (Grade 1 –4) and thirty-eight (41%) patients had one or more episodes of Grade 3 or 4 hematological toxicity.

At baseline twenty-three (24.7%) participants had NCI CTC grade 0 hemoglobin values, thirty-six (38.7%) had grade 1 values, twenty-nine (31.3%) had grade 2 values, and 5 (5.4%) had grade 3 values. The number and percentage of patients who had improvement, no change, or worsening in hemoglobin status including the number (percentage) patients with grade 3 / 4 hemoglobin toxicity is reported in Table 211-5. Baseline information was not available on three patients.

Table 211-15: Change in Hemoglobin NCI-CTC Grade from Baseline: All Patients (N= 90)

Weeks on Study	No. Patients	No. Improved (%)	No. Unchange (%)	Decline ≥ Gr. 1 N (%)	New Gr. 3 / 4 (%)
Weeks 1 – 2	90	3 (3.3)	44 (48.9)	43 (47.8)	13 (14.4)
Weeks 3 – 4	88	3 (3.4)	35 (39.8)	50 (56.8)	18 (20.4)
Weeks 5 – 6	74	4 (5.4)	28 (37.8)	42 (57.8)	14 (18.9)
Weeks 7 - 8	67	6 (8.9)	23 (34.3)	38 (56.7)	12 (17.9)
Weeks 9 – 10	43	7 (16.2)	22 (51.2)	14 (32.6)	0 (0.0)
Weeks 11 – 12	41	7 (24.4)	20 (48.8)	11 (26.8)	1 (1.1)
Weeks 13+	15	2 (13.3)	9 (60.0)	4 (26.6)	0 (0.0)
1 Month F/U	82	26 (31.7)	41 (50.0)	15 (18.3)	1 (1.1)
2 Month F/U	61	31 (49.2)	23 (37.7)	8 (13.1)	1 (1.6)

As shown in Table 211-15 during the first eight week of study only 14 – 20% of patients developed grade 3 / 4 anemia. This information is somewhat misleading since: 1) over half of patient on this study received two or more units of RBCs: 2) at least seven patients were reported to have received EPO while on study; and 3) disease progression or Campath-1h therapy may contribute to worsening anemia. Table 211-16 looks at the changes in hemoglobin in responders as compared to nonresponders. Three patients are excluded from the analysis.

Table 211- 16:Change in Hemoglobin NCI-CTC Grade from Baseline: Responders (N = 30) vs. Non-Responders (N = 60)

Weeks On Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	30	0 (0.0)	17 (56.7)	30 (43.3)	60	3 (5.0)	27 (45.0)	30 (50.0)
Wks. 3 – 4	31	0 (0.0)	10 (32.3)	21 (67.7)	52	4 (7.0)	25 (43.9)	28 (49.1)
Wks. 5 – 6	28	1 (3.5)	10 (35.7)	17 (60.7)	46	3 (6.5)	18 (39.1)	25 (54.3)
Wks. 7 – 8	27	2 (3.7)	9 (33.3)	16 (59.3)	40	4 (10.0)	14 (35.0)	22 (55.0)
Wks. 9– 10	18	2 (12.5)	9 (50.0)	7 (38.9)	25	5 (20.0)	13 (52.0)	7 (28.0)
Wks. 11- 12	18	5 (27.8)	9 (50.0)	4 (5.6)	23	5 (21.7)	11 (47.8)	7 (30.4)
Wk. 13+	4	1 (25.0)	1 (25.0)	2 (50.0)	11	1 (9.1)	8 (72.7)	2 (18.2)
1 Month F/U	29	9 (31.0)	16 (55.2)	4 (13.8)	53	17 (32.1)	25 (47.1)	11 (20.8)
2 Month F/U	24	10 (41.7)	11 (45.3)	3 (12.5)	37	20 (54.1)	12 (32.4)	5 (13.5)

An increase in the incidence of hemoglobin toxicity is noted through the first to the eighth week of study in both groups. Interesting, a higher percentage of responders are reported to have a decrease in hemoglobin grade as compared to nonresponders. For those patient continued on study after eight weeks the number of patients who develop a new decline in hemoglobin concentration decreased. Recovery to baseline hemoglobin value or improvement over baseline is noted at the two month follow-up in more responders versus nonresponders. In both group about 13% of the patients have a hemoglobin value lower than baseline at two months follow-up.

Among the three responders one had a decline from grade 0 to grade 1, while two had a decline from grade 0 to grade 2. Five nonresponders (all five reported to have stable disease at end of therapy) were reported to have a decline in hemoglobin value. One patient's value declined from Grade 0 at baseline to Grade 1 hemoglobin at completion of study. Two nonresponders with Grade 0 at baseline were reported as Grade 2 hemoglobin at completion of study. One nonresponder with Grade 1 hemoglobin toxicity developed Grade 2 at follow-up while the fifth non-responder with Grade 2 baseline value declined to Grade 3 with follow-up.

Changes in the grade of hemoglobin toxicity for RBC transfused / EPO treated patients and non-transfused / EPO treated patients are shown in Table 211-17.

Table 211-17:Changes in NCI-CTC Hemoglobin Grade from Baseline: Transfused / EPO Patients (N = 59) vs. Non-Transfused, Non-EPO Treated Patients (N =31)

Week on Study	Transfused / EPO Patients (N =59)				Non-Transfused or EPO Treated Patients (N = 31)			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	59	3 (5.0)	28 (47.5)	28 (47.5)	31	0 (0.0)	16 (51.6)	15 (48.4)
Wks. 3 – 4	57	3 (5.3)	20 (35.1)	34 (59.6)	31	0 (0.0)	15 (48.9)	16 (51.6)
Wks. 5 – 6	46	4 (8.7)	13 (28.3)	29 (63.0)	28	0 (0.0)	15 (53.1)	13 (46.4)
Wks. 7 – 8	41	5 (12.2)	9 (22.0)	27 (61.4)	26	1 (3.8)	14 (53.8)	11 (42.3)
Wks. 9 – 10	28	6 (21.4)	10 (35.7)	12 (42.9)	15	1 (6.7)	12 (80.0)	2 (3.3)
Wks, 11 – 12	26	8 (30.8)	9 (34.6)	9 (34.6)	15	2 (13.3)	11 (73.4)	2 (3.3)
Wks. 13+	10	2 (20.0)	5 (50.0)	3 (30.0)	5	0 (0.0)	4 (80.0)	1 (20.0)
I Month F/U	55	22 (40.0)	21 (38.2)	12 (21.8)	27	4 (14.8)	20 (74.0)	3 (11.1)
2 Month F/U	38	22 (57.9)	11 (28.9)	5 (15.2)	23	8 (34.8)	12 (52.2)	3 (13.0)

In both the transfused and non transfused groups about 50% of the participants have a decline of one grade in hemoglobin concentration during the first week of study. As

patients continue on study a more patients are noted to have a decline in hemoglobin concentration in the transfused / EPO group as compared to the untreated group. At two months of follow-up 15% of the EPO / transfused group and 13% of the nontransfused and non-EPO treated group continue to have a hemoglobin value lower than baseline.

In summary, changes in hemoglobin value are noted in the majority of patients, are serious requiring transfusion to maintain adequate levels of hemoglobin in more than half of the study population, do not appear to be influenced by response / non-response to therapy, and toxicity does not decrease over the duration of study.

Neutropenia

Changes in the WBC from baseline, during study, and for thirty days post study were reviewed. Eighty-three (89%) patients experienced one or more episodes of new or worsening neutropenia (any Grade 1 - 4). Sixty-four (69%) patients had one or more episodes of Grade 3 or Grade 4 neutropenia. Prolonged recovery from neutropenia was noted in some patients.

At baseline fifty-two (62.4%) participants had baseline NCI CTC Grade 0 neutrophil counts, eleven (11.8%) had Grade 1 neutropenia, seven (7.5%) had Grade 2 neutropenia, seven (7.5%) had Grade 3 neutropenia, and ten (10.8%) had Grade 4 neutropenia. Table 211-18 provides information on the number of patients who experienced changes in neutrophil counts over the course of study along with the number of patients experiencing new Grade 4 neutropenia. Baseline information was missing on one patient.

Table 211-18:Number of Patients (%) with Changes in Neutrophil Counts from Baseline by NCI CTC Grade: All Patients (N = 92)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Decline by ≥ Gr. 1 N (%)	No. with New Gr. 4 Neutropenia
Weeks 1 – 2	92	11 (12.0)	35 (38.1)	45 (48.9)	13 (14.1)
Weeks 3 – 4	88	10 (11.4)	25 (28.4)	53 (60.2)	16 (18.2)
Weeks 5 – 6	74	10 (13.5)	22 (29.7)	42 (56.8)	16 (21.6)
Weeks 7 - 8	67	6 (8.9)	25 (37.3)	35 (52.2)	12 (17.9)
Weeks 9 - 10	43	6 (14.0)	16 (37.2)	21 (48.8)	7 (16.3)
Weeks 11 - 12	39	6 (15.4)	16 (41.1)	17 (43.6)	3 (7.7)
Weeks 13+	15	1 (6.7)	8 (53.3)	6 (46.0)	3 (20.0)
1 Month F/U	81	12 (14.8)	31 (38.3)	38 (46.9)	10 (11.0)
2 Month F/U	61	14 (23.0)	27 (44.2)	20 (37.8)	5 (8.2)
4 Month F/U	66	19 (28.8)	30 (45.4)	17 (25.8)	3 (4.5)

During the first ten weeks of study 49 – 60% of the population had a one grade or greater decline in neutrophil count with 14 – 22% of the study population reported to have new Grade 4 neutropenia. At two months of follow-up 11% of the participants had new grade 4 neutropenia as compared to baseline. At two months of follow-up 8.2% of the participants had Grade 4 neutropenia, and at four months 4.5%. To determine if the state of disease played a role in the development of neutropenia on therapy, changes over time in neutrophil count for responders were compared to changes in nonresponders as shown in Table 211-19.

Table 211-19: Changes in Neutrophil Counts from Baseline: Responders (N = 31) vs. Non-Responders (N = 61)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	31	4 (12.9)	22 (35.5)	16 (51.6)	61	8 (13.1)	24 (39.3)	29 (47.6)
Wks. 3 – 4	31	3 (9.7)	10 (32.3)	22 (71.0)	57	7 (12.3)	15 (26.3)	25 (61.4)
Wks. 5 – 6	28	3 (10.7)	7 (25.0)	18 (64.3)	46	7 (15.2)	15 (32.6)	24 (52.5)
Wks. 7 – 8	27	1 (3.7)	11 (40.7)	15 (55.6)	40	5 (12.5)	15 (37.5)	20 (50.0)
Wks. 9– 10	18	1 (5.6)	8 (44.4)	9 (50.0)	25	5 (20.0)	8 (32.0)	12 (48.0)
Wks, 11 – 12	16	1 (6.2)	9 (56.3)	6 (37.5)	12	5 (21.7)	7 (30.4)	11 (47.8)
Wks, 13+	4	0 (0.0)	4 (00.0)	0 (0.0)	11	1 (9.1)	4 (36.3)	6 (54.5)
1 Month F/U	29	3 (10.3)	12 (41.4)	14 (48.3)	52	9 (17.3)	19 (36.5)	24 (46.3)
2 Month F/U	24	3 (12.5)	13 (54.2)	8 (33.3)	37	11 (29.7)	14 (37.8)	12 (32.5)

During the first ten weeks of study, the number of patients in both groups with a one grade or more change in neutrophil count is slightly higher in responders than nonresponders. At two months follow-up one third of both responders and non-responders have neutrophil counts one grade or more worse than baseline. Interestingly 12.5% of the responders and 29.7% of the nonresponders have improvement over baseline at two-month of follow-up suggesting recovery from therapy-related toxicity. Improvement is neutrophil counts noted in some patients may be due to the use of growth factor so the changes in neutrophil counts were compared for growth factor recipients compared to patients who did not receive growth factor. Table 211-20 includes the changes in neutrophil count in growth factor recipients as compared to non-recipients.

Table 211-20: Changes from Baseline in Neutrophil Count: Growth Factor (N=33) vs. No Growth Factor (N=59)

Week on Study	Growth Factor Use				No Growth Factor Use			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	33	4 (12.1)	9 (27.3)	21 (63.6)	59	8 (13.6)	26 (44.1)	25 (42.4)
Wks. 3 – 4	30	2 (6.7)	4 (13.3)	24 (80.0)	58	8 (13.8)	21 (36.2)	29 (50.0)
Wks. 5 – 6	21	2 (9.5)	4 (19.0)	15 (71.4)	53	8 (15.1)	18 (34.0)	27 (50.9)
Wks. 7 – 8	17	0 (0.0)	5 (29.9)	12 (70.6)	50	6 (12.0)	21 (42.0)	23 (46.0)
Wks. 9 – 10	9	0 (0.0)	3 (33.3)	6 (66.7)	34	6 (17.6)	13 (38.2)	15 (44.1)
Wks, 11 – 12	8	1 (12.8)	1 (12.5)	6 (75.0)	31	5 (16.1)	15 (48.4)	11 (35.5)
Wks. 13+	7	1 (14.3)	2 (28.6)	4 (57.1)	8	0 (0.0)	6 (65.0)	2 (25.0)
I Month F/U	33	2 (6.1)	13 (39.4)	18 (54.5)	48	10 (20.8)	18 (37.5)	20 (21.7)
2 Month F/U	24	2 (8.3)	10 (41.7)	12 (50.0)	37	12 (32.4)	17 (45.9)	8 (21.7)

As expected a higher percentage of the growth factor treated group had a decline from baseline in neutrophil counts as compared to non-recipients. In the group not exposed to growth factors improvement in neutrophil counts is noted in 13 – 18% over the course of study and in 32.4% at two months of follow-up. At two months follow-up 50% of the patients in growth factor group had lower neutrophil count than at baseline. (Four Grade 4 and one Grade 3 toxicity observed in four patients with grade 0 or 1 neutropenia at baseline.) In the non-recipients eight patients had neutrophil counts less than baseline. (Five Grade three neutropenias and one grade four neutropenia were observed in six patients with grade 0 or 1 at baseline.) Twelve non-recipients had a one grade or greater improvement in neutrophil counts.

In summary, neutropenia of some degree was noted in about 90% of the study population. New or worsening serious (Grade 3 or 4) neutropenia was observed at least once in 69% of the study participants on study or with thirty days of discontinuation of Campath-1h therapy. Neutropenia was observed in responders as well as non-responders. Prolonged

recovery from serious neutropenia was observed in a small number of patients. The increased incidence of infection and mortality associated with infection confirms Campath-1h therapy is associated with granulocyte toxicity.

Platelets

Seventy-two (77%) study participants experienced a new onset of thrombocytopenia or a worsening of at least one grade from baseline in platelet count at least once on study or within thirty days of discontinuation of Campath-1h therapy. Forty-nine (53%) participants experienced one or more episodes of grade 3 or 4 thrombocytopenia.

At baseline thirty-nine (41.9%) of the participants had NCI CTC grade 0 thrombocytopenia (normal platelet count), sixteen (17.2%) grade 1, twenty-one (22.6%) grade 2, fifteen (16.1%) grade 3, and one (1.1%) grade 4 thrombocytopenia. In one patient baseline platelet count was not reported. Table 211-21 presents information by two-week intervals about the number of patients who experienced changes in their platelet count from baseline over the course of the study.

Table 211-21:Changes from Baseline in Platelet Count: All Patients (N = 92)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Decline ≥ Gr. 1 N (%)	No. with New Gr. 4 Thrombocytopenia
Weeks 1 – 2	92	0 (0.0)	27 (29.3)	65 (70.7)	8 (8.7)
Weeks 3 – 4	88	3 (3.4)	42 (47.7)	43 (48.9)	8 (9.1)
Weeks 5 – 6	74	4 (5.4)	39 (52.7)	31 (41.9)	2 (2.7)
Weeks 7 - 8	67	7 (10.4)	40 (59.7)	20 (29.9)	3 (4.5)
Weeks 9 – 10	43	7 (16.3)	20 (46.5)	16 (37.2)	2 (4.7)
Weeks 11 – 12	41	8 (19.5)	24 (58.5)	9 (21.9)	0 (0.0)
Weeks 13+	15	1 (6.7)	9 (60.0)	5 (33.3)	1 (6.7)
1 Month F/U	82	25 (30.5)	41 (50.0)	16 (19.5)	4 (4.9)
2 Month F/U	61	19 (31.1)	35 (57.4)	7 (11.5)	2 (3.3)

During the first two week of study sixty-five (70.7%) of the participants had decrease in platelet count. About 8.7% of the patients developed new grade 4 thrombocytopenia. In the third and fourth week of study 48.9% of the participants had a decrease in platelet count by at least one grade, while 9.1% developed grade 4 thromboctyopenia. The number of patients with new grade 4 thrombocytopenia decreased by more than half for the remainder of study. Two patients were reported with new grade 4 thrombocytopenia at two months of follow-up due to disease progression. Changes from baseline in platelet count were analyzed for responders compared to non-responders to determine if progression of underlying disease influenced the change in platelet count. Data is shown in Table 211-22.

Table 211-22: Changes from Baseline in Platelet Grade: Responders (N = 31) vs. Non-Responders (N = 61)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	31	0 (0.0)	9 (29.0)	22 (71.0)	61	0 (0.0)	18 (29.5)	43 (70.5)
Wks. 3 – 4	31	1 (3.2)	15 (48.4)	15 (48.4)	57	3 (5.3)	26 (45.6)	28 (49.1)
Wks. 5 – 6	28	3 (10.7)	13 (46.4)	12 (42.9)	46	1 (2.2)	26 (56.5)	19 (41.3)
Wks. 7 – 8	27	3 (11.1)	19 (70.4)	5 (18.5)	40	4 (10.0)	21 (52.5)	15 (37.5)
Wks. 9– 10	18	4 (22.2)	10 (55.6)	4 (22.2)	25	3 (12.0)	10 (40.0)	12 (48.0)
Wks, 11 – 12	18	4 (22.2)	12 (66.7)	2 (11.1)	23	4 (17.9)	12 (51.2)	7 (30.4)
Wks, 13+	4	0 (0.0)	2 (50.0)	2 (50.0)	11	1 (9.1)	7 (63.6)	3 (27.2)
1 Month F/U	29	8 (27.6)	19 (65.6)	2 (6.8)	53	16 (30.2)	23 (43.4)	14 (26.4)
2 Month F/U	24	8 (33.3)	14 (58.3)	2 (8.3)	37	11 (29.7)	21 (56.8)	5 (13.5)

No difference is noted during the first six weeks of study between the responders and non-responders with regard to the development of thrombocytopenia. After week six more non-responders have decline in the platelet count value of one grade or more. At two months follow-up more nonresponders are noted to be thrombocytopenia. Two responders are reported with a decrease in platelet count one with grade 2 (grade 1 at baseline) and one with grade 3 (grade 0 at baseline). The change in grade of platelet count was also compared in patients who received platelet transfusions as compared to those who did not require transfusion. Data is presented in Table 211-23.

Table 211-23: Changes from Baseline in Platelet Count:
Transfused (N = 34) vs. Non-Transfused Patients (N = 59)

Week on Study	Transfused (N = 11)				Non-Tranfused (N = 13)			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	33	0 (0.0)	10 (30.3)	23 (69.7)	59	0 (0.0)	17 (28.8)	42 (71.2)
Wks. 3 – 4	31	1 (3.2)	10 (33.3)	20 (64.5)	57	2 (3.5)	32 (56.1)	23 (40.4)
Wks. 5 – 6	22	1 (4.5)	12 (54.6)	9 (40.9)	52	3 (5.8)	27 (51.9)	22 (42.3)
Wks. 7 – 8	20	4 (20.0)	7 (35.0)	9 (45.0)	47	3 (6.4)	33 (70.2)	11 (23.4)
Wks. 9 – 10	13	4 (30.8)	3 (23.1)	6 (46.1)	30	3 (10.0)	17 (56.7)	10 (33.3)
Wks, 11 – 12	13	5 (38.4)	4 (30.8)	4 (30.8)	28	3 (10.7)	20 (71.4)	5 (17.6)
Wks. 13+	5	1 (20.0)	2 (40.0)	2 (40.0	10	0 (0.0)	7 (70.0)	3 (30.0)
I Month F/U	33	13 (39.4)	12 (36.4)	8 (24.2)	49	12 (24.5)	29 (59.2)	8 (16.3)
2 Month F/U	24	11 (45.8)	9 (37.5)	4 (16.7)	37	8 (21.6)	26 (70.3)	3 (8.1)

In both groups decline in platelet count of one or more grades in reported for 70% of the patients in both groups. Except for week 5 – 6 decreases in platelet count are more common in the transfused as compared to the non-transfused group. Persistent decrease in platelet count grade from baseline is noted at two month follow-up in four of the transfused patients (two with grade 3 and two with grade 4 thromboctyopenia) and three of the non-transfused patients (none greater than grade 2). Eight (21.6%) of the non-transfused patients had improvement in platelet count over baseline at two months of follow-up.

In summery, Campath-1h therapy is responsible for in hematological toxicity. The toxicity appears to continue over the entire course of therapy for RBC and WBCs and less so for platelets. A decline in hemoglobin of one grade or more was noted in 82% of the participants. New or worsening Grade 3 or 4 anemia was observed in 41% of patients. Seventy percent of the study population required RBC transfusions. A decrease in neutrophil count of one or more grades was observed in almost 90% of the study

participants. New or worsening grade 3 or 4 neutropenia was observed in 64% of patients. The large number of infections and treatment delays attest to the potent effect of Campath-1h on the bone marrow granulocytes. As noted previously about half of the infections were associated with grade 3 / 4 neutropenia. The effect of Campath-1h therapy on thrombopoeisis is not as severe as on hematopoeisis and granulocytopoeisis. While 77% of the study participants experienced a one or more grade decrease in platelet count, 52% experienced new or worsening Grade 3 or 4 thrombocytopenia. Campath-1h's effect on thrombopoeisis was most pronounced during the first two weeks of therapy possibly due to acute infusional related thrombocytopenia. As noted above declines in platelet count after the eight week were more often observed in non-responders. Twenty-three (25%) of the study participants with no history of platelet transfusions in the month prior to enrollment received platelet transfusions one or more times while on Campath-1h therapy.

At two month follow-up recovery to baseline or improvement in hemoglobin values over baseline is noted in over 85% of patients. Recovery to baseline or improvement over baseline in platelet counts is noted in over 90% of the study participants. Neutrophil recovery is more prolonged but at four month follow-up for the entire group neutrophil counts were at baseline or improved over baseline in about 75% of the population.

CD4+ Recovery

Table 211-24 provides information on median CD 3+/ CD 4+ counts (range) at baseline, at 4 weeks of study, and at two, four and six months of follow-up by cohorts including the median, minimum and maximum count reported. Study week 4 was selected for the nadir measurement since at this point the most pronounced nadir (2/ul) was observed.

Table 211-24: CD 3+/4+ Counts over the Course of Therapy

	Two Month Cohort (N = 22)		Four Month Cohort (N=10)		Six Month Cohort (N=23)	
Time Point	**No.**	**Median Count (/ul) (Min., Max. / ul)**	**No.**	**Median (Min., Max. / ul)**	**No.**	**Median (Min., Max. /ul)**
Baseline	22	534 (0 , 4145)	10	501 (239 – 3301)	23	647 (0 – 3767)
Study Week 4	21	1 (0, 546)	10	2 (0, 29)	20	3 (0, 272)
Post Study Two Months	22	196 (0, 1010)	8	256 (30, 490)	19	183 (3, 1876)
Four Months	-	-	10	301 (86, 578)	17	309 (12, 2380)
Six Months	-	-	-	-	23	470 (29, 2079)

At two months of follow-up about 50% of the sample continue to have CD3+ / CD 4+ below 200/ul. CD 3+/ CD4+ counts continue to improve at four and six months after discontinuation of therapy but do not reach the baseline median even in the six-month cohort. The finding of continued CD4+ suppression raises questions as to how long PCP and anti-viral prophylaxis should be continued after completion of therapy.

CLINICAL (PATIENT) BENEFIT

Attempts to demonstrate clinical (patient) benefit in responders are limited due to the type of study (single arm open-label) and the fact that the benefit may also involve a response parameter. What follows is a description of the ways in which the reviewer considered responders to demonstrate "benefit" after Campath-1h therapy. Included also is information on patient experienced negative benefit.

With regard to disease symptomatology, ten (100%) of ten patients with B symptoms at study entry had resolution of their B-symptoms. Thirteen (92.9%) of fourteen patients who complained of fatigue at study entry had resolution of this symptom. Nineteen (90.5%) of twenty-one patients with lymphadenopathy at study entry had complete or near complete resolution of adenopathy. In fourteen patients, the adenopathy was bulky and its resolution would be associated with increased comfort and improved appearance. Fifteen (71.4%) of twenty-one patients with significant organomegaly at study entry had resolution of the organomegaly with relief of the symptoms of upper abdominal fullness and early satiety.

Eighteen (81.8%) of twenty-three patients who entered study with Hgb $\leq$ 11 gm% had improvement. Seventeen had normalization of hemoglobin (12 gm% or more). Five had grade 2 hemoglobin at baseline and twelve had grade 1 hemoglobin at baseline. During study nine of these patients required transfusion support. Four developed pancytopenia on study but all had marrow recovery. Grade 0 hemoglobin values (without transfusion support) were noted consistently during the period of objective disease response. Perhaps the most dramatic improvement in hemoglobin is in patient 27-067 who entered study with Hgb 9.5 gm% having received 10 units packed RBCs in the month prior to study. While this patient required twenty-six units RBCs during therapy, at one month post study this patient was transfusion free and remain so for at least six months of follow-up.

One patient had a worsening hemoglobin grade on study with continued transfusion support post therapy. Three patients with grade 1 hemoglobin values at entry had no improvement after completion of therapy, while one patient achieved normalization of hemoglobin with continued use of EPO. Improvement in anemia can be correlated with an improvement in the energy level and decreased feeling of tiredness.

Seventeen patients had evidence of thrombocytopenia (platelet count < 150,000/ul) at study entry. Four patients with platelet counts between 100 – 150,000/ul at baseline had platelet counts over 150,000/ul post therapy. Patient 27-067 had grade 4 thrombocytopenia at entry and required intensive platelet support during therapy (32 transfusion episodes reported on study). This patient became platelet transfusion independent within one month of completion of Campath-1h therapy. Five patients had grade 1 thrombocytopenia at entry. Four of the five had sustained platelet counts > 150,000/ul after completion of therapy. The fifth patient's platelet count improved to greater than 100,000/ul after completion of therapy until disease progression was noted. Two patients with grade 2 thrombocytopenia and two patients with grade 3

thrombocytopenia at baseline had platelet counts post therapy > 100,000/ul that were sustained. One patient with grade 3 improved to a sustained grade 2 platelet counts post study. In toto fifteen of seventeen patients had improvement on or after completion of study drug therapy. Four of these seventeen required platelet transfusions during study. Two patients had a decrease in platelet counts during Campath-1h therapy, a decrease that did not improve post therapy. One of the two patients developed fatal ITP related to Campath-1h therapy. Improvement in platelet count in some of these patients could be linked to decrease bruisability.

Five patients entered study with grade 3 / 4 neutropenia. Four had resolution to grade 0 while one patient improved to grade 2 by the end of study without the use of growth factors. One patient (5-013) whose neutrophil count improved from grade 4 to grade 0 had two serious infections post study, Listeria meningitis and Staphylococcal sepsis. The other four patients with improvement in neutrophil count had no serious infections post study. Eleven of thirty-one responders are noted to have one or more serious infections during or post study. Eight were noted to have grade 3 or 4 infusion related reactions while on study demonstrating that the clinical benefit may be a mixture of positive and negative effects. In conclusion one responder, 4-0092, with stage II CLL at entry was noted to have improved healthwise to such an extent after completion of Campath-1h therapy that he was able to resume fulltime employment.

SUMMARY

This single arm phase II study was conducted in ninety-three CLL patients who had failed alkylating agents (≤ five regimens) and were refractory to fludarabine. The objective of this study was to determine the response rates and the confidence interval around the response rates with Campath-1h therapy. Secondary objectives included evaluation of the safety profile and determination of the clinical benefit of Campath-1h therapy in this patient population. With regard to eligibility eighty-six patients had typical CLL, two atypical CLL, and five to have lymphoma with a hemic phase. Ninety (97.7%) met the NCIWG criteria[3] for treatment of CLL, while all ninety-three met the protocol inclusion criteria for treatment of CLL. After review six patients did not meet the strict definition of "fludarabine refractory". Other deviations from the eligibility criteria are listed in the body of the review.

Patient disposition with regard to discontinuation of therapy is as follows: fifty-nine (63.4%) completed Campath-1h therapy; five (5.4%) discontinued therapy for disease progression; three (3.2%) patients died on study; twenty-two (21.5%) patients were discontinued due to adverse events related to study drug; six (6.5%) refused to continue therapy; and one (1.1%) patient was discontinued by the investigator for "immunosuppression" which on review was actually the expected decline in lymphocyte count secondary to Campath-1h therapy.

An objective response to Campath-1h therapy was observed in thirty-one patients. The overall response rate was 33.3% [95% CI: 23.4, 42.6%]. Median time to response was 1.6 months [95% CI: 1.1, 1.8 months]. Median duration of response as determined by the agency was 6.9 months [95% CI: 4.6, 8.4 months]. At the time of this review, ninety-two (98.9%) of the study participants had progressed with a median progression free survival of 4.0 months [95% CI: 3.2, 4.7 months]. Of the thirty-one responders, thirty (96.9%) had progressed at the time of this review with a median progression free survival reported as 8.8 months [95% CI: 6.2, 10.2 months]. Median time to treatment failure was 3.0 months [95% CI: 2.4, 4.3 months] with ninety-two patients regarded as failed treatment. The one month difference noted between median time to progression and median time to treatment failure is attributed to the fact that 29% of the study population discontinued therapy for reasons other that disease progression or death. Median overall survival is 15.9 months [95% CI: 11.8, + months] with forty-two patients alive as of the cutoff date of February 15, 2000.

All ninety-three patients enrolled on this study received at least one dose of study drug and ninety-two (98.9%) reached the target dose of 30 mg. Thirty (32.3%) study participants had thirty-seven dose delays $\geq$ 7 days. Twenty (21.5%) patients (including seven reported to have dose delays $\geq$ seven days) missed thirty-one single doses of therapy. Over 50% of the missed single doses were related to toxicities associated with Campath-1h therapy while approximately 90% of the dose delays $\geq$ seven days were due to Campath-1h related toxicity.

Nine deaths were noted on study or within thirty days of completion of study drug therapy. Four deaths were infectious in nature and are considered to be related to Campath-1h therapy, four deaths were related to disease progression, and in one case the cause of death is not clear. For the period from greater than thirty days after completion of Campath-1h therapy to six months after completion of therapy, Campath-1h is implicated in nine of fifteen deaths reported during this period. In toto thirteen (14.0%) patients were considered to have expired from causes related to or partially related to Campath-1h therapy.

Nineteen (20.4%) patients were discontinued from therapy for adverse event related to Campath-1h. Six (6.5%) patients refused to continue therapy, three for therapy-related adverse events. In addition two other patients, one reported as completer and one as a progressor, were actually discontinued from study drug therapy for drug related adverse events. Sixty-two (66.7%) of the study participants experienced one hundred fifteen episodes of adverse events requiring hospitalization or /or discontinuation from study during treatment or within one hundred eight days of treatment completion. Eighty-four of these episodes are considered to be related to Campath-1h therapy. Included are ten episodes of infusion related adverse events, sixteen episodes of infections without myelosuppression, thirty episodes of infections with neutropenia (gr. 3 or 4), and twelve episodes of hematological toxicity without fever. Six (6.5%) study participants were identified as having transformation to a higher grade malignancy on therapy. Two participants were noted have developed a new second malignancy other than basal cell carcinoma.

The most common adverse events associated with Campath-1h therapy include infusion related events, infectious complications, and hematological complications. Common infusion related toxicities include rigor (89.2%) with Grade 3 rigors in 11.8% fever (81.7%) with Grade 3 fever in 12.9%; nausea (47.3%), vomiting (33.3%), rash (28%), urticaria (21.5%) and dyspnea (17.2%). Less common but serious side effect include: bronchospasm was reported in 9.7% with Grade 3 or 4 bronchospasm reported in two patients, hypotension (15.1%) with Grade 3 hypotension in one patient. Note that all patients were premedicated with acetaminophen and diphenhydramine (or other antihistamine). Other medications used to control infusion related side effects included: corticosteroid usage on more than five occasions in 40.9% of the study population, antiemetics in 42.6%, and narcotic analgesia (merperidine) in 61.3%. Tolerance to infusion related hypotension may have developed over the course of study drug therapy, but the decline in nausea, vomiting, fever, and rigors may be due to the judicious use of other pre- and post therapy medications rather than induction of tolerance.

PCP and antiviral prophylaxis was administered to eighty patients on therapy. PCP prophylaxis was discontinued prior to the end of therapy for allergic or other reasons in seven patients. PCP prophylaxis only was administered to two patients, antiviral prophylaxis only in two patients, and nine patients received no prophylaxis during therapy including two patients who had therapy discontinued after one and three infusions respectively. Sixty-one patients received prophylaxis for one or more months after completion of the Campath-1h infusions. One patient who discontinued PCP prophylaxis while on study developed the only case of PCP pneumonia reported on this study. Two cases of 3 CMV infection were reported in this study population. One patient with CMV infection received no prophylaxis and the other had inadequate prophylaxis.

One-hundred twenty-nine infections that occurred on study drug therapy or within six months (180 days) after completion of study drug therapy are considered to be drug related. Fifty-two (40.3%) infections were of Grade 3 or 4 severity and sixty-five (50.4%) were associated with Grade 3 or 4 neutropenia. Ten deaths on study or within six months of discontinuation of study drug therapy were due to infections. Grade 3 / 4 neutropenia was reported in seven of these events. Twenty-seven (29%) participants had serious opportunistic infections on or post treatment including PCP, CMV, Aspergillus, Candida, Mucormycosis, Toruloposis, Cryptococcus, Candida, H. simplex, H. zoster and Listeria.

Autoimmune thrombocytopenia was observed in three, possibly four patients, with death secondary to the immune thrombocytopenia reported in one patient. Autoimmune hemolysis due to Campath-1h was reported in one patient. Pancytopenia was noted in eight patients and was fatal in three cases. Bone marrow recovery was observed in the remaining five patients at four to ten months after discontinuation of Campath-1h therapy.

Declines in hemoglobin values, neutrophil counts, and platelets are reported over the course of study. Seventy-seven (83%) patients experienced new or worsening hemoglobin toxicity (all grades). Thirty-eight (41%) patients experienced one or more

new episode of Grade 3 or 4 anemia. Eighty-three (89%) patients experienced new or worsening neutropenia (all grades). Sixty-four (69%) patients experienced one or more episodes of Grade 3 or 4 neutropenia. Seventy-two (77%) patients experienced new or worsening thrombocytopenia. Forty-nine (53%) patients experienced one or more episodes of Grade 3 or 4 thrombocytopenia. Over the course of studies sixty-seven (72%) patients required transfusions of RBCs and / or platelets. The median number of RBC transfusion was five units [range: two –fourteen] and the median number of times that platelets were transfused was three time [range: 1 –10]. Seven patients received EPO and thirty-five patients receive growth factor during study.

Review of information on CD3+/CD4+ counts indicates maximal suppression occurs at four weeks after initiation of therapy with over half of the sample population reported to have CD3+/CD4+ counts < 3/ ul. At two month after discontinuation of therapy approximately 50% of the sample had CD3+ / CD4+ counts > 200/ul with a continuing increase in counts over the six months of follow-up. However no cohort's CD4+ counts reach baseline values at the end of follow-up.

In conclusion Study 211 does demonstrate that treatment with Campath-1h results in an objective response rate of 33.3% with duration of response of 6.9 months in a group of CLL patient who have a history of prior alkylator therapy and who were refractory to fludarabine. This study also demonstrates that Campath-1h therapy is associated with a significant degree of toxicity including a 14% incidence of a therapy-related mortality in the study population. The degree of toxicity that would be expected with a new therapy in a heavily pretreated population of CLL patients is not known, but the amount of and degree of Campath-1h-related toxicity observed on this study seems excessive. Further information from a comparative trial is required to better characterize the efficacy and the toxicity profile of Campath-1h. Campath-1h is recommended for accelerated approval.

009 STUDY REVIEW

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009 STUDY REPORT

Title: A Multi-Centre Phase II Study of Campath® in Patients with Chronic Lymphocytic Leukemia Who Have Failed Treatment with Fludarabine

Introduction:

This open-label single arm study was conducted under the sponsorship of Burroughs Wellcome Co from February 8, 1993 until February 3, 1995. Patients were enrolled at six centers in the US. The study was originally designed as an exploratory efficacy study with a first stage enrollment of fourteen patients. If evidence of disease activity was observed in the first fourteen patients, up to fourteen additional patients would be enrolled on study. The study report submitted to the agency was completed on October 28, 1999 under the present sponsor, L & I Partners, LP. The Case Report Forms for the twenty-four patients enrolled on study were submitted for review. The present sponsor obtained additional follow-up survival information through March 1997 for all patients who completed study.

Brief Summary of Protocol:

The objectives of the protocol were:

(1) To evaluate the safety and efficacy of Campath-1h in patients with CLL who had failed to respond to or relapsed following first-line treatment with fludarabine or other chemotherapy regimens followed by second- or third- line fludarabine; and,
(2) To measure the incidence and titers of any antibody raised against Campath-1h.

Pertinent study inclusion criteria included: diagnosis of CLL (B-Cell, T-Cell, or PLL) confirmed on clinical and histological /cytological assessment / flow cytometry; unresponsive to or relapsed following fludarabine therapy; WHO PS $\leq$ 1; life expectancy $\geq$ 12 months; creatinine $\leq$ 1.25 x ULN; bilirubin; aspartate transaminase, alanine transaminase, alkaline phosphatase < 1.25 x ULN; and, adequate venous access. No hematological inclusion / exclusion criteria were included in the eligibility criteria. Pertinent exclusion criteria include: history of bone marrow or other organ transplant; steroid therapy except for maintenance doses; debilitating non-malignant diseases.

Treatment with Campath-1h was initiated at 10 mg daily intravenously until infusion-related toxicities were acceptable, then dose was escalated to 30 mg three times / week. Patients could be escalated to 80 mg three times per week at the investigator's discretion. Premedications including steroids were at the investigator's discretion. Prophylaxis for PCP and herpetic infections was at the investigator's discretion. Use of other antineoplastic agents, gamma globulin, radiation, and prophylactic growth factors was contraindicated. Patients were assessed for disease status every eight weeks. Patients with progressive disease were discontinued at week eight. Patients with complete response

could continue on therapy or be observed off-therapy. For partial responders and stable disease, therapy was continued with assessments for response every eight weeks on study and at completion of therapy. All objective responses were to be reassessed eight weeks after initial observation to confirm response. Responders could be "rested" on study with resumption of Campath-1h therapy at a later time provided no alternative therapy was administered in the interim.

DESCRIPTION OF STUDY POPULATION:

Demographic of Study Population:

Table 009-1: Study Demographics

Demographic Variable	All Patients (N = 24)
Gender	
Male	**15 (62.5%)**
Female	**9 (37.5%)**
Ethnic Group	
White	**24 (100.0%)**
Age (years)	
Median Age	**62**
(Minimum, Maximum)	**(44, 77)**
Rai Stage	
I	**1 (4.2%)**
II	**6 (25.0%)**
III	**3 (12.5%)**
IV	**14 (58.3%)**

Demographics reported in Table 009-1 for the study population are consistent with information from epidemiological studies for gender and age. Lack of inclusion of black patients in the study population is noted.

ELIGIBILITY FOR STUDY:

Disease Type

Twenty-three (95.8%) study participants had B-cell disease while twenty-two (87.5%) had B-CLL. Review of CRFs provided the following information about disease type. Patient 1-001 may have had a B-cell lymphoma with a leukemic phase rather than B-CLL. This patient's disease progressed to a more aggressive lymphoma at the time of discontinuation of Campath-1h therapy. Patient 6-002 had T-PLL as indicated on the prestudy bone marrow report while patient 7-001 had B-PLL.

Stage of Disease

For Study 009 eligibility requirements allowed for the inclusion of all stages of CLL provided that the patient had (1) failed first line therapy with fludarabine or (2) failed first line therapy with another chemotherapy agent(s) and had also failed second or third line therapy with fludarabine. After review of the resubmitted data (August 18, 2000),

FDA and sponsor agree on the Rai stage for twenty-three of the twenty-four study participants. One patient, 002-014, was assessed as Stage 0 by the sponsor, while the FDA considers this patient to be Stage II due to the presence of hepatosplenomegaly on the enrollment CT scan.

Prior Therapies, Refractoriness to Fludarabine

All patients had prior therapy with fludarabine. Twenty-two (91.7%) patients had prior therapy with alkylators. For review purposes the definition of 'fludarabine refractory' that was used to evaluate refractoriness to fludarabine in Study 211 was applied to the Study 009 population. Patients were considered refractory to fludarabine if no objective response (CR, PR) was observed after therapy or if relapse after objective response occurred within six months of completion of fludarabine therapy. Seven (29.2%) patients (002-003, 002-005, 002-010, 002-011, 002-012, 002-014, and 005-001) were assessed as **not** refractory to fludarabine by the sponsor and by the FDA. Two patients (002-007, 006-002) who were not treated with alklylators prior to enrollment on study were refractory to fludarabine, one with no initial response to fludarabine while the other had an objective response lasting less than six months. Prior to entry on study, one patient (002-007) had received only one therapeutic regimen (fludarabine), nine patients had received two therapeutic regimens, six patients three regimens, four patients four regimens, and four patients five or more therapies. Note that intravenous gamma globulin therapy, splenic radiation, and splenectomy were counted as therapeutic regimens on this study.

Other Eligibility Issues

Two patients (002-003, 006-003) had other chemotherapy within three weeks of study entry. One patient (002-006) had a second malignancy (prostate cancer) within five years of enrollment. Four patients (001-003, 002-007, 006-002, and 006-003) had WHO performance status 2. Five patients (004-001, 005-001, 006-001, 006-002, and 006-003) did not have diagnostic histological material available for central review. One patient (004-001) was treated with therapeutic doses of prednisone (60 mg /day) for management of AIHA for the first eleven days of study.

EFFICACY EVALUATION

Patient Disposition

Table 009-2 provides information about patient disposition at completion of Campath-1h therapy. Nine (37.5%) patient completed therapy with remission / stabilization of disease. One of the nine patient died due to Aspergillus / CMV pneumonia during disease remission. Eight (33.3%) patients were reported to have disease progression at discontinuation from study. Three of the eight patients who died had disease progression that occurred within thirty days of the last dose of therapy. One patient, who died with interstitial pneumonia thirty-five days after discontinuation of study drug due the pneumonia, was reported by the sponsor to have progressive disease. Review of CFR did

not provided any documentation of disease progression at the time of the patient's demise. Six (25%) patients discontinued study due to adverse events. Five of these adverse events were clearly related to Campath-1h therapy.

Table 009-2: Patient Disposition

Reason for Discontinuation	No. (%)
Completed Therapy	8 (33.3%)
Progressed on Therapy	5 (20.8%)
Discontinued Due to Adverse Event	11 (45.8%)
Deaths	5
Interstitial Pneumonitis, ?Progressive Disease	1
Invasive Aspergillus, CMV Pneumonia	1**
Cerebral Hemorrhage, Progression	1
Suicide, Progression	1
Sepsis, Progression	1*
Other Adverse Events	6
Fever	2
Pneumonia	2
PCP Pneumonia	1
Pancytopenia, Pneumonia	1

* Discontinued for depression and progression. Had started alternative therapy for disease progression; died within thirty days of last dose of CAMPATH

** Reported to be in remission at time of death

Response Rate, Duration of Response, and Time to Response

Table 009-3 compares the response rates, duration of response and time to response using an intent-to-treat analysis as determined by the FDA and by the sponsor.

Table 009-3: Response Rates, Time to Response, and Duration of Response

Response Category	FDA N = 24 (100%)	Sponsor N = 24 (100%)
Complete Response	--	--
Partial Response	7 (29.2%)	8 (33.3%)
Stable Response	7 (29.2%)	6 (25.0%)
Progressive Disease	4 (16.7%)	6 (25.0%)
Not Evaluable	6 (25.0%)	4 (16.7%)
Estimated Objective Response Rate [95% Confidence Interval]	7 (29.2%) [11.0%, 47.4%]	8 (33.3%) [16%, 55%]
Median Time to Response (Months) (95% Confidence Interval in Months)	3.8 [2.3, 4.0]	3.9 [1.6, 4.2]
Median Duration of Response (95% Confidence Interval in Months) No. Censored (Responders at Data Cutoff Date)	10.8 [5.6, 18.6] 2	15.4 [10.4, +] 4

Differences in response assessments are noted for the following patients.

- **Patient 001-003** was assessed as progressive disease by the investigator based on worsening anemia, thrombocytopenia, and leukopenia. However the CRF contains no other evidence of disease progression and the investigator notes that the criteria for progression have not been met. The FDA considers this patient non-evaluable for response as the pancytopenia may have been due to CAMPATH therapy rather than progression.

- **Patient 002-006** died on study due to interstitial pneumonitis without evidence of disease progression recorded in the CRF. The patient's ALC was 66/ul at the time of his death. No evidence of new or recurrent organomegaly or adenopathy was reported. The FDA considers this patient not evaluable for response. The sponsor's assessment of progressive disease was based on the Off-Study Record sheet check box in the CRF.

- **Patient 002-011**, assessed as stable disease by the review panel, was considered as non-evaluable by the FDA since the patient received only twelve Campath-1h infusions over a three week period (of an eight week cycle) prior to discontinuation for drug related toxicity. Patient had no disease assessments at week 8 and ALC at time that Campath-1h was discontinued was 600/ul.

- **Patient 002-014**, assessed as a partial responder by the sponsor's review panel, was considered as stable disease by the FDA since the patient had no further evaluation of hepatosplenomegaly reported on CT at study entry.

- **Patient 004-001**, who was considered as non-evaluable by the review panel, was assessed as a stable disease response after review of the CRF. All sites of disease were assessed prior to discontinuation of Campath-1h therapy. Adenopathy was slightly smaller, no new organomegaly or change in liver nodules was observed. Bone marrow was improved over baseline with regard to degree of marrow infiltration. New bilateral pleural effusion and upper abdominal ascites were reported on the CT scans at the assessment performed at discontinuation of CAMPATH therapy, however these finding were considered as related to an ongoing pneumonic process present at time that CAMPATH was discontinued.

Of the seven patients considered as objective responders, five were judged to be refractory to fludarabine. Two of five responders had RAI stage II disease and three had Stage IV disease. The range in duration of response for these five patients is from approximately five to thirty-eight months.

Looking at the time event information, the median time to response is slightly shorter when calculated by the FDA. This is due to the fact that an earlier date of response was assigned in three instances (Patient 002-005, Patient 002-008, and Patient 005-001) based on data included in the CRF. The shorter median duration of response reported by the FDA is due to the use of a different definition for disease progression after response. As stated previously, the FDA used the 1996 NCIWG definition for progressive disease,

while the sponsor used a newly defined set of parameters described in the August 18, 2000 BLA resubmission.

Time to Disease Progression (Progression Free Survival), Treatment Failure

Table 009-4 presents information with regard to disease progression and treatment failure. Last follow-up for progression for this study population was March 1997. The sponsor defined time to progression as the time from administration of Campath-1h to the first objective measurement of disease progression by the review panel. The criteria for progression after objective response that was utilized by the review panel was based on the NCI Working Group (1996) definition for progression and the investigator's assessment of disease progression. In the Resubmission (August 18, 2000) the sponsor defined new parameters for progression after response. The FDA has applied the 1996 NCI Working Group definition of progressive disease for progression after response. As a result of these differences, six patients are censored for progression in the sponsor's analysis as compared to two patients in the reviewer's analysis.

Time to treatment failure was defined by the sponsor as the time interval between the date of initial administration of Campath-1h and the date of the last Campath-1h dose for any patients who discontinued study for adverse events or the date given for disease progression or death. The FDA definition of time to treatment failure applied to this study is the time interval between the date of first treatment with Campath-1h to the date of study drug discontinuation due to an adverse event, progression, death, or other event. The sponsor's estimate of time to treatment failure is much shorter than that reported by the FDA because of the difference in definition.

Table 009-4: Information on Progression and Treatment Failure

Parameter	FDA N = 24	Sponsor N =24
No. Progressed (%)	22 (91.7)	18 (75.0)
No. Censored (%)	2 (8.3)	6 (25.0)
Median Disease Free Survival [95% Confidence Interval in Months]	7.1 [3.2, 8.7]	7.1 [2.0, 17.8]
No. of Treatment Failures (%)	23 (95.8)	20 (83.3)
No. Censored (%)	1 (4.2)	4 (16.7)
Median Time to Treatment Failure (Months) [95% Confidence Interval in Months]	3.8 [1.6, 8.6]	2.8 [1.6, 12.1]

The estimate for the median progression free survival (time to progression) is similar for both the sponsor and the agency. Differences in response assessment between the sponsor and the reviewer are presented in Table 009-5.

Table 009-5: Differences in Progression Assessment

Patient No.	FDA Date of Progression (Censor)	Sponsor Date of Progression (Censor)	Reason
001-003	10/17/94 (1)	10/22/94 (0)	10/17/94 date CAMPATH discontinued due to worsening cytopenias; Considered a treatment failure; No other evidence of progression
002-007	8/1/94 (0)	8/1/94 (1)	Date of death due to Aspergillosis;

Patient No.	FDA Date of Progression (Censor)	Sponsor Date of Progression (Censor)	Reason
			Not evaluated after week 8 for disease progression
002-008	6/27/95 (0)	6/27/95 (1)	7/18/95 (end of therapy)– 3200/ul 2/28/95 ALC –5800/ul 6/6/95 ALC – 3950/ul Autologous bone marrow transplant – Pt. considered to have progressed date of autologous transplant.
002-010	8/6/96 (0)	8/6/96 (1)	8/6/96 ALC – 5540/ul
002-011	7/28/95 (0)	1/2/96 (0)	7/28/95 ALC - 8800/ul No follow-up until 1/2/96 ALC - 41,934/ul
002-013	4/19/95 (0)	4/19/95 (1)	Death due to unknown causes (? PTE)
002-014	8/23/95 (0)	9/20/95 (0)	8/23/95 New lymphadenopathy reported (not measured); ALC – 5070/ul; progression reported 9/20/95 ALC- 7320/ul Progression reported again
004-001	6/2/95 (0)	7/6/95 (0)	5/5/95 ALC – 3900/ul 6/2/95 ALC – 9638/ul 7/6/95 ALC – 36,300/ul
005-001	10/13/94 (0)	9/29/94 (1)	7/25/94 ALC – 646/ul with CD52 52/ul (flow) 10/13/94 ALC – 4588/ul with CD52 count 3074/ul No further follow-up information in the CRF; patient is considered to have progressed on this date
005-002	10/24/94 (0)	3/13/95 (0)	10/24/94 ALC – 10,767/ul (flow cytometry) with CD52+ lymphocytes 9690/ul
006-002	10/4/94 (0)	9/1/94 (0)	10/4/94 Progression documented with new liver lesion by CT Scan. No evidence of progression on 9/1/94 on CFR review
006-003	7/27/94 (0)	10/4/94 (0)	6/20/94 ALC –1144/ul with CD52+ lymphs –752/ul (flow) 7/27/94 ALC – 7303/ul with CD52+ 7230/ul (flow) 8/1/94 ALC – 6480/ul 10/4/94 WBC – 65,500/ul

The median time to treatment failure as determined by the FDA is about 1.5 months shorter than the median time for progression-free survival. The shorter duration of the time to treatment failure is due to the fact that the Campath-1h therapy was discontinued in eleven (45.8%) patients for adverse events prior to documented disease progression.

Survival

Median survival for this study is 27.5 months [95% CI: 7.1, 32.6 mos.] with eighteen patients (75%) dead and six (25%) patients alive as of the cut-off date of March 21, 1997. Among the long-term survivors are three patients with Rai Stage II at entry and three patients with Rai Stage IV disease. Two patients, one with Stage II and one with Stage IV disease, were judged partial responders by the agency.

SAFETY ASSESSMENT

Drug Delivery

All patients received at least one dose of Campath-1h. One patient 7-001 receive five doses at the 10 mg dose level before removal from study for drug related toxicity. One

patient (2-002) had dose escalation to 40 mg for two doses apparently a dosing error. This patient received Campath-1h 30 mg for the remaining thirty-one treatments. Patient 2-001 had dose escalation to Campath-1h 80 mg for nine doses until development of grade 1 fever, chills and grade 2 / 3 neutropenia. Campath-1h dose was reduced to 30 mgs for the remaining twenty treatments.

Six (25%) study subjects received Campath-1h therapy for one to fours weeks, four (16.7%) for five to eight weeks, two (8.3%) for twelve weeks, five (20.8%) for thirteen to sixteen weeks, and seven (29.2%) for seventeen or more weeks.

Treatment Delays

Thirteen (54.2%) study participants had thirty-one single dose omissions during the course of the study. Twelve (50%) of these patients also had eighteen episodes of dose delays for periods of ≥ seven days with the longest dose interruption reported as eighty days. The reason for the dose omissions particular or dose delays greater than seven days was not captured in the CRF. On this protocol patients could be "rested" during the course of treatment at the investigator's discretion. The sponsor provided further information in the resubmission regarding the reasons for dose delays. Reasons provided for the thirty-one single dose delays include:

- infection in two instances;
- thrombocytopenia in two instances;
- neutropenia in eight instances,
- "other" in two instances, and "unknown" in seventeen instances.

For the nineteen episodes of dose delays for periods ≥ 7 days including three dose delays ≥ twenty-one days, the following reasons were supplied by the sponsor:

- infection in ten instances including four hospitalizations for infection
- febrile neutropenia in one instance
- neutropenia and / or myelosuppression without fever in five instances,
- and unknown in three instances.

Myelosuppression and / or infections were the primary reasons for dose delays in those instances where the reason is known.

Deaths on Study, Within Thirty Days of Treatment, and Late Deaths

Five (20.8%) study participants died on study or within thirty-five days of last dose of Campath-1h. Information about the patient including the cause of death and reviewer's assessment as to the relationship to Campath-1h therapy is presented here.

- **Patient 002-012** with Rai Stage IV disease entered the study with a Hgb 11.8 gm%, WBC 393,000/ul, and a platelet count – 30,000/ul. The patient received eight treatments with CAMPATH between July 11 and [redacted]. On [redacted] he was hospitalized with a grade 4 cerebral hemorrhage considered secondary to leukostasis with bleeding due to thrombocytopenia. Admission WBC was reported as > 500,000/ul (increased from 393,000/ul at study entry) and platelet count was reported as 20,000/ul (decreased from 60,000/ul on July 18, 1998). Patient expired on [redacted] from the CVA. Patient

is considered to have died from progressive disease. Campath-1h therapy could possibly have caused a worsening in the patient's thrombocytopenia at time of CVA.

- **Patient 006-001,** with Rai Stage IV disease, received Campath-1h therapy from April 5 until June 20, 1994 for Stage IV disease. At study entry (April 4, 1994) WBC was reported as 321,400/ul (no neutrophils), and platelet count was 81,000/ul. On day 1 of study (April 5, 1994) ANC was 11,000/ul. On [redacted] patient was hospitalized for PCP pneumonia. CBC on admission included a Hgb-10.3 gm%, ANC-4730/ul, and Platelets –97,000/ul. With antibiotic therapy PCP pneumonia resolved on July 20, 1994. On September 8 Campath-1h infusions were resumed. After the infusion the patient was hospitalized for severe abdominal pain considered secondary to Campath-1h and hypoxia secondary to pneumonitis, which was observed on the admitting chest x-ray. Admitting CBC included a Hgb 12.3 gm%, ANC 4730/ul, and platelets 212,000/ul. The pneumonia responded to treatment with Ticarcillin and clindamycin and resolved on September 21, 1994. Campath-1h was continued during this hospitalization and in the outpatient setting until [redacted]. On [redacted] the patient was hospitalized for grade 3 depression with suicidal ideation. On October 4 new hepatic lesions are reported. Pathological examination of a lymph node biopsy reported on October 6 was consistent with transformation to Richter's syndrome. On October 7, 1994 alternative therapy was initiation. The patient committed suicide on [redacted]. This death is clearly not related to Campath-1h therapy.

- **Patient 006-002** with T-PLL, Rai Stage IV, and WHO performance status 2 entered the study with a WBC – 420,000/ul, ANC- 0/ul, and platelet count –24,000/ul. The patient received seven infusions of CAMPATH, three between April 13 and April 15 and four between April 26 and April 29, 1994. On [redacted] patient was hospitalized with bacterial sepsis / pneumonia (Klebsiella pneumoniae, Enterococcus). With antibiotic therapy the infections resolved. Campath-1h therapy was resumed on April 26. On May 1 the patient developed grade 3 hematuria due to a Candida torulopsis bladder infection. At this point Campath-1h therapy was discontinued. On May 3 the patient's WBC increased from 564,000/ul to 816,000/ul so alternative therapy (ACOPP-B) was initiated. On May 9 the patient developed pneumonia with respiratory insufficiency requiring ventilatory support. The patient expired on [redacted] This death is due to progressive disease and unrelated to Campath-1h.

- **Patient 002-007** with Rai Stage IV B-CLL entered study with Hgb – 9.2 gm%; platelet count – 16,000/ul; and WBC – 12,700/ul with ANC – 50/ul. The patient received thirty infusions of CAMPATH between April 8 and June 10, 1994. On June 3, the patient achieved PR status. On [redacted] the patient was hospitalized with grade 4 pneumonia, grade 2 sepsis, and grade 2 hemolytic anemia. ANC at time of admission was 3.780/ul. Patient was initially treated with antibiotics. A closed lung biopsy performed [redacted] was consistent with CMV infection. Despite antibacterial and antiviral therapy the patient continued to deteriorate. An open lung biopsy, performed showed invasive Aspergillosis. Despite the addition of Amphoterecin therapy the patient expired on [redacted] ALC at time of death was 800/ul. Investigator lists the cause of death as invasive Aspergillosis and CMV pneumonia and progressive disease. There is no evidence in the CRF / SAE of progression at the time of death. This death is considered to be due to immune suppression secondary to Campath-1h therapy.

- **Patient 002-006** entered this study with Rai Stage IV B-CLL and the following hematologic values: Hgb 7.4 gm%, WBC 8900/ul, ANC 2420/ul, platelet count 35,000/ul. The patient received fifteen infusions of Campath-1h between February 13 and [redacted] The patient received prophylactic Bactrim and was on oral Acyclovir for herpetic stomatitis. The patient was hospitalized on [redacted] with grade 4 pneumonitis (bilateral interstitial infiltrates) treated initially with Unasyn. Acyclovir therapy for the grade 1 herpetic stomatitis was continued. No admitting CBC is included in the CRF, SAE or Patient Narrative, but last ANC (3/14/94) prior to admission was 1672/ul. On March 19 the patient was reported to be confused. Atypical pneumonia was suspected and therapy with erythromycin, tobramycin, IV acyclovir as well as gamma globulin was added. Patient refused bronchoscopy / lung biopsy. The patient became progressively more obtunded and died on [redacted] from interstitial pneumonitis thirty-five days after the last dose of Campath-1h. Last ALC prior

to death was 370/ul. The investigator lists the cause of death as progressive disease with adverse event unrelated to study drug therapy. Review of the CRF provides no evidence of disease progression. This infection / death is considered related to Campath-1h therapy by the FDA.

Two other deaths were reported within six months prior to completion of Campath-1h therapy.

- **Patient 001-003** died six months after completion of study drug therapy from progressive disease.
- **Patient 007-001** died at four months after completion of study drug therapy due to progressive disease.

In summary two of the five deaths on study are considered to be due to CAMPATH therapy.

Discontinuations due to Adverse Events

Ten (41.7%) patients discontinued from Campath-1h therapy due to adverse events. The reason for discontinuation and relationship to study drug is presented in Table 009-6. Note that in seven of the nine patients adverse events related to Campath-1h therapy were responsible for the discontinuation of study drug.

Table 009-6: Treatment Discontinuations due to Adverse Events

Patient No.	Rai Stage	Response	Reason for Discontinuation	Relationship to CAMPATH
002-006	IV	NE	Interstitial Pneumonitis (Death)	Yes
002-007	IV	SD	Pneumonia, CMV & Aspergillosis (Death)	Yes
002-011	IV	NE	Grade 2 Fever Grade 4 Neutropenia Gr. 4 Thrombocytopenia	Yes
002-012	IV	NE	CVA with Progressive Disease (Death)	No
004-001	III	SD	Gr. 3 Pneumonia, (?PCP)	Yes
005-001	I	SD	Gr. 3 Fever (Probably due to PCP) Gr. 1 Neutropenia, Otitis Media Pharnygitis (Probably Bacterial)	Yes
006-001	IV	PD	Depression, Gr. 3	No
006-002	IV	PD	Gr. 3 Hematuria due to Candida torulopsis bladder infection (Death)	Unlikely
006-003	II	NE	Gr. 2 Dyspnea Gr. 4 Anemia Gr. 4 Interstitial Pneumonia (CAMPATH induced)	Yes
007-001	III	NE	Gr. 3 Fever, Gr. 4 Anemia Gr. 2 Thrombocytopenia Gr. 4 Neutropenia Gr. 3 Pneumonia (Organism unknown)	Yes

Serious Adverse Events including Hospitalizations

Nineteen (79.2%) patients experienced thirty-six episodes of serious adverse events on study or within six months of discontinuation of study drug therapy. The following table includes a listing of the events, along with the patient identifier, stage of disease, response, occurrence of event(s) in relationship to first day of study drug, investigator and FDA assessment of relationship to study drug. Hematological toxicity is reported if

the toxicity is new or represents a change from baseline. Events that occurred on retreatment which are listed in Table 009-7 are not counted in total number of serious adverse events.

Table 009-7: Serious Adverse Events Included in Patient Narratives
(+ Sign indicates the number of days after last Campath-1h Infusion)

Patient No.	Rai	Obj. Resp.	Serious Adverse Event	Timing	Investigator Assessment Relationship to Campath-1h	FDA Assessment Relationship to Campath-1h
001-001	II	PD	Transformation to Higher Grade Lymphoma	+ 27	Possibly	None
001-003	III	PD	Leukopenia, gr. 4 Neutropenia, gr. 3 / 4 Anemia, gr. 2	+2	Possibly	Definite
002-002	IV	PR	Hypotension, gr. 4	1	Reasonably	Definite
			Hypotension, gr. 4 with syncope	2	Reasonably	Definite
			PCP Pneumonia, gr. 4	+45	Reasonably	Definite
002-003	IV	SD	Neutropenia, Gr. 3	+4	Not Discussed	Definite
			Herpes Zoster Disseminated gr. 3	+21	Reasonably	Definite
002-005	II	PR	Fever, Gr. 2 (no organism identified; responded to antibiotics; ANC-5500/ul)	+21	Not Reasonably	Probably
002-006	IV	NE	Pneumonitis, Gr. 4, NOS (Fatal) Fever	+2 (29)	Not related	Definite
002-007	IV	SD	CMV, gr. 4 (Fatal) Aspergillosis, gr. 2 Confusion Hypotension Renal Failure	+14	Possibly Related	Definite
002-008	II	PR	Gr. 4 Fever, Rigors (Infusional) (Solucortef for remaining infusions)	37	Reasonably	Definite
002-009	IV	PD	Abcess, Rt. thigh (no organism identified)	1	Possibly	None
			Hemoptysis, Thrombocytopenia, Gr. 4 Abscess, Rt. thigh (Pseudomonas)	45	Not reasonably Possibly	None Definite
002-010	IV	SD	Iritis (incorrect dx.), Neutropenia, gr. 3	30	Not reported	Definite
			Candida vitreous infection (?gr. with partial vision loss) Port Infection, Candida albicans Gr. 3 Pneumonia with pleural effusion, (? Bacterial) six wks. Duration	72 (+1)	Possibly Reasonable	Definite
002-011	IV	NE	Gr. 2 fever , NOS, responded to antibiotics; Neutropenia, Gr. 4 Thrombocytopenia, gr. 4	22	Possibly	Definite*
002-012	IV	PD	CVA (Leukostasis) ; (Fatal)	+3	Not Related	Not Related
002-014	II	SD	Fever, Gr. 2 Neutropenia, gr. 2 / 3 Pneumonia, (NOS); responded to antibiotics)	17 22	Possibly	Definite
004-001	III	SD	Gr. 3 Hypotension (infusion related)	1	Possibly	Definite
			Gr. 3 Hypocalcemia	2	Possibly	Indirectly
			Gr. 3 Pneumonia (NOS responded to Septra, erythromycin)	111	Reasonably	Definite
005-001	I	PR	Gr. 3 Fever (? PCP Pneumonia) Otitis Media, Pharyngitis, Malaise, Gr 1	30	Possibly	Definite

Patient No.	Rai	Obj. Resp.	Serious Adverse Event	Timing	Investigator Assessment Relationship to Campath-1h	FDA Assessment Relationship to Campath-1h
			Retreatment PCP pneumonia, gr.3; Fever, gr. 3	+7 (RT)	Not reasonably	Definite
005-002	IV	PR	Gr. 3 Rigors, Gr. 2 Fever	1	Reasonably	Definite
			Gr. 2 Fever, Gr. 4 Neutropenia	5	Reasonably	Definite
			Gr. 2 Fever; Gr. 2 Chills; Gr. 2 Anemia, Gr. 4 Neutropenia, Epistaxis; Gingival Bleeding; Gr. 4 Thrombocytopenia; Grade 3 Oral Ulcer Gr. 2 Candida Esophagitis Gr. 3 Pneumonia (Candida, Aspergillosis) Renal Failure, Gr. 2 due to Amphotericin	6 7 14 17 30	Reasonably Not Reasonably Not Reasonably Not Reasonably Not Reasonably	Definite Indirectly Definitely Definitely Definitely Indirectly
			Hemoptysis, gr. 1, Gr. 3 Thrombocytopenia Gr. 3 Pneumonia, (Candida, Aspergillus), Ongoing	36	Not reasonably	Definite
			AIHA (Rxed w steroid, splenectomy)	+16	Not reasonably	None
			Retreatment 10/9 – 10/20/95 Pseudomonas Infection, gr. 2	11 (RT)	Not reasonably	Definite
006-001	IV	SD	PCP Pneumonia, ? grade	77	Possibly	Definite
			Abdominal Pain, gr. 4 (Infusion Related)	156	Reasonably	Definite
			Pneumonitis, gr. 3, NOS, ? Aspiration Hypoxia, Gr. 3	157	Not reasonably	Possibly
			Depression, grade 3 Disease Progression (Richter's)	172	Not reasonable	None
006-003	II	NE	Gr. 2 Dyspnea, (first attributed to mild CHF with Gr. 3 Anemia)	+1	Possibly	Definite
			Continuing Dyspnea, Sinusitis Interstitial Pneumonia, Gr. 4 (NOS; unresponsive to antibiotics; resolved with steroids -?CAMPATH induced interstitial pneumonitis)	+6	Possibly	Definite
			Bacteremia, Strep, gr.?,	+79	Not Discussed	Possibly
			Fever, Gr. 2 Moraxella catarralis infection (Line) Diarrhea, C. difficele	+116	Not Discussed	Possibly
007-001	III	NE	Gr. 4 Pneumonia, NOS; Gr. 3 Fever, (Study drug discontinued) Pancytopenia (Gr. 4 Neutropenia, Gr. 3 Anemia; Gr. 2 Thrombocytopenia)	+1	Reasonably	Definite
			Pneumonia, Ongoing; Neutropenia, gr. 4	+17	Reasonably	Definite
			Infected Decubitus (posterior) Progression; Death due to progression	+65	Not discussed	None

Thirty of these thirty-six events were judged definitely related to Campath-1h after review. The investigator (and sponsor) tended not assign causality to Campath-1h in some instances where Campath-1h therapy is clearly relevant.

- For patient 2-005 the investigator assessed the fever in this patient, a partial responder, as unrelated to study drug therapy. The patient's fever responded to antibiotics suggesting Campath-1h related infection.
- Patient 1-003 discontinued Campath-1h for leukopenia. When disease progression was noted approximately two weeks later the WBC and ANC had improved.
- For patient 2-011 myelosuppression and fever were definitely related to Campath-1h. The neutropenia resolved with discontinuation of Campath-1h. The fever resolved with antibiotic therapy.
- Patient 2-014 had pneumonia that occurred while the patient was receiving Campath-1h therapy. The patient was myelosuppressed. The fever resolved with antibiotic therapy.
- Patient 4-001 developed hypotension after initiation of Campath-1h therapy and required fluid resuscitation in the hospital. The hypocalcemia reported during this event was considered dilutional according to the Patient Narrative, secondary to the large volume of fluid required to manage the Campath-induced hypotension.
- Patient 5-001 had Campath-1h discontinued after development of the grade 3 fever. Campath-1h was resumed three weeks later. Seven weeks after resumption of therapy and after many episodes of fever, PCP pneumonia was diagnosed. The investigator did not consider the PCP pneumonia related to Campath-1h. The same investigator found several serious adverse events reported for patient 5-002 unrelated to Campath-1h therapy.

In summary twenty-two of these serious adverse events were due to infection or probable infection. In eight instances neutropenia is reported with the infection. One hospitalization for hematological toxicity, leukopenia, is reported. Six adverse events were hospitalizations for infusion related adverse events. One additional hospitalization was for interstitial pneumonitis secondary to Campath-1h. Transformation to more malignant lymphoma was noted in two patients.

Adverse Event Profile

All (100%) study participants experienced at least one adverse event while on study. Seventeen (70.8%) participants experienced as least one grade 3 / 4 event. All study (100%) participants experienced at least one adverse event related to study drug. Fifteen (62.5%) participants experienced at least one grade 3 /4 adverse event related to study drug. The following table includes a listing of all adverse events that were reported in $\geq$ 5% of the study population (N=24) while on study or within thirty days of study drug discontinuation; a listing of adverse events that occurred in $\geq$ 5% of the study population on study or within thirty days of discontinuation of study drug considered related to Campath-1h; a listing of all patients with NCI CTC grade 3 / 4 adverse events; and, a listing of all patients with NCI CTC grade 3 / 4 drug related adverse events.

Table 009-8: Incidence of Adverse Events Reported in $\geq$ 5% of the Study Population On Study Or Within Thirty Days of Study Drug Therapy Including All NCI CTC Grade 3 / 4 Adverse Events

Adverse Event	All Adverse Events			Drug Related Adverse Events		
	Total N (%)	Gr. 3 N (%)	Gr. 4 N (%)	Total N (%)	Gr. 3 N (%)	Gr. 4 N (%)
Total	24 (100.0)	8 (33.3)	9 (37.5)	24 (100.0)	7 (29.2)	8 (33.3)
Body as a Whole	24 (100.0)	7 (29.2)	2 (8.3)	24 (100.0)	7 (29.2)	2 (8.3)
Anorexia	5 (20.8)	1 (4.2)	-	4 (16.7)	1 (4.2)	-
Asthenia	3 (12.5)	-	-	3 (12.5)	-	-
Back Pain	4 (16.7)	1 (4.2)	-	2 (8.3)	1 (4.2)	-
Chest pain	2 (8.2)	-	-	1 (4.2)	-	-
Edema	5 (20.8)	-	-	1 (4.2)	-	-
Fatigue	10 (41.7)	-	-	10 (41.7)	-	-
Fever	24 (100.0)	3 (12.5)	1 (4.2)	23 (95.8)	3 (12.5)	1 (4.2)
Malaise	5 (20.8)	-	-	5 (20.8)	-	-
Pain	7 (29.2)	-	-	4 (16.7)	-	-
Rigors	22 (91.7)	3 (12.5)	1 (4.2)	22 (91.7)	3 (12.5)	1 (4.2)
Cardiovascular	17 (70.8)	2 (8.3)	1 (4.2)	16 (66.7)	2 (8.3)	1 (4.2)
Hypotension	16 (66.7)	2 (8.3)	1 (4.2)	16 (66.7)	2 (8.3)	1 (4.2)
Central, Peripheral Nervous System	10 (41.7)	2 (8.3)	-	8 (33.3)	1 (4.2)	-
Dizziness	4 (16.7)	1 (4.2)	-	3 (12.5)	-	-
Headache	7 (29.2)	1 (4.2)	-	6 (25.0)	1 (4.2)	-
Parathesias	2 (8.3)	-	-	2 (8.3)	-	-
Gastrointestinal	22 (91.7)	4 (16.7)	1 (4.2)	21 (87.5)	4 (16.7)	1 (4.2)
Constipation	3 (12.5)	-	-	1 (4.2)	-	-
Diarrhea	2 (8.3)	-	-	2 (8.3)	-	-
Dyspesia	2 (8.3)	-	-	2 (8.3)	-	-
Flatulence	3 (12.5)	-	-	2 (8.3)	-	-
Nausea	15 (62.5)	2 (8.3)	-	15 (62.5)	2 (8.3)	-
Vomiting	13 (54.6)	4 (16.7)	-	13 (54.2)	4 (16.7)	-
Stomatitis (All)	6 (25.0)	-	-	6 (25.0)	-	-
Hearing & Vestibular	3 (12.5)	-	-	0 (00.0)	-	-
Earache	3 (12.5)	-	-	0	-	-
Heart Rate & Rhythm Disorders	5 (20.5)	-	-	2 (8.3)	-	-
Palpitations	2 (8.3)	-	-	1 (4.2)	-	-
Tachycardia	3 (12.5)	-	-	1 (4.2)	-	-
Metabolic & Nutritional	10 (41.7)	-	-	3 (12.5)	-	-
Hypokalemia	4 (16.7)	-	-	1 (4.2)		
Hyponatremia	2 (8.3)	-	-	0 (00.0)	-	-
Weight Decrease	2 (8.3)	-	-	1 (4.2)	-	-
Musculoskeletal Disorders	6 (25.0)	-	-	5 (20.8)	-	-
Myalgias	4 (16.7)	-	-	4 (16.7)	-	-
Respiratory System Disorders	18 (75.0)	5 (20.5)	3 (12.5)	10 (41.7)	3 (12.5)	2 (8.3)
Coughing	5 (20.8)	-	-	0 (00.0)	-	-
Dyspnea	5 (20.8)	1 (4.3)	-	5 (20.8)	1 (4.2)	-
Hemoptysis	2 (8.3)	-	-	0 (00.0)	-	-
Hypoxia	2 (8.3)	1 (4.3)	-	1 (4.3)	-	-
Pharyngitis	4 (20.8)	-	-	1 (4.2)	-	-
Pneumonia, Pneumonitis	8 (33.3)	4 (16.7)	3 (12.5)	6 (25.0)	2 (8.3)	1 (4.2)
Pulmonary Edema	3 (12.5)	1 (4.2)	-	0 (00.0)	-	-
Rhinitis	2 (8.3)	-	-	0 (00.0)	-	-
URI	2 (8.3)	-	-	1 (4.2)	-	-
Resp. Disorder	1 (4.2)	-	-	1 (4.2)	1 (4.2)	-
Resp. Insufficiency	1 (4.2)	-	1 (4.2)	0 (00.0)	-	-

Adverse Event	All Adverse Events			Drug Related Adverse Events		
	Total N (%)	Gr. 3 N (%)	Gr. 4 N (%)	Total N (%)	Gr. 3 N (%)	Gr. 4 N (%)
Skin & Appendage	17 (70.8)	2 (8.3)	-	16 (66.7)	2 (8.3)	-
Pruritis	5 (20.8)	-	-	4 (16.7)	-	-
Rash	10 (41.7)	1 (4.2)	-	6 (25.0)	1 (4.2)	-
Urticaria	10 (41.7)	1 (4.2)	-	10 (41.7)	1 (4.2)	-
Increased Sweating	5 (20.8)	-	-	5 (20.8)	-	-
Urinary System	5 (20.8)	1 (4.2)	-	2 (8.3)	-	-
Hematuria	2 (8.3)	1 (4.2)	-	1 (4.2)	-	-
Decreas. Urine Flow	2 (8.3)	-	-	1 (4.2)	-	-
Platelets, Bleeding & Clotting	2 (8.3)	-	-	0 (0.0)	-	-
Gingival Bleeding	2 (8.3)	-	-	0 (0.0)	-	-
Thrombocytopenia	1 (4.2)	-	-	0 (0.0)		
RBC Disorders	3 (12.5)	-	1 (4.2)	1 (4.2)	-	-
Anemia	1 (4.2)	-	-	0	-	-
Hemolytic Anemia	2 (4.2)	-	1 (4.2)	1 (4.2)	-	-
WBC & Resistance Disorders	5 (20.8)	1 (4.2)	1 (4.2)	4 (16.7)	1 (4.2)	1 (4.2)
Granulocytopenia	2 (8.3)	1 (4.2)	1 (4.2)	2 (8.3)	1 (4.2)	1 (4.2)
Leukopenia	1 (4.2)	-	1 (4.2)	1 (4.2)	-	1 (4.2)
Lymphadenopathy	2 (8.3)	-	-	0 (0.0)	-	-
Pancytopenia	2 (8.3)	1 (4.2)	-	2 (8.3)	1 (4.2)	-
Resistance Mechanism Disorders	8 (33.3)	4 (16.7)	2 (8.3)	6 (25.0)*	2 (8.3)	1 (4.2)
Abscess	1 (4.2)*	-	-	1 (4.2)*	-	-
CMV Infection	1 (4.2)	-	1 (4.2)	1 (4.2)	-	1 (4.2)
Herpes Simplex	3 (12.5)	-	-	0 (0.0)	-	-
Herpes Zoster	2 (8.3)	1 (4.2)	-	2 (8.3)	1 (4.2)	-
Moniliasis	1 (4.2)	-	-	0 (0.0)	-	-
PCP Infection	1 (4.2)	1 (4.2)	-	1 (4.2)	-	1 (4.2)
Sepsis	2 (8.3)	-	1 (4.2)	2 (8.3)	-	1 (4.2)

* Grade not reported

The majority of adverse events reported on Study 009 were related to CAMPATH therapy. Adverse events can be divided into three types: acute infusional related events, infections, and myelosuppressive events. Review of the above adverse event listing suggests that hematological toxicity is rare and nonserious, which is not the case. Underreporting of hematological toxicity in this listing is related to the fact that information about hematologic toxicity was not regularly reported / graded in the adverse event section. This is because the protocol stated that hematological toxicity was "expected with Campath-1h" and was not reportable.

Infusion Related Adverse Events

In reviewing the infusion related adverse events one should remember that patients were premedicated with acetaminophen and antihistamines at the investigator's discretion. Use of antihistamines was reported at least in twenty-three (87.5%) of the study population presumably related to Campath-1h therapy. Use of narcotic analgesia is reported in eighteen (75%) patients. Information about the number of patients who received meperidine to control infusion related rigors is not reported. Systemic steroids usage was reported in seven patients to control acute infusion related toxicities. Five patients

required more than five days of systemic therapy. Acute adverse events related to Campath-1h infusion that were reported for this study include:

- Fever reported in twenty-three (95.8%) participants with grade 3 / 4 fever in four (16.7%) participants;
- Rigors reported in twenty-two (91.7%) participants with grade 3 /4 rigors in four (16.7%) participants;
- Hypotension reported in sixteen (66.7%) participants with grade 3 / 4 hypotension in three (12.5%) participants; dizziness in three (12.5%) with grade 3 dizziness and syncope reported in one (4.2%) participant;
- Nausea reported in fifteen (62.5%) participants with grade 3 nausea in two (8.3%) participants with anorexia reported in four (16.7%) participants;
- Vomiting reported in thirteen (54.2%) participants with grade 3 vomiting in four (16.7%) participants;
- Diarrhea reported in two (8.3%) patients of grade 1 severity;
- Fatigue reported in ten (41.7%) of grade 1 / 2 severity, malaise reported in five (20.8) participants of grade 1 / 2 severity, and asthenia reported in three (12.5%) participants of grade 1 severity;
- Urticaria reported in ten (41.7%) participants with one (4.2%) participant experiencing grade 3 urticaria;
- Rash reported in six (25.0%) participants with grade 3 rash reported in one (4.2%) participant;
- Pruritis reported in four (16.7%) participants with grade 3 pruritis reported in one (4.2%) participant;
- Pain, back and chest pain reported in seven (29.3%) participants with one (4.2%) participant experiencing grade 3 back pain with myalgias reported in four (16.7%) patients;
- Stomatitis reported in six (25%) participants with no grade 3 / 4 stomatitis;
- Headache reported in six (25%) participants with one (4.2%) participant reporting a grade 3 headache;
- Palpitation or tachycardia reported in five (20.8%) of grade 1 severity; and
- Dyspnea reported in five (20.8%) participants with grade 3 dyspnea in one (4.2%) in participant.

Only one (4.2%) patient reported pain at the injection site. The types of infusion related toxicities are similar to those reported to Study 211. The incidence of grade 3 / 4 infusion related toxicities appears to be slightly higher on this study as compared to Study 211, probably due to the lack of a standard premedication regimen.

Prophylaxis

Prophylaxis was optional on this study. Fourteen patients (58.3%) are reported to have received trimethoprim-sulfamethazole or other PCP prophylaxis. Four (16.7%) patients received antiviral prophylaxis with acyclovir for herpetic infections.

Infections on Study, within Thirty Days of Study, and Late Infections

The actual incidence and severity of infections is difficult to ascertain. Information about infections during study was collected in the adverse section of the CRF, while post-study information about infections was collected on a form specifically designed to capture the occurrence of infection but not the grade of infection or the relationship to study drug. Another problem is that the same infection may have reported using two different terms (i.e. pneumonia, pneumonitis). The same infection may have been identified differently, graded differently, and the relationship to Campath-1h therapy variably reported. Fifteen (51.7%) patients were identified as having infections during study or in the six-month period following the first cycle of treatment with Campath-1h. Many of these events are described in the SAE section and in the hospitalization section of this review. Table 009-9 identifies the types and occurrence of the reported infections and the grade if known.

Table 009-9: Infections Reported During and Post-Study (≤ 180 Days)

	All Grades N (%)	Gr. 1 N (%)	Gr. 2 N (%)	Gr. 3 N (%)	Gr. 4 N (%)	Not Graded
Total Number Infections	34 (100%)	7 (20.6)	4 (11.8)	12 (35.3)	6 (17.6)	5 (14.7)
Type of Infection						
Bacterial	8					
Abscess	1			1		
Colitis	1	1				
Gastroenteritis	2			2		
Sepsis	2		1			1
Sepsis with Pneumonia	1				1	
Urinary Tract Infection	1			1		
Fungal	7					
Monialiasis	2	2				
Esophagitis	1		1			
Enophthalomitis	1			1		
Pneumonia	3			1	2	
Protozoan	4					
PCP	4			2	1	1
Viral	6					
Viral Syndrome	1	1				
Herpes Zoster	4		1	1		2
CMV	1				1	
Herpes Simplex	1	1				
Unspecified	9					
Pneumonia	4		1	2		1
Pneumonitis	2			1	1	
Otitis Media	1	1				
URI	3	1	2			

Twelve patients had grade 3 / 4 infections. Nine of the twelve patients with serious infections had Stage IV disease and one had Stage III disease. Two of the RAI stage IV patients with Gr. 3 /4 infections had an objective (partial response) to therapy, while four

were judged to have stable disease. Patients with advanced stage disease had a greater likelihood of developing more serious infections with Campath-1h therapy on this study.

On this study the following opportunistic or potentially opportunistic infections were reported:

- PCP pneumonia, four episodes in three patients;
- Pneumonitis, NOS in two patients
- disseminated H. zoster in one patient; with localized Zoster in three (grade 2 in one, grade unknown in two)
- Aspergillosis pneumonia in two patients;
- CMV pneumonia in one patient;
- Candida esophagitis in one patient; and
- Candida enopthalamitis in one patient.

Ten (41.7%) study participants had serious opportunistic infections on study or within six months of completion of study drug therapy. Two other patients with pneumonic processes of unknown etiology may also have had opportunistic infections. The high incidence of opportunistic infections is thought to be secondary to the suppression of CD4+ cells with Campath-1h therapy in CLL patients who have previously been exposed to fludarabine.

Hematological Adverse Events

Pancytopenia

Three cases of pancytopenia were reported on study.

- Patient 1-003 developed pancytopenia on study. At time of last follow-up two weeks after study patient continued to have gr. 2 anemia, gr. 4 neutropenia, and gr. 3 thromboctyopenia. This patient had study drug discontinued for pancytopenia although considered progression by the investigator. No documentation of progression was found in the CRF. Patient died six months later from "progression".
- Patient 7-001 completed one week of Campath-1h therapy and was discontinued from study for pancytopenia and pneumonia. Two months later patient's blood counts have returned to baseline.
- Patient 5-002 developed worsening of grade 2 anemia and grade 3 thrombocytopenia during study requiring RBC and platelet support. Patient had continuation of grade 4 neutropenia. Patient had several SAEs on therapy including Aspergillus, Candida pneumonia, grade 3 Candida esophagitis, bleeding due to thrombocytopenia. Two months after completion of approximately three months of Campath-1h therapy, platelet count and neutrophil count were grade 0.

Hemoglobin Toxicity

The hematologic values for all patients enrolled on this study were reviewed. While on study or within thirty days after discontinuation of study drug therapy, sixteen (67%) patients had some degree of hemoglobin toxicity (Grade 1 – 4). Nine (38%) patients had

one or more episodes of grade 3 or grade 4 hemoglobin toxicity. Eighteen (75%) patients were transfused 181 units of RBCs during the course of this study.

Baseline hemoglobin grades were collected for nineteen of the twenty-four study participants and include: grade 0 in four patients; grade 1 in three patients; grade 2 in nine patients; and, grade 3 in three patients. Table 009-10 provides information about the change in the NCI hemoglobin grade by two weeks intervals throughout the study and for two months of follow-up. [Improved indicates a change ≥ one grade from baseline. No Changes indicates the same grade as baseline. Worse indicates a decrease of ≤ one grade.]

Table 009-10: Change in Hemoglobin: All Patients (N=19)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Worse by ≥ Gr. 1 N (%)	New Gr. 3 / Gr. 4 N (%)
Weeks 1 – 2	19	2 (10.5)	9 (47.3)	8 (42.1)	6 (31.6)
Weeks 3 – 4	18	3 (16.7)	11 (61.1)	6 (33.3)	1 (5.5)
Weeks 5 – 6	16	2 (12.5)	11 (68.8)	3 (18.8)	0 (0.0)
Weeks 7 - 8	15	3 (20.0)	9 (60.0)	2 (20.0)	0 (0.0)
Weeks 9 – 10	12	3 (25.0)	5 (41.7)	4 (33.3)	1 (8.3)
Weeks 11 – 12	10	2 (20.0)	5 (50.0)	3 (30.0)	1 (10.0)
Weeks 13+	10	4 (40.0)	2 (20.0)	4 (40.0)	0 (0.0)
1 Month F/U	18	9 (50.0)	5 (27.7)	4 (22.2)	0 (0.0)
2 Month F/U	13	9 (69.3)	3 (23.0)	1 (7.7)	1 (7.7)

Table 009-10 does not provide information about the effect of transfusion and / or erythropoietin usage during study or the effect of disease progression on hemoglobin values during study or at two months post study. Table 009-11 and 009-12 display this information.

Table 009-11: Change in Hemoglobin from Baseline over Study: Responders (N = 7) vs. Non-Responders (12)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	7	0	3 (42.9)	4 (57.1)	12	2 (16.7)	6 (50.0)	4 (33.3)
Wks. 3 – 4	7	0	3 (42.9)	4 (57.1)	11	1 (9.1)	8 (72.7)	2 (18.2)
Wks. 5 – 6	7	1 (14.3)	4 (57.1)	2 (28.6)	9	1 (11.1)	7 (77.7)	1 (11.1)
Wks. 7 – 8	6	1 (14.3)	3 (42.9)	2 (28.6)	9	1 (11.1)	8 (88.9)	0 (0.0)
Wks. 9– 13+	6	1 (14.3)	2 (28.6)	3 (42.9)	9	2 (22.2)	6 (66.7)	1 (11.1)
1 Month F/U	7	2 (28.6)	2 (28.6)	3 (42.9)	11	7 (63.6)	3 (27.3)	1 (9.1)
2 Month F/U	7	6 (85.7)	1 (14.3)	0 (0.00)	6	3 (50.00	3 (50.0)	0 (0.0)

Review of Table 009-11 indicates that a decrease in hemoglobin is observed in both responders and non-responders over the duration of the study. More responders continue to have a decrease in hemoglobin throughout treatment. At two months after discontinuation of study drug six (85.7%) of seven responders and three (50%) of six non-responders had an hemoglobin grade better than a baseline. No participants have a follow-up grade worse than baseline. Additional information about changes in hemoglobin grade for transfused and / or erythropoeitin treated patients compared to nontransfused / EPO treated patients are present in Table 009-12.

Table 009 -12: Changes in Hemoglobin from Baseline:
Transfused / EPO Patients (N=15) vs. Non-Tranfused, Non-EPO Treated Patients (N=4)

Week on Study	Transfused / EPO Patients N = 15				Non-Tranfused or EPO Treated Patients N = 4			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	15	2 (13.3)	7 (46.7)	6 (40.0)	4	0 (0.0)	2 (50.0)	2 (50.0)
Wks. 3 – 4	14	1 (7.1)	9 (64.3)	4 (28.6)	4	0 (0.0)	2 (50.0)	2 (50.0)
Wks. 5 – 6	12	2 (16.7)	9 (75.0)	1 (8.3)	4	0 (0.0)	2 (50.0)	2 (50.0)
Wks. 7 – 8	11	3 (27.3)	7 (63.6)	1 (9.1)	4	0 (0.0)	2 (50.0)	2 (50.0)
Wks. 9 – 10	9	3 (33.3)	4 (44.5)	2 (22.2)	3	0 (0.0)	1 (33.3)	2 (66.7)
Wks, 11 – 12	7	2 (28.6)	4 (57.1)	1 (14.3)	3	0 (0.0)	1 (33.3)	2 (66.7)
Wks. 13+	7	3 (42.9)	2 (28.6)	1 (14.3)	3	1 (33.3)	2 (66.7)	0 (0.0)
I Month F/U	14	8 (57.1)	5 (35.7)	1 (7.1)	4	1 (25.0)	0 (0.0)	3 (75.0)
2 Month F/U	10	5 (50.0)	4 (40.0)	1 (10.0)	3	1 (33.3)	2 (66.7)	0 (0.0)

Hemoglobin values were lower in grade for six (40%) of the fifteen transfused / EPO-treated patients during the first two weeks of study. Four (29%) of the fourteen transfused / EPO treated patients had lower hemoglobin values during the third-fourth week of study. For the four non-transfused / non EPO-treated patients, the decline in hemoglobin grade persisted throughout treatment for two patients. At two months after completion of study hemoglobin values were improved in eight (57%) patients, at baseline in five (35.7%) of the transfused / EPO treated patients, while three of the four non-transfused patients continue to have hemoglobin values one grade or more lower than baseline.

Campath-1h therapy appears to have a suppressive effect on the erythropoiesis resulting in an increased use of RBC transfusion during therapy. Responder appears to have as much problem with hemoglobin toxicity as non-responders. The effect on hemoglobin production appears to resolve after discontinuation of Campath-1h therapy. In responders after recovery from myelotoxicity improvement in hemoglobin may be observed. As expected, patients with more advanced stage disease are more likely to require transfusion support during therapy.

Neutrophils

Eighteen (75%) patients enrolled on this study had the onset of new or worsening neutropenia of any grade while receiving therapy or within thirty days of discontinuation of study drug therapy. Fourteen (58%) had one or more episodes of grade 3 or grade 4 neutropenia on therapy or within thirty days of discontinuation of Campath-1h. Over half of the population was reported to have infections on or post study often with neutropenia.

Information on neutrophil counts is available for twenty-four patients at baseline. Thirteen patients entered study with gr. 0 neutropenia, four with grade 1 neutropenia, two with grade 2, one with grade 3, and three with grade 4 neutropenia. (One patient, 002-006, is reported as Gr. 4, however review of the neutrophil counts indicate that this is error since neutrophil count one day later was 11,000/ul.) Table 009-13 provides information about the change in NCI CTC grade for neutrophil counts during study. [Improved indicates a change $\geq$ one grade from baseline; No Change indicates the same grade as baseline; and, Worse indicates a decrease of $\leq$ one grade.]

Table 009-13: Changes in Neutrophil Counts over Study: All Patients (N = 24)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Worse by ≥ Gr. 1 N (%)	No. (%) with New Gr. 4 Neutropenia
Weeks 1 – 2	24	3 (12.5)	8 (33.3)	13 (54.2)	3 (12.5)
Weeks 3 – 4	22	2 (9.1)	4 (18.2)	14 (67.3)	6 (27.2)
Weeks 5 – 6	18	3 (16.7)	5 (27.8)	10 (55.5)	4 (22.2)
Weeks 7 - 8	17	4 (23.5)	4 (23.5)	9 (52.9)	1 (5.9)
Weeks 9 – 10	14	3 (21.4)	5 (37.5)	6 (42.9)	0 (0.0)
Weeks 11 – 12	11	1 (9.1)	2 (18.2)	8 (72.7)	1 (9.1)
Weeks 13+	12	2 (16.7)	2 (16.7)	8 (66.7)	1 (8.3)
1 Month F/U	19	3 (15.7)	7 (36.8)	9 (37.4)	0 (0.0)
2 Month F/U	13	4 (30.8)	4 (30.8)	5 (38.5)	0 (0.0)

The majority of patients had a one grade or greater decrease in neutrophil counts over the course of Campath-1h therapy with a 12 - 27% incidence of new Grade 4 neutropenia during the first six weeks of therapy. Grade 4 neutropenia occurs less frequently after week six. Slightly more than one third of the patients continued to have a lower neutrophil count after discontinuation of Campath-1h therapy. To better understand the effects of disease progression and the effect of growth factors (G-CSF, GM-CSF) information was requested about changes in neutrophil grade for responders compared to non-responders and for participants treated with growth factors (G-CSF, GM-CSF) as compared to patients who did not receive growth factors.

Table 009-14: Changes in Neutrophil Counts from Baseline Over Study: Responders (N = 8) vs. Non-Responders (N=16)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	8	0 (0.0)	3 (37.5)	5 (62.5)	16	4 (25.0)	4 (25.0)	8 (50.0)
Wks. 3 – 4	8	0 (0.0)	3 (37.5)	5 (62.5)	14	2 (14.3)	3 (21.4)	9 (64.3)
Wks. 5 – 6	8	0 (0.0)	5 (62.5)	3 (37.5)	10	3 (30.0)	0 (0.0)	7 (70.0)
Wks. 7 – 8	7	1 (14.2)	3 (42.9)	3 (42.9)	10	3 (30.0)	1 (10.0)	6 (60.0)
Wks. 9– 10	7	1 (14.2)	3 (42.9)	3 (42.9)	10	3 (30.0)	2 (20.0)	5 (50.0)
Wks, 11 – 12	6		2 (33.3)	3 (50.0)	5	1 (20.0)		4 (80.0)
Wks, 13+	7	1 (14.2)	2 (28.6)	4 (57.5)	5	1 (20.0)		4 (80.0)
1 Month F/U	8	1 (14.2)	3 (28.6)	4 (57.1)	11	1 (18.0)	4 (36.4)	5 (45.5)
2 Month F/U	7	1 (14.2)	3 (28.6)	3 (28.6)	6	3 (50.0)	1 918.7)	2 (33.3)

For both responders and non-responders, as shown in Table 009-14, worsening neutropenia (one or more grade increase) is observed over the course of therapy in both groups although somewhat more in nonresponders. In both groups a decrease in neutrophil count as compared to baseline is observed at two months after completion of therapy.

Table 009-15: Changes in Neutrophil Count from Baseline over Study: Growth Factor Recipients (N= 5) vs. No Growth Factor Exposure (N = 19)

Week on Study	Growth Factor Use				No Growth Factor Use			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	5	0 (0.0)	0 (0.0)	5 (100.0)	19	3 (15.8)	8 (42.1)	8 (42.1)
Wks. 3 – 4	4	0 (0.0)	0 (0.0)	4 (100.0)	18	2 (11.2)	6 (33.3)	10 (55.5)
Wks. 5 – 6	3	0 (0.0)	0 (0.0)	3 (100.0)	15	3 (20.0)	5 (33.3)	7 (46.7)
Wks. 7 – 8	3	0 (0.0)	0 (0.0)	3 (100.0)	14	4 (28.6)	4 (28.6)	6 (42.8)
Wks. 9 - 10	3	0 (0.0)	1 (33.3)	2 (66.7)	11	3 (27.3)	4 (36.4)	4 (36.4)
Wks, 11 – 12	2	0 (0.0)	0 (0.0)	2 (100.0)	9	1 (11.1)	2 (22.2)	6 (66.7)
Wks. 13+	2	0 (0.0)	0 (0.0)	2 (100.0)	10	2 (20.0)	2 (20.0	6 (60.0)
I Month F/U	5	0 (0.0)	2 (40.0)	3 (60.0)	14	3 (21.4)	5 (35.7)	5 (35.7)
2 Month F/U	4	3 (75.0)		1 (25.0)	9	3 (33.3)	2 (22.2)	4 (44.4)

The five patients, identified as growth factor recipients, had worsening neutrophil counts during the entire course of therapy. Three of four growth factor treated patients had improved over baseline at two months after completion of therapy. For the nineteen patients who did not receive growth factor during or post Campath-1h therapy, a decrease in neutrophil count of one grade or more was observed over the entire course of therapy in slightly more than one-third of the group. At two month follow-up four of nine study untreated subjects still had a neutrophil count lower than baseline values, while three had improved counts over baseline. The observations made here are similar to those made for Study 211 and confirm that Campath-1h therapy affects neutrophil production during therapy and that recovery to baseline may be delayed after completion of therapy.

Platelets

Twelve (50%) patients enrolled on this study were noted to have some degree of worsening thrombocytopenia (any grade) while receiving Campath-1h therapy or within thirty days of discontinuation of Campath-1h therapy on this study. Eight (33%) patients had new or worsening grade 3 or 4 thrombocytopenia. During the course of the study eleven (45.8%) participants received 101 single donor platelet transfusions.

Information about baseline platelet counts is available on all twenty-four study participants. Seven participants were reported to have baseline grade 0 thrombocytopenia; four patients with grade 1; three with grade 2; six with grade 3; and, four with grade 4 thrombocytopenia.
The following table provides information about the change in NCI-CTC platelet grade during study although the use of platelet transfusions may prevent an accurate description of the changes. [Improved indicates a change $\geq$ one grade from baseline. No Changes indicates the same grade as baseline. Worse indicates a decrease of $\leq$ one grade.]

Table 009-16: Changes in Platelet Count from Baseline Over Study: All Patients (N = 24)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Worse by ≥ Gr. 1 N (%)	No. with New Gr. 4 Thrombocytopenia
Weeks 1 – 2	24	2 (8.3)	11 (45.8)	11 (45.8)	3 (12.5)
Weeks 3 – 4	22	4 (18.2)	14 (63.6)	4 (18.2)	1 (4.5)
Weeks 5 – 6	18	4 (22.2)	12 (66.7)	2 (22.2)	1 (5.6)
Weeks 7 - 8	17	7 (41.2)	9 (52.9)	1 (5.9)	0 (0.0)
Weeks 9 – 10	14	4 (28.6)	10 (71.4)	0 (0.0)	0 (0.0)
Weeks 11 – 12	12	4 (33.3)	7 (58.3)	1 (8.3)	0 (0.0)
Weeks 13+	12	5 (41.7)	7 (58.3)	0 (0.0)	0 (0.0)
1 Month F/U	20	9 (45.0)	9 (45.0)	2 (10.0)	0 (0.0)
2 Month F/U	14	6 (42.8)	8 (57.2)	0 (0.0)	0 (0.0)

Review of the tabulations indicates Campath-1htherapy results in fewer changes in platelet count values as compared to hemoglobin or neutrophil counts. Four patients were developed new grade 4 thrombocytopenia during the first four weeks of study. At completion of two months of follow-up all participants for whom information is available had a platelet count value the same or improved over baseline. Platelet counts in responders as compared to non-responders are presented in the Table 009-16.

Table 009-16: Changes in Platelet Count from Baseline: Responders vs. Non-Responders

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	8	0 (0.0)	3 (37.5)	5 (62.5)	16	2 (12.5)	8 (50.0)	6 (37.5)
Wks. 3 – 4	8	0 (0.0)	6 (75.0)	2 (25.0)	14	4 (28.6)	8 (57.1)	2 (14.3)
Wks. 5 – 6	8	0 (0.0)	8 (100.0)	0 (0.0)	10	4 (40.0)	4 (40.0)	2 (20.0)
Wks. 7 – 8	8	1 (12.5)	7 (87.5)	0 (0.0)	10	5 (50.0)	4 (40.0)	2 (20.0)
Wks. 9– 10	7	2 (28.6)	5 (7.14)	0 90.00	7	2 928.6)	5 (71.4)	0 (0.0)
Wks, 11 – 12	7	2 (28.6)	5 (71.4)	0 (0.0)	5	2 (40.0)	2 (40.0)	1 (20.0)
Wks.13+	7	2 (28.6)	5 (71.4)	0 (0.0)	5	3 (60.0)	2 (40.0)	0 (0.0)
1 Month F/U	8	2 (25.0)	6 (75.0)	0 (0.0)	12	7 (5.83)	3 (25.0)	2 (16.7)
2 Month F/U	8	2 (25.0)	6 (75.0)	0 (0.0	6	4 (66.7)	2 (33.3)	0 (0.0)

Five (62.5%) of eight responders had a decline in platelet count of one or more grades during the first two weeks of study, and two (25%) during week 3-4. After the fourth week of therapy platelet counts improved or returned to baseline levels. Nonresponders showed similar trends, however, at the one and two month follow-up nonresponders were noted to have declines in platelet value due to disease progression. To better appreciate the effect of Campath-1h on platelet counts, changes in the NCI-CTC platelet grade were analyzed in transfused compared to non-transfused patients. No difference was observed between the transfused and nontransfused groups with regard to the number of patients with a decline in platelet counts over the course of therapy or in the number of patients with improved platelet counts at one month post study. The maximal effect of Campath-1h therapy on platelet counts appears to be during the first four weeks of therapy.

Table 009-17: Changes in Platelet Count from Baseline: Transfused (N=11) vs. Non-Transfused Patients (N=13)

Week on Study	Transfused (N = 11)				Non-Tranfused (N = 13)			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	11	1 (9.0)	5 (45.5)	5 (45.5)	13	1 (7.6)	6 (46.2)	6 (46.2)
Wks. 3 – 4	10	1 (10.0)	7 (70.0)	2 (20.0)	12	3 (25.0)	7 (58.3)	2 (16.7)
Wks. 5 – 6	7	2 (28.6)	4 (57.1)	1 (14.3)	11	1 (18.2)	8 (27.7)	1 99.1)
Wks. 7 – 8	7	4 (57.1)	3 (42.8)	0 (0.0)	10	3 (30.0)	6 (60.0)	1 (10.0)
Wks. 9 - 10	7	3 (42.8)	4 (57.1)	0 (0.0)	7	1 (14.3)	6 (85.7)	0 (0.0)
Wks. 11 – 12	5	3 (60.0	2 (40.0)	0 (.0)	7	1 (14.3)	5 (71.4)	1 (14.3)
Wks. 13+	5	3 (60.0)	2 (40.0)	0 (0.0)	17	2 (28.6)	5 (71.4)	0 (0.0)
I Month F/U	9	4 (44.4)	5 (55.6)	0 (0.0)	11	5 (45.5)	4 (45.5)	2 (18.1)
2 Month F/U	7	4 (57.1)	3 (42.8)	0 (0.0)	7	2 (28.6)	5 (71.4)	0 (0.0)

Blood Product Use on Study

As noted above 12 (50%) of the patients had no transfusions in the year prior to study entry.

- Five patients (four with Rai Stage II and one with Rai Stage IV disease) were not transfused during the period of Campath-1h therapy.
- Five patients (one with Rai stage I, one with Stage II, and one with Stage III, and two with Rai Stage IV) required RBC transfusions during study.
- Two patients (both with Rai Stage IV) who had no prestudy transfusions, needed RBC and platelet support to complete therapy.

Twelve (50%) patients enrolled on study had been transfused in the year prior to study entry. Two had Rai Stage III disease and ten had Rai Stage IV disease.

- One of the Stage III patients with a history of transfusion with eight units RBCs in the year prior to study did not require further transfusions on study.
- The other Rai Stage III patient who previously required both RBC and platelet support prior to Campath-1h therapy required only RBC support during study.
- Four of the ten Rai Stage IV patients who had only RBC support in the year prior to study required both RBC and platelet transfusions during the study.
- Four Rai Stage IV patients received both RBC and platelets in the year prior to study and continued to require both RBC and platelet support during study.
- Two Rai Stage IV patients had platelet support only in the year prior to study entry. One of these patients required only RBC transfusion on study, while other required both platelets and RBC support on study.

If the number of transfusions in the year prior to study is compared to the number of transfusions administered over the study period (in weeks), an increase in number of transfusions on study is noted. An increase in the rate of both RBC transfusions and platelet transfusions for ten of the twelve previously transfused patients is noted.

In the eighteen patients who received RBC transfusion on therapy, if the three patients who required 20, 22, and 31 units RBCS are excluded from the analysis, the median number of transfusions is 6.5 units (range: 2, 16 units). For the eleven patients, if the two

patients who required excessive platelet transfusions (16.5 times, 27 times) are excluded, the median number of times platelets were transfused is 6 times (range: 2, 10).

Other blood products used on study include gamma globulins, FFP, and growth factors One patient (002-007) received three units of fresh frozen plasma for bleeding. Use of gamma globulin is reported prior to enrollment for four patients. Use on study was reported in one patient. Use of neutrophilic growth factors was reported in five patients. One patient with fever and normal neutrophil counts received G-CSF for two days. Four patients received G-CSF for treatment of neutropenia in association with infection for periods of seven days, seventeen days, and three months respectively. A fourth patient received G-CSF for grade 3 /4 neutropenia without fever for a period of eight days.

Lymphocyte Subpopulations

Median CD3+/ CD4+ are reported in nineteen patients at study entry as 1.089 x 10^9/L (range: 0, 34.9 X 10^9 /L). Median CD4+ count at week 4 in fourteen patients is reported as $\leq$ 0.01 x 10^9/L (range: 0, 586 x 10^9 /L). Information at two months post study ($\pm$ 30 days is available in eleven patients. Median CD4+ count was reported as 0.272 x 10^9/L (range: 0, 1.022 x 10^9 / L. Information is available on five patients at four months and four patients at six months. Improvement in noted in the median CD4+ count with the lower limit of the range reported as > 240/ul at both time points.

Anti-CAMPATH Antibodies

Ten patients had fifty-three samples analyzed for the development of anti-Campath-1h antibodies. One patient (001-001) was reported to have a 171 U/ml (date unknown) positive immune response. The clinical impact of this finding is unclear. All other samples were negative.

CLINICAL (PATIENT) BENEFIT

In order to obtain approval of a drug in cases where non-comparative studies are used in addition to objective evidence of efficacy, evidence of clinical benefit (benefit to the patient) is necessary. In an attempt to show benefit, the FDA requested that that sponsor evaluate objective responders with regard to the following parameters: performance status, disease related symptoms, improvement in bulky disease, improvement in hematological parameters, and the nature of and incidence of adverse events and infections. On this study the following benefits of Campath-1h therapy were noted for the seven objective responders:

- Six patients had the potential to improve performance status. Interesting one patient improved, two remained at the same level, and three were reported to have decline in performance status. One patient's performance status declined by one level, and two patient's decline of performance status of two levels was reported. Since performance status information was not reported on long term follow-up CRFs, it is not known if the reported declines were transient or permanent.

- One of the seven responders was reported to have B-symptoms at study entry. This patient had resolution of B-symptoms.
- All seven responders had complete or near complete resolution of bulky adenopathy. Five patients had resolution of hepatosplenomegaly. Improvement adenopathy and organomegaly should be of cosmetic benefit and improve symptoms of early satiety associated with organomegaly.
- Three of four objective responders, in whom an improvement in hemoglobin value was possible, had improvement. One patient improved from grade 3 to grade 0 with a loss of transfusion requirement and need for EPO. One patient's hemoglobin improved from grade 1 to grade 0 and one patient from grade 2 to grade 1. Improvement in hemoglobin should improve sense of wellbeing, feelings of fatigue. On the opposite one responder with Stage I disease had a decline in hemoglobin value from grade 0 at baseline to grade 1. During therapy this patient required RBC transfusions in two occasions. The decrease in hemoglobin value persisted at last follow-up.
- Four responders had the potential for improvement in platelet count at study entry. All four had improvement. Three stage IV patients had improvement in platelet count. Two responders' platelet counts improved from Grade 3 to Grade 0, one for grade 2 to grade 1. The fourth responder with stage I disease had improvement in platelet count from 116,000/ul at baseline to 223,00/ul at follow-up.
- One responder with Stage IV disease had potential for improvement in neutrophil count with a gr. 2 neutropenia at initiation of therapy. Neutropenia resolved to grade 0 at completion of therapy. On the other hand, the stage I patient (005-001) had a slight decline in ANC from grade 0 at baseline to grade 1 at last follow-up post.
- Four of the seven responders had infections during or after therapy. Patient 2-002, Stage IV, had a grade 1 viral syndrome and gr. 4 PCP pneumonia. Patient 2-013 had gr. 1 oral candidiasis and gr. 2 Herpes Zoster. Patient 5-001 had two episode of PCP and one episode of otitis media. Patient 5-002 had gr. 3 aspergillosis and gr. 2 Candida esophagitis.
- Two patients had non-infectious serious adverse events. Patient 2-002 had two episodes of gr. 4 hypotension related to Campath-1h infusion with gr. 3 rash. One patient (5-002) developed gr. 3 / 4 hemolytic anemia requiring splenectomy after therapy. Other grade 3 / 4 adverse events related to therapy include infusion-related gr. 3 rigors reported for patient 5-002; infusion-related grade 2 dyspnea, gr. 3 nausea and vomiting, and gr. 3 fever reported on one occasion for patient 2-008.
- Baseline and CD34 counts are available in four of the seven responders. None of the responders returned to baseline CD34 count but three of the four had CD34+ counts > 200/ul. One responder, 5-001, with Stage I disease had a CD4+ count of 65/ul at last follow-up after completion of therapy.

Improvement was observed in organomegaly, lymphadenopathy, and hematological parameters. In one case the need for RBC transfusion and growth factors was abolished. Few serious infusion-related side effects were observed. Few non-infectious serious adverse events were reported. The relatively high rate of opportunistic infections is not unexpected since prophylaxis was optional. Low CD34+ counts are a known consequence of CAMPATH therapy and were observed on this study. The duration of response for this group of seven ranged from 5.5 months to 38 months.

SUMMARY

ON Study 009, conducted between February 8, 1993 and February 3, 1995 under the auspices of Burroughs-Wellcome, twenty-four participants of whom twenty-three had B-cell disease were treated with Campath-1h therapy three time per weeks for eight weeks. One of the twenty-four subjects had T-PLL, one had B-PLL, and one may have had lymphoma with a leukemic phase. Fourteen of the twenty-four patients had Rai Stage IV disease, three had Rai Stage III, six had Rai Stage II, and one patient had Rai stage I. Seven patients did not meet the definition of fludarabine refractory using the criteria established of Study 211.

Efficacy data from this study include an objective partial response in seven (29.2%) participants [95% CI: 11.0, 47.4%] with a median time to response of 3.8 mos. [95% CI: 2.3, 4.0 mos.] Median duration of response for responders is 10.8 months [5% CI: 5.6, 18.6 mos.]. Five of the objective responders were refractory to fludarabine. Of these five, two had Stage II disease and three had Stage IV disease. The duration of response for these five patients ranged from 4.7 months to 38+ mos.

At the cutoff date in March 21, 1997 twenty-two (91.7%) patients had progressed. Median progression-free survival for the entire study population is 7.1 months [95% CI: 3.1, 8.7 months]. Median time to treatment failure is much shorter at 3.8 months [95% CI: 1.6, 8.6] and is due to discontinuations from study secondary to adverse events. Six (25%) participants were reported as alive at last date of follow-up. Eighteen (75%) deaths had been reported as of March 21, 1997 (date of the last post study follow-up conducted by L & I Partners, Inc.). The estimated median survival is 27.5 months [95% CI: 7.1, 32.6 months].

On this study a cycle of Campath-1h therapy was eight weeks in duration. Campath-1h was administered for a period from < one day up to four weeks in six (25%) subjects; for a period of five to eight weeks in four (16.7%) subjects; for a period of nine to twelve weeks in two (8.3%) subjects; for a period of twelve to sixteen weeks for five (20.8%) subjects; and, a period of $\geq$ seventeen weeks in seven (29.2%) study subjects. Thirty-one single dose omissions were reported in thirteen patients. The reason for the dose delay is unknown or stated as "other" in 19 instances, infection in two instances, thrombocytopenia in two instances, and neutropenia in eight instances. Nineteen dose delays of greater than seven days were reported in twelve patients. Reasons for the prolonged dose delays include infection or complications related to infection in ten instances, febrile neutropenia in one instance, myelosuppression in four instances, and unknown in four instances.

With regard to the Campath-1h safety profile, the following information is available. Five (20.8%) deaths occurred on study or within thirty-five days of discontinuation of Campath-1h therapy. Two of the five deaths were secondary to infections due to Campath related immunosuppression. In addition to the two deaths on study, five (20.8%) patients discontinued therapy for fever and hematological toxicity related to CAMPATH therapy.

Nineteen (41.6%) patients had thirty-two serious adverse events as discussed in the patient narratives. On review the majority of these serious adverse events were regarded as related to Campath therapy. Seventeen events involved myelosuppression and / or infection.

All twenty patients experienced at least one adverse event on study. All patients experienced at least one treatment related adverse event. Seventeen (70.8%) patients experienced grade 3 / 4 adverse events. Fifteen (62.5%) patients experienced grade 3 / 4 study drug-related adverse events.

Commonly reported infusion related toxicities reported on this study include: fever (95.8%), rigors (91.7%), hypotension (66.7%), nausea (62.5%), vomiting (54.2%), fatigue (41.7%), urticaria (41.7%), back, chest, or pain in 29.3%), myalgias (16.7%), rash (25%) with pruritis (16.7%), stomatitis (25%), headache (25%), palpitations / tachycardia (25%), dyspnea (20.8), and diarrhea (8.3%). Grade 3 / 4 infusion-related toxicities include: fever (16.7%), rigors (16.7%), hypotension (12.5%), vomiting (16.7%), nausea (8.3%), urticaria (4.2%), rash (4.2%), pruritis (4.2%), back pain (4.2%), dyspnea (4.2%), and headache (4.2%).

Fifteen (62.5%) patients experienced thirty-four infections on study or within six months of study completion. Eighteen of the thirty-four infections were of grade 3 / 4 severity. Ten (41.6%) patients experienced opportunistic infections. Thirteen of the thirty-four infections were opportunistic in nature (four infections due to PCP, two due to Candida, two due to Aspergillosis, one due to CMV, and four due to Herpes Zoster one of which was disseminated).

Hematologic toxicities secondary to Campath-1h therapy were observed on this study. Sixteen (67%) participants were noted to have declines in hemoglobin value (any grade) while nine (38%) participants developed grade 3 or 4 hemoglobin toxicity. Eighteen (75%) participants required RBC transfusions on study including six participants who had no prestudy transfusion requirement. Eighteen (75%) participants had some degree of new or worsening neutropenia. Fourteen (58%) participants had one or more episodes of grade 3 or 4 neutropenia. Five patients received G-CSF on this study. Platelet counts were less severely affected by Campath-1h therapy. Twelve (50%) participants experienced some degree of thrombocytopenia. Eight (33%) participants had one or more episodes of grade 3 or 4 thrombocytopenia. Eleven patients required one or more platelet transfusions on study. Six patients had history of platelet transfusions in the year prior to study enrollment. Three study participants developed pancytopenia. In two, recovery was documented at two –four months after discontinuation of study drug.

Nadir CD 3+ / 4+ occurred at 4 weeks after initiation of Campath-1h therapy with the median count about 20/ul. At two months after discontinuation of study drug, median CD 4+ count (with a sample size of twelve) was 231/μ. The CD4+ count continued to improve in the small number of patients followed to six months but did not reach baseline. Samples for anti-Campath antibodies were obtained from ten study participants.

Anti-Campath antibodies were identified in one sample out of the fifty-three samples tested at an unknown time point.

CONCLUSION

Therapy with Campath-1h in this single arm study of twenty-four patients, twenty-three of whom had B cell disease, resulted in an objective partial response rate of 29.2% with a median duration of response of 10.8 months. All of the participants had been exposed to fludarabine and seventeen of these patients were considered refractory to fludarabine.

Campath-1h therapy is associated with serious toxicity / fatalities. Two deaths on study are due to infection resulting from Campath-1h therapy. Five discontinuations of Campath-1h therapy were for serious drug-related adverse events. Twenty-three of the 32 serious adverse events in nineteen patients were considered related to Campath-1h. One or more serious opportunistic infections related to study drug therapy occurred in ten patients. Serious infusion-related toxicities were reported in two patients. Hematological toxicity related to study drug therapy was observed in over 50% of the patients. Transfusion support was required during study for 75% of the participants. Pancytopenia was also reported.

In a patient population for which there a few therapies available, Campath-1h may provide for a delay in disease progression provided that the patient is carefully monitored to avoid serious hematological toxicity and monitored closely to avoid serious / potential fatal infectious complications. The lack of a comparator arm makes it difficult to appreciate the relative benefits of Campath-1h in light of the severity of toxicities.

005 Study Report

Table of Contents

005 Study Report

Title: A Multi-Centre Phase II Study of Campath-1h Given Three Times a Week to Patients with Non-Hodgkins Lymphoma (Including Chronic Lymphocytic Leukemia)

Introduction

This open-label, non-comparative study was conducted in Europe between February 12, 1993 and May 8, 1995 and enrolled patients with NHL or CLL who had failed to respond to or who had relapsed following conventional chemotherapy. The study was conducted in Europe in accordance with Good Clinical Practices under the auspices of Burroughs Wellcome Co. The study report was completed on November 10, 1999 under the sponsorship of L & I Partners, LP. A total of 125 patients were enrolled including 60 patients with NHL (≥ Stage II), 61 patients with CLL, and four patients with other malignancies. Protocol amendment No. 9 (3/29/1992) allowed enrollment of patients with minimal residual disease in preparation for bone marrow transplant. Protocol amendment No. 11 (3/3/94) allowed the administration of subcutaneous Campath-1h in a cohort of 25 patients with CLL or PLL since subcutaneous administration was associated with fewer acute drug-related side effects.

The last study termination visit conducted by Burrough Wellcome was conducted in February 1996. In 1997 ILEX and their _____ conducted monitoring visits at seventeen (? nineteen) sites to verify the safety and efficacy data. Verification of demographic data, central pathologic review of CLL, prior therapy for CLL, adverse events, and concomitant medication, disease assessments including bone marrow aspirates / biopsies, radiologic studies, progress notes, and laboratory data was attempted. Information was source verified for approximately 50% of the patients. The CRFs were found to be accurate when compared to the source documents according the sponsor. Additional response information and patient survival data was obtained through a post study survey conducted by ILEX in 1997. Last date of follow-up for duration of response was March 3, 1997. Last date of follow-up for survival was September 10, 1997.

An independent review panel was established by L & I Partners to verify eligibility criteria and to verify response to therapy. The panel used the 1996 NCI Working Group CLL criteria for staging and response. The FDA determined that eight patients did not have B-CLL after review of the CRFs for forty "B-CLL" patients, which provided the basis for the original study report (submitted December 1999). The sponsor and the agency agreed that the focus of the 005 Study Report should be only patients with B-CLL. A revised report that includes information and analyses for the thirty-two B-CLL patients was submitted on August 18, 2000. Safety information for the eighty-five patients enrolled on Study 005 who had other disease such as T-CLL, lymphoma, and myeloma is not reviewed here.

Brief Description of the Study Protocol

Study objectives for 005 were:

(1) to evaluate the safety and efficacy of Campath-1h in patients with different pathological subtypes of NHL and CLL;
(2) to measure peak and trough levels of Campath-1h;
(3) to perform a limited pharmacodynamic analysis of effects on lymphocytes and / or other circulating abnormal lymphoid cells; and,
(4) to measure the incidence / titers of any antibodies raised against Campath-1h.

Inclusion criteria for the study included: diagnosis of NHL or CLL confirmed by clinical or histological / cytological assessment who had failed to respond to or relapsed following conventional first line or subsequent chemotherapy; age $\geq$ 18 years; WHO performance status $\leq$ 1; life expectancy $\geq$ 12 weeks; creatinine, bilirubin, SGOT / SGPT, and alkaline phosphatase $\leq$ 125% of the ULN unless attributable to disease.

Exclusion criteria include: AIDS-related or known HIV-positive lymphoma; chemotherapy, biological response modifiers, gamma globulin, or radiation therapy < three weeks prior to the initiation of study drug therapy; use of steroids in other than maintenance dose (10 mg); pregnancy; lactation; inadequate contraception; debilitating systemic disease including active uncontrolled infections or complications due to malignancy; known CNS involvement; prior radiation to the only site of measurable disease; previous bone marrow or other organ transplant with the exception of autologous transplant; autologous bone marrow transplant with inadequate hematological recovery (Hgb < 9.5 gm%; ANC < 1500/ul, or platelets < 75,000/ul); history of prior malignancy within five years of enrollment excluding basal cell carcinoma or carcinoma in situ of the cervix; prior exposure to Campath-1h; and, for administration of subcutaneous Campath-1h platelet count < 25,000/ul.

Patients were initially dosed with Campath-1h 3 mg or 10 mg daily then escalated to 30 mgs three times per week based on the patient's ability to tolerated acute infusion-related toxicities. Campath-1h dose could be escalated to 80 mg with the permission of the sponsor. Prior to the first dose, patients were premedicated with paracetamol 1 gm and either hydrocortisone 200 mg IV or chlorpheniramine 10 mg IV (or clemastine 2 mg IV). Steroid or antihistamine could be repeated post-injection after the first infusion as clinically indicated. Use of steroids for prophylaxis with subsequent infusions was prohibited, but other premedication could be given at the investigator's discretion. A subgroup of twenty-five patients received Campath-1h by subcutaneous injection with an initial dose of 10 mg with escalation to 30 mg. Topical steroids could be used to control local injection site reactions. Prophylaxis with trimethoprim / sulfamethoxazole and acyclovir was optional. Use of other anti-neoplastic agents, gamma globulins, prophylactic growth factors, other investigational drugs, and radiation therapy was prohibited.

Patients were evaluated for evidence of disease response after six weeks on treatment. Patients with no evidence of disease had treatment discontinued and observed for six to eight weeks to confirm response. Patients with evidence of disease improvement or no change in disease status at six weeks were continued on Campath-1h therapy at 30 mgs for a total of twelve weeks of therapy had been completed then reassessed. Patients also receive additional six week courses of Campath-1h if further therapy was considered beneficial to the patient. Patients with disease progression at the six-week evaluation were discontinued from study. At completion of therapy patients were to be followed monthly for six months and then every three months until relapse, administration of alternative therapy, or death. At relapse patients were eligible for retreatment with Campath-1h.

Serum samples for determination of Campath-1h levels and anti-Campath-1h antibodies were obtained before and at the end of the first infusion in each week of treatment, upon completion of therapy, and twenty-eight days after the last Campath-1h infusion.

Description of the Study Population

Study Demographics

Demographic data for this study is presented in Table 005-1.

Table 005-1: Demographic Data

Demographic Parameter	B-CLL Patients (N=32)
Gender	
Male	22 (68.8%)
Female	10 (31.3%)
Ethnicity	
White	32 (100%)
Other	
Age in years	57
(Range, years)	(46, 75)
Rai Stage	
Stage I	3 (9.4%)
Stage II	5 (15.6%)
Stage III	5 (15.6%)
Stage IV	19 (59.4%)

Demographic data for this study population is consistent with demographic data from epidemiological studies of CLL. Lack of enrollment of minority populations is consistent with local population demographics for European studies.

Eligibility for Study

Type and Stage of Disease

All thirty-two patients in this preselected study population had B-CLL. A difference in assessment of stage of disease occurs in one instance. Patient 019-001 assessed as Stage II disease by the sponsor, was assessed as Stage III disease by the FDA since the

participant's Hgb was 10.3 gm% on the day Campath-1h therapy was initiated. At study entry, twenty-four (75%) study participants had Stage III / IV disease.

Prior Therapies: Fludarabine and Other Treatments

For entry on Study 005, prior therapy with fludarabine was not required. Twenty-one (65.6%) patients did not have prior therapy with fludarabine. Of the eleven (34.4%) patients treated with fludarabine, nine (28.1%) were considered fludarabine refractory (i. e. the patient failed to respond initially to fludarabine therapy, relapsed within six months of an objective response, or failed to respond on retreatment with fludarabine). The sponsor assessed patient 006-104 as not refractory to fludarabine. On review of the CRF this patient was found to have relapsed at six months after response to fludarabine therapy with a new therapy instituted for treatment of his CLL. The agency considers this patient refractory to fludarabine. The CRF for patient 006-106 contains no record of prior treatments. The line listings contain the following information. The patient had one five-day cycle of fludarabine with no response reported.

Eight of the eleven patients previously treated with fludarabine had five or more chemotherapy regimens other than fludarabine prior to initiation of CAMPATH-1H therapy. In addition, two of these patients had immunotherapy with interferon or cyclosporin, four had received prednisone or high dose methylprednisolone as therapy, three had had splenectomy for management of disease, and two had received therapeutic leukophereses.

All thirty-two study participants had at least one course of therapy with an alkylator. Twenty-four (75%) participants were reported to have failed one or more alkylator based therapy. Of the twenty-one patients without a history of fludarabine therapy, seven were found on review to have received one course of therapy of an alkylator-containing regimen, seven patients had received two courses of therapy with alkylator-containing regimens, and the remaining seven patients received from three to nine different alkylator containing regimens. Six of these twenty-four had received immunotherapy with interferon or cyclosporin, one had splenectomy, three had radiation therapy (TBI in one, splenic RT in one, and cervical node RT in one). One participant had received therapeutic leukopheresis. In conclusion the majority of patients enrolled on Study 005 had had two or more therapies for treatment of their CLL, about one-fourth had been heavily pretreated with alkylator regimens other than fludarabine prior to entry, and nine were refractory to fludarabine.

Deviations in Eligibility Parameters

- Two patients (018-001, 018-002) did not have pathology reviewed centrally.
- Patient 006-002 had been treated with fludarabine within three weeks of study entry.
- Patient 009-006 entered study with a WHO performance status of 3 and a life expectancy < 12 weeks.

- Two patients (009-004, 009-006) were on therapeutic doses of prednisone at study entry.
- One patient (001-003) had an AST = 50 IU/L, greater than the 125% of the ULN allowed at study entry.
- One patient (006-002) had a history of another malignancy within five years of study entry.

EFFICACY ANALYSES

Patient Disposition

Patient disposition on this study is as follows:

- Fifteen (46.9%) participants completed therapy.
  - Thirteen study participants were assessed by the investigator as having disease improvement. Two of these patients did not have the Off-Study Records completed by the investigator. Review of the Disease Assessment Sheet for these two patients revealed the following information. Patient 006-101 completed therapy with an unconfirmed partial response and was retreated with Campath-1h eight months after initial therapy. Patient 006-104 completed therapy on 9/14/94 and began retreatment on 11/11/94 with evidence of progression at time of retreatment.
  - Two participants were discontinued. The investigator indicated no disease improvement after assessment at completion of therapy.
- Five (15.6%) patients were discontinued due to progressive disease.
- Three patients died on study.
  - Two (009-006, 006-103) died from sepsis and possibly disease progression.
  - One (011-001) died from interstitial pneumonitis (?PCP) without evidence of disease progression.
- Six (18.8%) patients were discontinued by the investigator for drug related toxicity / adverse events.
  - Two patients, discontinued for drug-related adverse events, were considered by the investigator to be in remission at the time therapy was discontinued.
    - Patient 001-004 experienced drug-related nausea, vomiting, rigors, and gr. 3 urticaria.
    - Patient 002-008 developed grade 4 thrombocytopenia that resolved on discontinuation of Campath-1h infusions.
  - Four other patients had therapy discontinued after experiencing a serious drug related adverse event in the investigator's judgement.
    - Patient 001-003 developed Staphylococcus sepsis with DIC, GI bleeding, and disseminated Herpes Zoster.
    - Patient 022-001 developed Klebsiella sepsis with shock.
    - Patient 009-004 was discontinued for grade 4 neutropenia that responded to G-CSF.
    - Patient 022-002 developed grade 3 hypotension during the nineteenth Campath-1h infusion. Campath-1h was discontinued permanently.

- Two (6.2%) patients (017-001, 019-005) refused to continue therapy according to the investigator.
  - Patient 017-001 had achieved remission according to the investigator. At the time he withdrew from study, he was reported to have grade 2 sinusitis and grade 2 fever.
  - Patient 019-005 had grade 3 fatigue and grade 2 fever at the time CAMPATH-1H was discontinued. He developed pneumonia five days after the last CAMPATH-1H infusion.
- One (3.1%) patient (006-106) was discontinued on 11/16/ 94 for the holidays. He was assessed with limited disease improvement at that time having completed twelve weeks of therapy. The patient resumed therapy as a re-entry on 1/30/95. Disease progression was evident at reentry.

Response, Time to Response, and Duration of Response

Information about response, time to response, and duration of response is included in Table 005-2.

Table 005-2: Response Information

Response Parameter	FDA N = 32 (100%)	Sponsor N = 32 (100%)
Response Category		
Complete	0 (00.0)	0 (00.0)
Partial Response	7 (21.9%)	9 (28.1%)
Stable Disease	17 (53.1%)	14 (43.8%)
Progressive Disease	6 (18.8%)	8 (25.0%)
Not Evaluable	2 (6.3%)	1 (3.1%)
Estimated Objective Response [95% Confidence Interval]	21.9% [7.6%, 32.6%]	28.1% [14%, 47%]
Median Time to Response in Months [95% Confidence Interval in Months]	3.9 [1.4, 4.6]	3.8 [1.4, 4.4]
Median Duration of Response in Months [95% Confidence Interval in Months]	7.1 [4.6, 23.2]	7.1 [4.6, +]

Differences in response assessments are noted for five patients.

- Patient 001-004, considered a PR by the responder, did not have a 50% reduction in lymph nodes, a CT to evaluate chest adenopathy, and was reported to have splenomegaly that was not measured at the week 6 evaluation. At the second disease assessment performed after the patient had been discontinued from study after the twenty- sixth infusions for drug related adverse events, lymph nodes were not evaluated and CT was not repeated. The spleen was not longer palpable. Major disease improvement was reported by the investigator. Due to the failure to assess all sites of disease at the time that Campath-1h was discontinued, the patient was assessed as stable disease.

- Patient 006-101, assessed as partial responder by the sponsor's review panel, was assessed as stable disease by the agency since partial response observed for a first time on 8/12/94 was not confirmed before relapse was reported on 10/14/94.

- Patient 006-104 was assessed by the sponsor's review panel as having progressive disease. Review of the CRF did not provide evidence to support the response of disease progression at time of completion

of Campath-1h therapy. The investigator reported progression approximately two months after discontinuation of Campath-1h therapy.

- Patient 009-006, assessed as stable disease by the sponsor's review panel, was considered nonevaluable by the agency since the investigator failed to repeat abdominal ultrasound used to assess intraabdominal disease at completion of therapy. This patient was discontinued from therapy for "progressive weakness", had documented weight loss, and died shortly after removal from study reportedly from sepsis and progression.

- Patient 011-001 was assessed with a progressive disease designation by the sponsor's review panel. CRF review did not provide evidence of progression, the investigator reported limited disease improvement, and the agency assessed this patient's response as stable disease.

Of the seven responders, two had Stage II disease, one had stage III disease, and four had Stage IV disease. One (002-008) of the seven responders, treated with intravenous Campath-1h, was refractory to fludarabine. This patient had also been treated with one alklyator regimen and interferon. The other six partial responders had not been treated with fludarabine therapy. Two of these six had received one alkylator regimen. One had received one alkylator regimen and one type of immunotherapy. Three patients had been treated with two different alkylator-containing regimens. One responder, with Stage III disease, was treated with subcutaneous Campath-1h therapy. The other six responders had received intravenous Campath-1h therapy.

The slight difference in the median time to response as calculated by the sponsor and the agency relates to the assignment of a slightly later date of response by the agency for patient 017-001. The sponsor assigned a date of response of 9/8/93. Review of disease assessment sheets revealed that the cervical and jugular nodes were not assessed until 10/14/93, which was the response date assigned by the agency.

Progression Free Survival (Time to Progression) and Time to Treatment Failure

Table 005-3 provides information about progression free survival, time to progression, and time to treatment failure for the thirty-two patients evaluated for efficacy.

Table 005-3: Progression and Treatment Failure Information

Parameter	FDA	Sponsor
No. Progressed	30 (93.8%)	26 (81.3%)
No. without Progression	2 (6.2%)	6 (18.7%)
Median Progression Free Survival in Months	4.9	
Median Time to Progression in Months		6.5
[95% Confidence Interval in Months]	[2.9, 7.0]	[3.7, 7.7]
No. Treatment Failures	31 (96.9%)	***27 (84.4%)***
No. without Treatment Failure	1 (3.1%)	***5 (15.6%)***
Median Time to Treatment Failure in Months	3.0	***3.6***
[95% Confidence Intervals in Months]	[1.9, 4.7]	[2.4, 6.6]

The difference in the median time to progression and the median progression free survival of approximately 1.6 months occurs for the following reasons. First the sponsor used a new definition for progression in the resubmission, while the FDA used the

definition provided in the original submission. Second differences in the assigned date of progression are noted for eight participants. Differences in censoring occurred in four instances. Table 005-4 provides information about the dates assigned by the sponsor and the reviewer, the censoring (0 = progressed, 1= no evidence of progression), and the reason for the difference in the date assigned for progression or the censoring symbol. Patient 022-003 is considered to have progress at the last follow-up although the patient's absolute lymphocyte count did not quite reach 5000/ul at the time of the last follow-up. The ALC was 4630/ul on that date. In addition the differential count included 11.4% other cells (? prolymphocytes). Since this patient had no further follow-up information available, this date was used as the progression date by the agency.

Table 005-4: Differences in Assessment of Progression

Patient No.	FDA Date of Response	Censor	Sponsor Date of Response	Censor	Comments
001-004	1/6/94	0	3/4/94	0	1/6/94 ALC – 7420/ul 3/4/94 ALC - 16,200/ul
006-102	8/17/94	0	4/10/95	0	8/17/94 Tip of liver palpable at enrollment; New hepatomegaly 3-4 cm on 8/17/94. Bone Marrow post therapy reported to have increase in leukemic infiltrate. Investigator reported "major disease improvement" on 8/17/94! 4/10/95 Prolymphocytes – 6% on peripheral smear; progression reported by investigator
006-105	1/6/95	0	11/17/94	1	Pt. completed therapy 10/5/94; no evidence of progression until death reported on due to transformation to more aggressive histology
006-106	10/10/94	0	10/10/94	1	Pt. began radiotherapy on for abdominal disease while continuing CAMPATH-1H
008-003	11/5/93	0	11/5/93	1	ALC –6083/ul on this first follow-up after therapy
011-001	6/3/93	0	5/14/93	0	CRF does not contain any evidence of progression at time of death due to interstitial pneumonitis on
013-001	4/7/93	0	7/7/93	0	4/7/93- Two new pulmonary nodules on CT in spite of which patient is reported to have "limited disease improvement". 6/10/93- Five additional new pulmonary nodules are reported. 7/7/93 Started on Chlorambucil for progression
017-002	6/17/94	0	8/2/94	0	6/17/94 – Investigator date of progression due to reappearance of lymphocytosis 7/5/94 ALC – 9626/ul
018-002	11/10/94	1	3/11/96	1	New date for follow-up reported by sponsor in resubmission; CRF not updated so disease status could not be verified.
019-002	7/28/93	0	7/26/93	0	7/26/93 Date of last therapy; 7/28/93 date investigator assigned progression
022-003	1/9/95	0	1/9/95	1	1/9/95 ALC 4630 with 11.4% other cells also reported on the differential (? Prolymphocytes); No further follow-up

The median time to treatment failure as assessed by the sponsor and the agency differs by less than one month. Table 005-5 presents information about differences in the assessment of treatment failure and / or the date assigned for treatment failure.

Table 005-5: Differences in Treatment Failure Assessments

Patient No.	FDA Treatment Failure Date	Censor	Sponsor Treatment Failure Date	Censor	Comment
006-102	8/17/94	0	4/10/95	0	Difference in date assigned for progression
006-105	1/6/95	0	11/17/94	1	— Date of death due to transformation to more aggressive disease
006-106	10/10/94	0	10/10/94	1	Pt. began radiotherapy on this date for abdominal disease while continuing CAMPATH-1H
008-003	11/5/93	0	11/5/93	1	Date of progression. ALC –6083/ul
009-006	2/25/94	0	3/5/94	0	2/25/94 – Campath-1h discontinued after infusion #16 due to weakness
011-001	6/3/93	0	5/14/93	0	No evidence of progression at time of death due to Interstitial pneumonitis attributed to drug related toxicity
013-001	4/7/93	0	7/7/93	0	4/7/93 Date of progression assigned due to new pulmonary nodules
017-002	6/17/94	0	8/2/94	0	Difference in date assigned for progression
018-002	11/10/94	1	3/11/96	1	New date for follow-up reported by sponsor in resubmission; CRF not updated so disease status could not be verified.
018-003	11/5/93	0	11/5/93	1	Date of progression as ALC-6083/ul
019-002	7/28/93	0	7/26/93	0	7/26/93date of last treatment; 7/28/98 date progression documented
022-003	1/9/95	0	1/9/95	1	Date assigned for progression

Survival

The last date of follow-up for survival was September 10, 1997. Eighteen (56.3%) patients had died and fourteen (43.7%) were alive as of this date. Median survival is 25.8 months (95% CI: 11.7 mos., 44.2 mos.) as determined by the agency. Median survival time is as calculated by the sponsor is 25.9 months (95% CI: 11.7 mos., 44.3 mos.) The sponsor reports the death date for Patient 006-105 as —— On review of the CRF the death date was listed as —— with cause listed as probable transformation to more malignant disease. Hence slight difference in the calculation of the median survival is noted. Six of the fourteen participants were censored for survival. Follow-up after the last dose of Campath-1h was less than six months for all of these patients.

SAFETY ANALYSIS

Dosing Information

Twenty-five (78.1%) patients received Campath-1h intravenously while seven (21.9%) received subcutaneous therapy. Twenty of the twenty-five patients treated with intravenous therapy had Campath-1h initiated at a dose of 3 mg. Five of these twenty-five patients began therapy at the 10 mg dose level. Twenty-one patients treated intravenously reached the targeted dose of 30 mg within five infusions. Ten patients required six to ten

treatments to reach the 30 mg target dose level. One patient, 019-003, was discontinued prior to achieving the targeted 30 mg dose level.

Three patients had dose reductions during therapy.

- Patient 019-003 received twelve Campath-1h infusions between 6/14/93 and 9/1/93 with eleven infusions at the 3 mg dose and one at the 10 mg dose level. Infusion related toxicities (fever, headache, itching, rash, neutropenia, and thrombocytopenia) prevented further dose escalation.
- Patient 001-004 was not treated according to protocol guideline. The patient's dose was escalated from 30 mg to 60 mg for the nineteenth infusion because the patient had transportation problems and was unable to attend clinic more frequently than once per week. For the twentieth infusion one week later, Campath-1h dose was escalated to 90 mg. The patient experienced infusion related side effects with this dose. For the twenty-first infusion administered one week later, the patient was premedicated with paracetamol, antiemetics, antihistamines, and steroids and the dose of Campath-1h was reduced to 40 mg. For the twenty-second infusion (one week later) the dose was again escalated to 90 mg and administered with premedication. As the 90 mg dose was not as well tolerated, the dose was reduced to 60 mg weekly for the remaining four infusions. At this time the patient was discontinued for therapy with disease improvement and drug related toxicity (thrombocytopenia).
- Patient 019-002 received sixteen infusion of Campath-1h. Therapy was interrupted for fever, rash, and peripheral vasoconstriction. Dosing was resumed two weeks later. After two additional infusions Campath-1h was permanently discontinued for disease progression.

Seven patients treated subcutaneously with Campath-1h began therapy with a 10 mg dose. All were escalated to 30 mg for the remainder of therapy. No dose reductions or changes in the dosing schedule were reported for this group of patients.

With regard to the duration of therapy, eleven patients received five to eight weeks of therapy. Eight patients received nine to twelve weeks of therapy. Ten patients received thirteen to sixteen weeks of therapy. Three patients were treated from seventeen to twenty weeks. The actual number of weeks of therapy may be less than reported due to dose delays during therapy.

Treatment Interruptions during Therapy

Eighteen (56.3%) patients had one or more treatment interruptions. This information was difficult to obtain since the information about missed doses due to adverse events or for other reasons was not collected on the infusion record in the CFR. Patient 001-004, discussed in the previous section, missed multiple doses due to the weekly treatment schedule. This patient is excluded for further discussion about treatment delays or interruption.

Three patients missed a single dose of therapy; one for unknown reasons; one due to a Klebsiella infection; and, one due to neutropenia. Fifteen patients had twenty-four dose

delays of seven days or more as discussed below. Three of these fifteen patients also missed a single dose on another occasion (two for unknown reasons and one because of a holiday).

- Nine dose delays of ≥ seven days were reported for four patients.
  - Six delays occurred while the patient was awaiting disease assessment.
  - Two delays occurred for personal reasons.
  - One delay occurred as the patient wanted to be off therapy for the holidays.
- Fifteen dose delays of ≥ seven days occurred in nine patients. These fifteen delays were related to adverse events.
  - Fever and myelosuppression were responsible for eight interruptions.
  - Infusion related symptoms were reported as the cause for two dosing interruptions.
  - Infections including E. coli bacteremia, herpetic stomatitis, Staph. aureus, were responsible for three dose delays.
  - Thrombocytopenia was the cause of one interruption.
  - Ventricular tachycardia was the cause of one treatment interruption.

Deaths on Study, within Thirty Days of Study, and Late Deaths

Three (9.4%) patients died on study or within thirty days of study drug discontinuation. Two patients died at greater than thirty days after study drug discontinuation. The circumstances surrounding the death, the cause of death, and relationship to Campath-1h therapy are discussed for each of these patients.

- **Patient 006-103** with Rai Stage IV disease entered study with Hgb 11.0 gm%, platelets 30,000/ul, WBC 44,6000, ALC 41480/ul and ANC 2680/ul. Patient received twenty-one subcutaneous injections of Campath-1h between 7/29 and ——. Patient was hospitalized from ———— for a Rt. femoral vein thrombosis. The thrombus was treated with heparin until thrombocytopenia occurred at which time Fragmin therapy was instituted. On 9/14/94 patient was seen for gr. 2 fever (38.4°) with WBC –2600/ul (no differential done) and platelet count 56,000/ul and sent home. Patient presented on —— with hypotension (60/40 mm Hg) gr. 4, hypoglycemia gr. 3, back pain, vomiting, diarrhea, and moist cough. WBC was reported as 1700/ul, ANC was 370/ul, platelet count 13,000/ul, and ALC 1330/ul. Patient expired within three hours of presentation. Patient is reported to have died from septic shock (no organism identified) and disease progression. Autopsy was reported to have shown massive tumor infiltration of all nodal sites. However, a marked decrease in ALC was reported during study and splenomegaly was reported to have resolved at the six week assessment. The report for the bone marrow biopsy performed at week six is not included in the CRF. The autopsy report is not included in the CRF. The sponsor regards the death as reasonably related to Campath-1h as does the reviewer. The tumor burden visible at autopsy may not have appreciated during study since intraabdominal disease was assessed and followed by ultrasound. The results of the bone marrow biopsy and a full autopsy report would have been particularly informative in this case since Campath-1h is known to cause pancytopenia.

- **Patient 009-006** entered study with WHO performance status 3, life expectancy < 12 weeks, Rai Stage IV B-CLL. CBC on entry included Hgb 5.5 gm%, platelet count 3000/ul, WBC 152,000/ul with ALC 149,000/ul and ANC 3000/ul. Patient had required erythropoeitin and RBC support prior to enrollment. The patient received eighteen Campath-1h infusions between 1/27/94 and . ——. On . —— patient was hospitalized with Pseudomonas sepsis and pneumonia, gr. 4 neutropenia (ANC-200/ul on —), a grade 1Herpes simplex oral infection and grade 4 thrombocytopenia (no change from baseline). The patient was treated with antibiotics and acyclovir. Campath-1h infusions were continued. WBCs

remained less than 500/ul until 2/21/94. On this day the WBC was reported as 600/ul with ANC 570/ul and ALC 30/ul. No further improvement during the remainder of the patient's life was observed. Platelet counts remained < 7000/ul despite multiple platelet transfusions. The patient's performance status declined to WHO 4. After several episodes of gastrointestinal bleeding due to thrombocytopenia Campath-1h was discontinued for progressive weakness with an assessment of limited disease improvement. The patient's respiratory status declined, all active treatment was discontinued on ___ and patient expired on ___ The investigator considered the death to be due to disease progression but possibly related to Campath-1h therapy. On review of the CRF improvement in adenopathy and splenomegaly is reported on 2/28/94 with ALC < 100/ul. No change in CLL infiltrate in the bone marrow was reported. Marrow cellularity and hematopoeisis were not evaluated at week six.

- **Patient 011-001** entered study with Rai Stage III B-CLL. CBC on study entry included Hgb 8.3 gm%, platelet count 168,000/ul, WBC 90,900/ul, ALC 76,500/ul and ANC 11,820/ul. The patient received twenty-seven Campath-1h infusions between 3/29/93 and ___ Campath-1h therapy was held from 5/7/93 to 5/12/93 for neutropenia. On 5/14/93 WBC was 1200/ul with ANC 1080/ul and therapy was resumed. On ___ Grade 4 neutropenia (ANC-300/ul) was reported. Campath-1h was discontinued permanently. On 5/28/93 WBC was 890/ul. On ___ patient was hospitalized with fever (39°) and cough. CBC from 6/1/93 included Hgb 10.8 gm%, platelet count 139,000/ul and WBC 1660/ul (no differential performed). Chest xray showed bilateral interstitial infiltrates. No organism is identified. Patient continued to have grade 3 leukopenia, developed multiorgan failure including renal failure, DIC, hypotension, ARDS, respiratory acidosis and expired on ___ The sponsor reports this death as reasonable related to Campath-1h therapy. The sponsor's review panel considered this patient to have disease progression. Review of the CRF does not support the review panel's designation of disease progression. The investigator reported major disease improvement prior to the patient's death..

All of the above deaths, which occurred on therapy or within 30 days of study drug discontinuation, are considered related to Campath-1h therapy. Two late deaths (after thirty days) are considered as reasonably or possibly related to study drug therapy.

- **Patient 009-004** was enrolled on study with Rai Stage IV disease. CBC at entry included Hgb 6.8 gm%, Plt. Ct. 87,000/ul, WBC 12,000/ul, ALC 8500/ul and ANC 2470/ul. The patient received twenty-nine infusions of Campath-1h between 1/17/94 and ___ Patient was hospitalized because of fatigue and weakness and suspicion of pneumonia on ___ Hgb was 4.7 gm%, Plt. Ct. 87000/ul, WBC 1000/ul with ANC 900/ul. Patient was transfused with four units packed cells, begun on antibiotics, and continued on Campath-1h therapy. The adverse event narrative states that the patient had increase hemolysis secondary to hemolytic anemia as the cause of the worsening anemia. On ___ the patient was diagnosed with PCP pneumonia which resolved on ___ While hospitalized the patient developed oral Candidaisis which was treated with fluconazole from ___ A Herpes simplex oral ulcer was treated with acyclovir. On 2/28/98 ANC was 500/ul with platelet count 30,000/ul and Hgb 6.2 gm%. On 3/4/94 patient complained of fatigue. Hgb on 3/7/94 is reported as 6.7 gm%, ANC 1100/ul, and platelet count 54,000/ul. The patient was transfused two units of packed cells on 3/13/94. CBC from 3/14/94 included Hgb 7.5 gm%, WBC 900/ul, ANC 750/ul, and platelet count 47,000/ul. On 3/18/94 Campath-1h therapy was discontinued for drug-related toxicity. Patient's response was assessed as stable disease. CBC from 3/24/94 included a Hgb 6.8 gm%, platelet count 42,000/ul and ANC 600. Patient was transfused two units PRBCs on 3/25/94 for anemia, G-CSF was initiated on 3/23/ 94 and continued until 3/29/94. Gamma globulin 12 gms was administered between 3/22 and 3/24/94. On 5/2/98 Hgb was 8.2 gm%, platelets 170,000/ul and ANC 1000/ul. On 6/15/94 hematological improvement was noted with Hgb 8.6 gm%, platelets 192,000/ul, WBC 6500/ul, ANC – 5700/ul, and ALC 455/ul. On ___ patient was hospitalized with Herpes Zoster involving the scalp with a superimposed bacterial infection, treated with intravenous acyclovir and antibiotics, and discharged on ___. On ___ the patient was hospitalized with fever (39.7°), dyspnea, gr. 3 pneumonia, fatigue, hypotension (BP 90/60), and grade 4 neutropenia (ANC-100/ul). Death occurred within three hours of admission with the cause reported as "probable sepsis". The investigator considered the death related to study drug therapy.

- **Patient 017-002** entered study with Rai Stage III disease. CBC on study entry included Hgb 11.0gm%, platelets 131,000/ul, WBC 97,100/ul, ALC 84,500/ul and ANC 9700/ul. The patient received eighteen Campath-1h infusions between 3/21/94 and [redacted] On [redacted] patient was hospitalized with fever (37.7°C), E. Coli sepsis, and pneumonia. CBC on 4/15/94 included Hgb 10.8gm%, platelets 40,000/ul, WBC 2900/ul with ANC 2800/ul. Patient was treated with antibiotics and infection resolved on 4/21/94. Campath-1h therapy was discontinued on 5/4/94. Limited disease improvement was assessed by the investigator at the time therapy was discontinued. On 6/17/94 disease progression was reported. ALC had increased to 9652/ul from 1645/ul on 5/17/94. Patient was retreated with Campath-1h therapy between 10/13/94 and [redacted] Therapy was discontinued a second time with a report of limited disease improvement. Patient developed Herpes zoster on 10/21/94, which was treated with oral acyclovir. On 1/6/95 patient reported a decrease in short term memory. On [redacted] patient was hospitalized with worsening memory loss, loss of orientation, and decreased ability to concentrate. MRI reveals vascular damage at multiple sites in the left parieto-occipital lobe. On 3/1/95 papovavirus was detected in the patient's CSF confirming the diagnosis of progressive multifocal leukoencephalopathy. Patient expired on [redacted]. PML is considered by the sponsor as possibly related to CAMPATH-1H.

Five (15.6%) deaths on study or within six months of discontinuation of Campath-1H therapy appear to be related to study drug therapy. This mortality rate for drug-related deaths is similar to the mortality rate in Study 211.

Discontinuations from Study due to Adverse Events

Table 005-6 lists the discontinuations from study for adverse events (excluding deaths). Three discontinuations were due to deaths on study. Eight (25%) patients discontinued study for adverse events. In seven (21.9%) patients the SAE was related to Campath therapy. One (3.1%) patient experienced an adverse event related to progressive disease. Six of the eight patients who had serious adverse events that lead to discontinuation of study drug therapy had advanced disease (Stage III or IV disease). Three of the eight patients in whom therapy was discontinued were assessed as objective responders.

Table 005-6: Study Discontinuations due to Adverse Events

Patient No.	Rai Stage	FDA Resp.	Reason for Discontinuation	Relationship to Campath-1h
001-003	IV	SD	Abdominal pain, gr. 3; Staphlococcus Sepsis, gr. 4 (line infection); Herpes-varicella, disseminated hemorrhagic, gr. 3; DIC, gr. 3; Gi hemorrhage, gr. 2; Renal failure, gr. 3, Hepatic function abnormalities, gr. 2	Definite
001-004	III	PR	Urticaria gr. 1, nausea gr.1, rigors gr. 3, vomiting gr. 3 related to infusion	Definite
002-008	II	PR	Thrombocytopenia, gr. 4	Definite
003-002	IV	SD	Abdominal pain due to disease progression	None
009-004	IV	SD	Fatigue, gr. 3 (PCP pneumonia)	Definite
017-001	IV	PR	Fever , gr. 2 Sinusitis, gr. 2	
022-001	IV	SD	Fever, gr. 3; Leukopenia, gr. 4 Septic shock, gr. 4 (Klebsiella)	Definite
022-002	IV	SD	Hyptension, gr. 3 (infusion related)	Definite

Serious Adverse Events

Twenty-one (65.6%) study participants experienced serious adverse events including death, discontinuation from study, and / or hospitalizations. Sixteen (50.0%) study participants were hospitalized twenty-two times during or within 180 days of Campath-1h therapy. Table 005-7 provides information about all serious adverse events during and post study. Some serious adverse events that occurred during retreatment are also included for completeness but not counted in the SAE tally.

Table 005-7: Serious Adverse Events

Patient No.	Rai Stage	FDA Resp	Description of Event	Study Day (+=Post Infusion)	Relationship to Study Therapy	
					Sponsor	FDA
001-003	IV	SD	Abdominal Pain, gr. 3 Sepsis, gr. 4 DIC, gr. 3 Gi hemorrhage , gr. 2 Disseminated Zoster Varicella, gr. 3 Hepatic Function Abnormalities, gr. 1 Renal Function Abnormalities, gr.	+3	Possibly Probably	Definite
001-004	III	PR	Urticaria, gr. 3; Rigors, gr. 3; Nausea, gr. 2 Vomiting, gr.2 *(Study Discontinuation)*	103	Reasonably	Definite
002-008	II	PR	Thromboctyopenia, gr. 4 *(Study discontinuation)*	63	Reasonably	Definite
003-002	IV	SD	Abdominal Pain, Disease Progression *(Study Discontinuation)*	66	Not Related	Not Related
006-101	IV	SD	Pneumonia, ? gr.1; NOS, responded to antibiotics Neutropenia, gr. 4 (ANC – 240/ul)	21	Not reasonably	Probably
			CMV reactivation, gr. 2	44	Reasonably	Definite
006-102	IV	PD	Fever, gr. 2, persistent cough requiring IV antiboitics and nasal O_2; ? Candida Pneumonia treated with IV fluconazole with resolution of fever Anemia, gr. 2 Neutropenia, gr. 4	38	Possibly	Definite
006-103	IV	PD	Fever, gr. 2; Respiratory Infection DVT	38	Not Reasonably	Not Related
			Septic Shock, NOS *(Fatal)* Neutropenia, gr. 4	48	Possibly	Related
006-106	IV	NE	Retreatment Sepsis, Staph. , gr. ? (Line Infection) Neutropenia, gr. 3 / 4	Retreatm'nt		Related
008-001	I	SD	Klebsiella sepsis (port infection) (ANC – 1600/ul)	23	Not reasonably	Definitely
008-003	I	SD	Gr. 3 Tachycardia (ventricular)	44	Not reasonably	Not related
			Fever, gr. 2 Dyspnea, gr. 2 Pneumonia, gr. 2, E. Coli Gr. 2 Neutropenia (ANC –1216/ul)	+5	Possibly	Definite
			Disseminated Varicella Infection	+225	Possibly	Probably
009-004	IV	SD	Weakness, gr. 3 Anemia, gr. 4 PCP Pneumonia, gr. 3 Candida, oroespophageal, gr. 3 Herpes simplex, gr. 1	25	Reasonably	Definite
			Herpes-Varicella, ? Gr.	+119	Possibly	Definite
			Sepsis, Pseudomonas, gr. 4 *(Fatal)*	+137	Possibly	Definite
009-006	IV	NE	Pseudomonas Sepsis *(Fatal)* Neutropenia, gr. 4 Herpes Simplex, gr.1	9	Possibly	Definite

Patient No.	Rai Stage	FDA Resp	Description of Event	Study Day (+=Post Infusion)	Relationship to Study Therapy	
					Sponsor	FDA
			Thrombocytopenia, gr. 4 (ongoing)			
011-001	III	SD	Neutropenia, gr. 2	41	Reasonably	Definite
			Neutropenia, gr. 3 *(Discontinuation)*	59	Reasonably	Definite
			Interstitial Pneumonitis, gr. 4 (?PCP) *(Fatal)* DIC Hypotension, Acidosis ARDS Acute Cardiac Failure	+2 (61)	Reasonably	Definite
013-001	IV	PD	Staph. aureus sepsis (ANC = 2040/ul)	61	Possibly	Possibly
017-001	IV	PR	Fever, Gr. 2 *(Study Discontinuation)* Sinusitis, gr. 2	+6	Possibly	Definite
017-002	III	SD	Sepsis, E. coli, gr. ?	27	Possibly	Definite
			Progressive Multifocal Leukoencephalitis *(Fatal)*	+34 Retreatm'nt	Possibly	Definite
018-002	IV	PR	Staph. aureus sepsis, gr. 3 (? Line related) Neutropenia, gr. 4 (ANC – 280/ul; ANC – 160/ul at study entry)	2	Possibly	Possibly
			Conjunctivitis, gr. 1 Neutropenia, gr. 3 (ANC-670/ul)	+1	Possible	Possibly
019-003	IV	PD	Nausea, gr. 3 post infusion, (not hospitalized)	1	Reasonably related	Definite
			Fevers, gr.2, [During CAMPATH-1H therapy patient had Rigors, gr. 3 / 4, chills, Stomatitis, Worsening thrombocytopenia (gr.3), Worsening Neutropenia gr. 4 requiring interruption of therapy; developed Anemia, gr. 3 requiring transfusion; bone pain, and pharnygitis. Pt. withdrew consent after 14 infusions over three months and died three months later due to progression / cardiopulmonary failure.]	+2	Reasonably related	Hematologic toxicity possibly related; other events unrelated
022-001	IV	SD	Diabetes Mellitus, decompensation, gr. 2	32	Not reasonably	?
			(Study Discontinuations for Adverse Events) Fever, gr. 3 Klebsiella sepsis, gr.3 (? Line infection) Septic shock, gr. 4 Anemia, gr. 2	34	Possibly	Related
022-002	IV	SD	*(Study Discontinuations for Adverse Events)* Hypotension, gr. 3	42		Related
			Diffuse interstitial pneumonitis,	+60	Possibly	?
022-003	IV	PR	Dyspnea, Fever, Hypoxemia (pO_2 = 55 mm Hg) Interstitial Pneumonitis, no organism identified, Responded to trimethoprim-sulfamethoxole	+8	Possibly	Definite

Differences in assessment of the relationship of adverse event between the sponsor assessment and the FDA assessment are noted in some instances.

- **Patient 006-101** entered study with a WBC 265,000 with a differential reported as 100% lymphocytes. As the lymphocytes cleared, patient was noted to have absolute neutrophil counts > 5000/ul for ten days. On the fourteenth day of study, WBC was 500/ul with ANC 250/ul. On the eighteenth day on study right lower lobe pneumonia, gr. 1 was reported. On review the pneumonia associated with the neutropenia was considered related to study drug administration.
- **Patient 008-001** developed Klebsiella sepsis due to a port infection on the thirty-third study day. The ANC was 1600/ul at the time that infection developed. At enrollment on study ANC was 4230/ul. The grade 1 neutropenia and port infection are considered related to Campath-1h.
- **Patient 006-102** was hospitalized on study day 38 for fevers and dyspnea secondary to a chest infection requiring IV antiboitics and nasal O_2. Sputum cultures were positive for Candida. Intravenous and then oral flucanozole was added to regimen. Campath-1h therapy was continued. The patient became progressively more anemic. Hgb decreased from 12.7 gm% prestudy to 8.9 gm% six days after onset of fevers. Patient was transfused two units packed cells. Two days prior to the onset of the febrile

episode ANC was reported 890/ul, a decrease from enrollment ANC of 4392/ul. ANC continued to decline during hospitalization. Thirteen days after the onset of fever, ANC was 420/ul. On this day Campath-1h was discontinued with "remission achieved" according to the investigator. Prolonged myelosuppression appears to have played a role in the discontinuation of study drug.

- **Patient 018-002** developed Staph. sepsis on day 2 of treatment. This infection can not reasonably be related to Campath-1h.
- **Patient 022-001** had decompensation of Diabetes one day prior to fever and two days prior to diagnosis of Klebsiella sepsis. This adverse event appears related to infection. This patient did not receive steroids during study.
- **Patient 022-002** developed diffuse interstitial pneumonitis two months after the last CAMPATH-1H infusion. Note that the patient had received two cycles of fludarabine after discontinuation of Campath-1h prior to the onset of the pneumonitis. The combination of Campath-1h and fludarabine therapy contributed to this adverse event due to their suppression of CD4+ cells.

Of the thirty-two episodes of serious adverse events occurring during or after initial therapy with Campath –1h, twenty-two were infectious in nature. Four of these infections were associated with severe neutropenia. Four SAEs were related to acute toxicities associated with Campath-1h infusions. Three SAEs were related to myelotoxicity secondary to Campath-1h. Three SAEs do not appear related to Campath-1h therapy.

Infections

Twenty-two (68.8%) patients experienced fifty-three infections on study or within six months of completion of Campath-1h. One additional infection, a case of disseminated Herpes-Varicella, is also included in the following table since this infection, which occurred 225 days after discontinuation of study drug therapy, is considered related to Campath-1h therapy. One patient (6-106) is not included in the following listing. This patient developed Staph pneumonia during retreatment after disease relapse. These events occurred about four months after the first round of Campath-1h therapy.

Table 005-10 is based on Table 14.3.2.3A entitled "Listing of Patients with Infections" and the Patient Narratives for Adverse Events, Study Discontinuations, and Deaths. Many of the infections and all of the serious infections have been listed in previous sections of the review along with assessment of causality. Each recurrence of Herpes simplex is reported as a separate infection if the recurrences were separated in time. Pneumonia and sepsis are listed once even if the event was listed more than once in the reference listings. The worst grade assigned in the reference listings is reported in this table.

Table 005-10: Infections on Study or Within 180* Days of Completion of Study Drug Therapy

Type of Infection	Total	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Not Graded
All Infections N (%)	51 (100.0)	20 (39.2)	17 (33.3)	6 (11.8)	4 (7.8)	4 (7.8)
Bacterial	11	--	--	--	--	--
Sepsis	9	-	-	-	-	-
Staph	3	-	-	2	1	-
Klebisella	2	-	1	-	1	-
E. coli	1	-	1	-	-	-
Fatal, NOS	2	-	-	-	1	1
W/ Pneumonia, ? Pseudomonas	1	-	1	-	-	-
Pneumonia	1	-	-	-	-	-
E. Coli	1	-	1	-	-	-

Type of Infection	Total	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Not Graded
Urinary Tract Infection	1	-	-	-	-	-
E. Coli	1	-	1	-	-	-
Fungal Infections	2	--	--	--	--	--
Candiasis, Oral	2	1	-	1	-	-
Viral Infections	21	--	--	-	--	-
Herpes-Varicella, Disseminated	2	-	-	1	-	1**
Herpes Zoster	1	-	-	-	-	1
Herpes Simplex	17	15	2	-	-	-
CMV	1	-	1	-	-	-
Protozoan	2	--	--	-	--	--
PCP Pneumonia	2	-	-	1	1*	-
Unspecified	15	--	--	--	--	--
Central Line	2	1	1	-	-	-
Chest Infections / Bronchitis	6	1	4	-	-	1
Interstitial Pneumonitis, NOS	2	-	2	-	-	-
Pneumonia, NOS	1	1	-	-	-	-
Otitis	1	-	-	1	-	-
Sinusitis	1	-	1	-	-	-
Nasal mucosa / lymph nodes	1	-	1	-	-	-
Tonsillitis	1	1	-	-	-	-

*Interstitial Pneumopathy responding to Trimethoprim-Sulfa.
**225 Days post study drug

Ten infections were grade 3 / 4 in severity. In four cases the grade of the infection is not reported. Information collected about infections that occurred after discontinuation of study drug therapy did not include information about the grade of the infection. In four cases of sepsis, central line infection was responsible for the sepsis.

Nine (28.1%) study participants experienced thirteen serious opportunistic infections.

- Two cases of PCP or probable PCP in two patients
- Two cases of interstitial pneumonitis, one fatal and one responding to trimethoprim-sulfamethazole in two other patients
- Three cases of Zoster-Varicella, two reported to be disseminated
- One case of CMV reactivation
- Two cases of Herpes Simplex, gr. 2 in two patients
- One case of grade 3 oro-esophageal Candidiasis
- One case of pneumonia responding to fluconazole presumed to be Candida in origin.
- One case of Progressive Multifocal Leukoencephalopathy

No patients are known to have developed second malignancies during or within six months of completion of therapy.

Prophylaxis

Eighteen (53.3%) study participants receive PCP prophylaxis at the discretion of the investigator. Seven (21.9%) patients received acyclovir for antiviral prophylaxis.

Summary of Tabulated Adverse Events and Drug-Related Adverse Events

Thirty-one (96.9%) patients reported at least one adverse event on treatment or within thirty days of discontinuation of Campath-1h therapy. Nineteen (59.4%) patients reported one or more WHO grade 3 / 4 adverse event. Thirty-one (96.9%) patients reported one or more drug-related adverse event on treatment or within thirty days of discontinuation of Campath-1h therapy. Nineteen (59.4%) reported drug related WHO grade 3 / 4 adverse events. Table 005-11 summarizes the adverse events, the drug related adverse events occurring in more than 5% of the study population, and any grade 3 / 4 adverse event, and any grade 3 / 4 drug related adverse event regardless of incidence. Note that a patient may be represented more than once in each category if the patient experienced more than one of the adverse events included in that category.

Table 005-11: Adverse Events and Drug-Related Adverse Events in > 5% of the Population and All WHO Grade 3 / 4 Adverse Events

Type of Adverse Event	All Adverse Events			Drug-Related Adverse Events		
	Total No. Patients N (%)	No. with Grade 3 Event	No. with Grade 4 Event	Total No. Patients N (%)	No. with Grade 3 Event	No. with Grade 4 Event
Body as a Whole	30 (93.8)	9	4	28 (87.5)	9	4
Anorexia	7 (21.8)	-	-	6 (18.8)	-	-
Pain	6 (18.8)	1	-	2 (6.3)	1	-
Edema	3 (9.4)	-	-	-	-	-
Fatigue	10 (31.3)	2	-	10 (31.3)	2	-
Fever	24 (75.0)	4	1	23 (71.4)	4	1
Malaise	2 (6.3)	-	-	2 (6.3)	-	-
Rigors	22 (68.8)	4	3	21 (65.6)	4	3
Temperature Change Sensation	2 (6.3)	-	-	2 (6.3)	-	-
Cardiovascular Disorders	15 (46.9)	1	1	14 (43.8)	1	-
Hypertension	2 (6.3)	-	-	-	-	-
Hypotension	15 (46.9)	1	1	14 (43.8)	1	-
Rate and Rhythm Disorders	6 (18.8)	2	-	4 (12.5)	-	-
Atrial Fibrillation	1 (3.1)	1	-	-	-	-
Tachycardia	3 (9.4)	-	-	2 (6.3)	-	-
Ventricular Tachycardia	1 (3.1)	-	-	2 (6.3)	-	-
Central and Peripheral Nervous System Disorders	15 (46.9)	-	-	14 (43.8)	-	-
Headache	10 (31.3)	-	-	9 (28.4)	-	-
Parathesias	3 (9.4)	-	-	3 (9.4)	-	-
Tremor	2 (6.3)	-	-	2 (6.3)	-	-
Vertigo	2 (6.3)	-	-	2 (6.3)	-	-
Gastrointestinal Disorders	22 (68.8)	4	1	18 (56.7)	4	-
Abdominal Pain	4 (12.5)	1	-	4 (12.5)	1	-
Constipation	2 (6.3)	-	1	1 (3.1)	-	-
Diarrhea	7 (21.9)	1	-	4 (12.5)	-	-
Gingivitis	3 (9.4)	1	-	1 (3.1)	-	-
Mucositis, NOS	2 (6.3)	-	-	1 (3.1)	-	-
Stomatitis	2 (6.3)	1	-	2 (6.3)	1	-
Nausea	16 (50.0)	1	-	14 (43.8)	1	-
Vomiting	13 (40.6)	1	-	11 (34.4)	1	-
Metabolic and Nutritional Disorders	7 (21.9)	-	1	3 (9.4)	-	-
Acidosis	1 (3.1)	-	1	-	-	-
Uncontrolled Diabetes Mellitus	2 (6.3)	-	-	1 (3.1)	-	-

Type of Adverse Event	All Adverse Events			Drug-Related Adverse Events		
	Total No. Patients N (%)	No. with Grade 3 Event	No. with Grade 4 Event	Total No. Patients N (%)	No. with Grade 3 Event	No. with Grade 4 Event
Musculoskeletal Disorders	8 (25.0)	-	-	8 (25.0)	-	-
Myalgias	5 (15.6)	-	-	5 (15.6)	-	-
Skeletal Pain	3 (9.4)	1	-	3 (9.4)	1	-
Psychiatric Disorders	4 (12.5)	-	-	4 (12.5)	-	-
Somnolence	2 (5.0)	-	-	2 (6.3)	-	-
Respiratory System Disorders	21 (65.6)	1	1	16 (50.0)	1	1
Bronchitis	3 (9.4)	-	-	2 (6.3)	-	-
Coughing	7 (21.9)	-	-	3 (9.4)	-	-
Dyspnea	8 (25.0)	1	-	6 (18.8)	-	1
Pharyngitis	5 (15.6)	-	-	3 (9.4)	-	-
Pneumonia	5* (15.6)	-	-	3 (9.4)	-	-
Pneumonitis	3 (9.4)	-	-	1 (3.1)	-	1
Pulmonary Infiltrates	1 (3.1)	1	-	1 (3.1)	1	-
Rhinitis	3 (9.4)	-	-	1 (3.1)	-	-
Skin & Appendage System Disorders	23 (79.4)	4	1	23 (71.9)	4	1
Pruritis	14 (43.8)	1	1	14 (43.8)	1	1
Rash	10 (31.3)	3	-	10 (31.3)	3	-
Rash, erythematous	3 (9.4)	-	-	3 (9.4)	-	-
Increased Sweating	7 (21.9)	1	-	5 (15.6)	1	-
Urticaria	11 (34.4)	2	-	11 (34.4)	2	-
Special Senses Disorders	3 (9.4)	1	-	3 (9.4)	1	-
Taste Loss	3 (9.4)	1	-	3 (9.4)	1	-
Urinary System Disorders	4 (12.5)	2	1	2 (6.3)	1	-
Abnormal Renal Function	2 (6.3)	1	1	1 (3.1)	1	-
Urinary Retention	1 (2.5)	1	-	-	-	-
Oligouria	1 (2.5)	1	-	-	-	-
Vascular (Extra-Cardiac Disorders)	5 (15.6)	1	-	4 (12.5)	-	-
Flushing	2 (6.3)	-	-	2 (6.3)	-	-
Thrombophlebitis	1 (2.5)	1	-	-	-	-
Vasospasm	2 (6.3)	-	-	2 (6.3)	-	-
Platelet, Bleeding, Clotting Disorders	12 (37.5)	2	3	6 (18.8)	2	2
DIC	2 (6.3)	1	1	1 (3.1)	1	-
Epistaxis	3 (9.4)	-	-	-	-	-
Purpura	2 (6.3)	-	-	1 (3.1)	-	-
Thrombocytopenia	5 (15.2)	2	2	4 (10.0)	1	2
Red Cell Disorders	7 (9.5)	2	2	5 (17.5)	2	1
Anemia	6* (18.2)	2	-	5* (17.5)	2	1
Hemolysis	1 (3.1)	-	1	-	-	-
WBC & RES Disorders	2 (6.3)	1	1	5 (7.5)	1	1
Granulocytopenia	2 (6.3)	1	1	2 (5.0)	1	1
Resistance Mechanism Disorders	19 (59.4)	3	3	14 (43.8)	2	3
CMV Infection	1 (3.1)	-	-	1 (3.1)	-	-
Herpes Simplex	10 (32.5)	-	-	8 (25.0)	-	-
Infection	5 (15.0)	-	-	2 (6.3)	-	-
Infection, Bacterial	1 (3.1)	-	-	1 (3.1)	-	-
Infection, Viral	2 (3.1)	1	1	1 (2.5)	1	-
Moniliasis	2 (6.3)	1	-	2 (3.1)	1	-
Otitis media	1 (3.1)	1	-	1 (3.1)	1	-
PCP Infection	1 (2.5)	1	-	1 (3.1)	1	-
Sepsis	6 (18.8)	2	3	5 (15.6)	1	3

*One event not graded

Note that Table 005-11 does not accurately present the incidence and severity of hematological toxicities. Information about hematologic toxicity was not usually reported

in the adverse event reporting section of the Case Report Form as hematologic toxicity. The protocol did not require collection of this information as hematological toxicity "was expected" with Campath-1h therapy. The majority of adverse events reported on study were related to Campath-1h therapy. These events can be divided into acute infusion-related toxicities, infectious toxicities, or hematologic toxicities. Infections have been discussed previously. Information on acute infusion related toxicities is presented next followed by a discussion of hematological toxicities and use of blood products.

Acute Infusion Related Toxicities

All patients on this study were premedicated for the first infusion with paracetamol and antihistamine or intravenous hydrocortisone 200 mg (randomized by country). Medication could be continued after the first injection as needed to control infusion related symptoms. After the first Campath-1h treatment premedication was optional. Prophylactic steroid usage was prohibited. Review of the information provided with regard to steroid usage reveals that systemic steroids were used in six (24%) of the twenty-five patients treated with intravenous Campath-1h therapy. The less frequent use of steroids may explain why the toxicity profile for Study 005 includes a higher incidence of gr. 3 / 4 infusion related toxicities than were reported for Study 211. The following toxicities related to CAMPATH-1H were reported:

- Fever in twenty-three (71.9%) patients with grade 3 / 4 fever in five (15.6%) patients;
- Rigors in twenty-one patients (65.6%) with grade 3 / 4 rigors in seven (21.9%) patients;
- Hypotension in fourteen (43.8%) patients with grade 3 hypotension in one (3.1%) patient resulting in study discontinuation;
- Nausea in fourteen (43.8%) patients with grade 3 nausea in one (3.1%) patient;
- Vomiting in eleven (34.4%) patients with grade 3 vomiting in one (3.1%) patient;
- Anorexia in six (18.8%) patients of grade 1 / 2 severity;
- Pruritis in fourteen (43.8%) patients with grade 3 / 4 pruritis in two (5.0%) patients;
- Urticaria reported in thirteen (32.5%) patients with grade 3 urticaria in two (6.3%) patients;
- Rash reported in ten (31.3%) patients with grade 3 rash in three (9.4%) patients and erythematous rash of grade 1 / 2 severity reported in three (9.4%) patients;
- Increased sweating related to study drug administration in five (15.6%) patients with grade 3 severity reported in one (3.1%) patient and temperature change sensation reported in two (6.3%) patients;
- Flushing related to study drug infusion in two (6.3%) patients and vasospasm in two (6.3%) patients;
- Headache related to study drug infusion in nine (28.4%) patients of grade 1 / 2 severity
- Dyspnea related to study drug in six (18.8%) patients with one patient (3.1%) experiencing grade 4 dyspnea, cough reported in three (9.4%) patients;
- Myalgias in five (15.6%) patients all of grade 1 / 2 severity;
- Pain in two (6.3%) with one patient complaining of gr. 3 pain; skeletal (bone) pain related to drug therapy in three (9.4%) patients with one patient reporting grade 3

skeletal pain, and abdominal pain in four (12.5%) patients with one (2.5%) patient reporting grade 3 abdominal pain; and,

- Tachycardia in two (6.3%) patients related to administration of study drug therapy.

No episodes of acute bronchospasm were reported on this study. The types of infusional related toxicities described on this study are similar in nature to those reported with use of other monoclonal antibodies.

Hematological Toxicities

Pancytopenia

None of the patients included in study were reported to have pancytopenia / marrow aplasia. However, fourteen patients were noted to have cytopenias of one or more cell lines on review of the hematological data. Patient 11-001 has cytopenias of all three cells lines prior to death from interstitial pneumonia.

Hemoglobin Toxicity

Review of the CBC indicated that twenty-six (81%) patients experience some grade of new or worsening hematological toxicity. Nine (28%) patients experienced one or more episodes of new or worsening Grade 3 or 4 hematological toxicity. The incidence of Grade 3 or 4 hematological toxicity is less on Study 005. Three reasons that would explain this difference are: 1) patients could be rested at the investigator discretion after a six-week cycle; 2) the majority of the patients had fewer prior treatments; and, 3) the smaller sample size. The study population for Study 005 is one third that of Study 211.

Table 005-12 presents the information about changes in hemoglobin grade during treatment and post administration follow-up for all patients on study.

Table 005-12: Change in NCI Hemoglobin Grade from Baseline: All Patients (N=32)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Worse by ≥ Gr. 1 N (%)	New Grade 3 / 4 Toxicity N (%)
Weeks 1 – 2	32	1 (3.1)	13 (40.1)	18 (56.2)	3 (9.3)
Weeks 3 – 4	32	2 (16.3)	12 (37.5)	18 (56.2)	2 (6.2)
Weeks 5 – 6	31	2 (6.5)	11 (35.5)	18 (58.0)	4 (12.5)
Weeks 7 - 8	24	3 (12.5)	10 (41.7)	11 (45.8)	1 (4.2)
Weeks 9 – 10	18	3 (16.7)	8 (44.4)	7 (38.9)	2 (11.1)
Weeks 11 – 12	16	3 (18.7)	6 (37.5)	7 (43.8)	2* (12.5)
Weeks 13+	11	3 (27.3)	3 (27.3)	5 (45.4)	0
1 Month F/U	24	8 (33.3)	12 (50.0	4 (16.7)	1 (4.2)
2 Month F/U	16	5 (31.3)	9 (56.2)	2 (12.5)	0

As shown in the above table, over the first six weeks of study, slightly more than half of the study population had a decline of one or more grades in hemoglobin value. Most patients recovered to baseline hemoglobin values after completion of therapy. About one-third of the patients had an improved hemoglobin value reported at follow-up compared to baseline. About one-sixth of the patients did not return to baseline hemoglobin values. Since response could play a role in the degree of hemoglobin toxicity information for responders and non-responders is presented in Table 005-13. Since twenty-three patients

were reported to be transfused, requiring more than 140 RBC transfusions while on study, changes in the hemoglobin grade were analyzed separately for in transfused / EPO treated patients as compared to untreated patients as shown in Table 005-14.

Table 005-13: Change in Hemoglobin from Baseline: Responders (N = 9) vs. Non-Responders (N =23)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	9	0 (0.0)	5 (55.6)	4 (44.4)	23	1 (4.3)	8 (34.8)	14 (60.9)
Wks. 3 - 4	9	2 (22.2)	6 (66.7)	1 (11.1)	23	1 (4.3)	6 (26.1)	16 (69.6)
Wks. 5 - 6	8	0 (0.0)	5 (62.5)	3 (37.5)	23	2 (8.7)	6 (26.1)	15 (65.2)
Wks. 7 – 8	8	2 (25.0)	4 (50.0)	2 (25.0)	16	2 (12.5)	6 (37.5)	9 956.2)
Wks. 9– 10	7	2 (28.6)	4 (57.1)	1 (14.3)	11	1 (9.1)	4 (36.4)	6 (54.5)
Wks. 11- 12	7	2 (28.6)	4 957.1)	1 (14.3)	9	1 (11.1)	2 (22.2)	6 (66.7)
Wk. 13+	6	3 (50.00	2 (33.3)	1 (16.7)	5	0(0.0)	1 (20.0)	4 (80.0)
1 Month F/U	8	5 (62.5)	3 (37.5)	0 (0.0)	16	3 (18.7)	9 (56.3)	4 (25.0)
2 Month F/U	7	4 (57.1)	3 (42.9)	0 (.00)	9	1 (11.1)	6 (66.7)	2 (22.2)

In this study both responders and non-responders had declines in hemoglobin grade early on, however the responders stabilized while non-responders continued to have declines in hemoglobin grade throughout the course of therapy. After discontinuation of Campath-1h therapy, all of the responders recovered to baseline or better. About one-fourth of the non-responders did not recover to baseline.

Table 005-14: Changes in Hemoglobin from Baseline: Transfused/ EPO Patients (N=21) vs. Non-Transfused, Non-EPO Treated Patients (N = 11)

Week on Study	Transfused / EPO Patients (N = 21)				Non-Transfused or EPO Treated Patients (N = 11)			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	21	1 (4.8)	7 (33.3)	13 (61.9)	11	6 (0.0)	6 (54.5)	5 (45.4)
Wks. 3 – 4	21	2 (9.5)	6 (28.6)	13 (61.9)	11	0	6 (54.5)	5 (45.4)
Wks. 5 – 6	20	2 (00.0)	6 (30.0)	12 (60.0)	11	0	5 (54.5)	6 (45.4)
Wks. 7 – 8	15	3 (20.0)	4 (26.7)	8 (53.3)	9	0	6 (66.7)	3 (33.3)
Wks. 9 - 10	10	2 (20.0)	4 (40.0)	4 (40.0)	8	1 (12.5)	4 (50.0)	3 (37.5)
Wks., 11 – 12	8	2 (25.0)	2 (25.0)	4 (50.0)	8	1 (12.5)	4 (50.0)	3 (37.5)
Wks. 13+	4	1(25.01)	1 (25.0)	2 (50.0)	7	2 (28.6)	2 (28.6)	3 (42.8)
I Month F/U	14	5 (35.7)	7 (50.0)	2 (14.3)	10	3 (30.0)	5 (50.0)	2 (20.0)
2 Month F/U	9	3 (33.3)	5 (55.5)	1 (11.1)	7	2 (28.6)	4 (57.1)	1 (14.3)

When changes in hemoglobin grade were analyzed for transfused / EPO treated patients as compared to non-transfused / EPO treated patients, the following was noted. Fifty to sixty per cent of the transfused patients had a decline in hemoglobin grade over the duration of therapy, while ~ 40% of the non-transfused patients had declines in hemoglobin concentration over the course of study. In both groups at two months post study follow-up, one patient in each group had failed to return to baseline values.

Neutrophils

Twenty-six (81%) patients experienced new or worsening neutropenia of any grade during the course of study. Eighteen (56%) patients experienced new or worsening grade 3 or 4 neutropenia while on study or within thirty days of discontinuation of study drug

therapy. The incidence of neutropenia is similar to that reported for Study 009 and is less than for Study 211. Table 005-15 provides information about the changes in neutrophil counts over the course of study for thirty-one patients with information available. This tabulation does not take into account the use of growth factors or rests on study.

Table 005-15: Changes in Neutrophil Counts from Baseline: All Patients (N = 32)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Worse by ≥ Gr. 1 N (%)	No. % with New Gr. 4 Neutropenia
Weeks 1 – 2	31	1 (3.2)	12 (38.7)	18 (58.1)	4 (12.9)
Weeks 3 – 4	31	2 (6.5)	10 (32.3)	19 (61.3)	4 (12.9)
Weeks 5 – 6	30	2 (6.7)	12 (70.0)	16 (53.3)	4 (6.7)
Weeks 7 - 8	22	0 (0.0)	9 (40.9)	13 (59.1)	2 (9.1)
Weeks 9 – 10	17	2 (11.8)	7 (41.2)	8 (47.1)	1 (5.9)
Weeks 11 – 12	15	2 (13.3)	6 (40.0)	7 (46.7)	1 (6.7)
Weeks 13+	11	2 (18.2)	4 (36.4)	5 (45.4)	0 (0.0)
1 Month F/U	23	6 (26.1)	10 (43.5)	7 (30.4)	0 (0.0)
2 Month F/U	15	2 (13.3)	5 (33.3)	8 (53.4)	0

To look at neutrophil toxicity more closely, the change in neutrophil counts in responders over two week intervals was compared to the change in neutrophil counts in non-responders. Over the course of study drug therapy 12 – 50% of the responders were noted to have a decline in neutrophil count of one or more grades during each two week interval, while 45 – 75% percent of the non-responders had a decline in neutrophil counts of one or more grades. At one-month post study approximately 30% of each group had neutrophil counts lower than baseline. About one-third of the responder group and more than one-half of the non-responders with data had neutrophil counts lower than baseline at two months post therapy.

Table 005-17: Changes in Neutrophil Counts from Baseline: Responders (N = 8) vs. Non-Responders (N = 23)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	8	0 (0.0)	7 (87.5)	1 (12.5)	23	1 (4.3)	5 (21,8)	17 (73.9)
Wks. 3 – 4	8	1 (12.5)	4 (50.7)	3 (37.5)	23	1 (4.3)	6 (26.1)	16 (69.6)
Wks. 5 – 6	7	2 (28.6)	3 (42.8)	2 (28.6)	23	0 (0.0)	9 (39.1)	14 (60.9)
Wks. 7 – 8	6	0	3 (50.0)	3 (50.0)	16	0 (0.0)	8 (50.0)	8 (50.0)
Wks. 9 – 10	6	1 (16.7)	2 (33.3)	3 (50.0)	11	1 (9.0)	5 (45.5)	5 (45.5)
Wks. 11 – 12	6	1 (16.7)	2 (33.3)	3 (50.0)	9	1 (11.2)	4 (44.4)	4 (44.4)
Wks. 13+	6	1 (16.7)	2 (33.3)	3 (50.0)	5	1 (20.0)	2 (40.0)	2 (40.0)
1 Month F/U	7	3 (42.8)	2 (28.6)	2 (28.6)	16	3 (18.8)	8 (50.0)	5 (31.2)
2 Month F/U	6	2 (33.3)	1 (16.7)	3 (33.3)	9	0 (0.0)	4 (44.4)	5 (55.5)

On Study 005 only three patients were reported to have received G- or GM –CSF. Two of these patients did not show improve in neutrophil count despite the use of growth factor over the course of study, while one patient's neutrophil count returned to baseline. Among the patients who did not receive growth factor, almost eighty percent were noted to have declines in neutrophil count by at least one grade sometime during the course of study. Twenty-six percent of the untreated patients at one month after discontinuation of therapy had neutrophil counts lower that baseline, while 28% of patients were noted to have improvement over baseline neutrophil count by one or more grade.

Table 005-16: Changes in Neutrophil Count from Baseline: Growth Factor (N = 3) vs. No Growth Factor (N = 28)

Week on Study	Growth Factor Use				No Growth Factor Use (Untreated)			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	3	0 (0.0)	1 (33.3)	2 (66.7)	28	1 (3.5)	12 (42.9)	15 (53.6)
Wks. 3 – 4	3	0 (0.0)	1 (33.3)	2 (66.7)	28	2 (7.1)	9 (32.1)	17 (60.7)
Wks. 5 – 6	3	0 (0.0)	1 (33.3)	2 (66.7)	27	2 (7.4)	11 (40.7)	14 (51.8)
Wks. 7 – 8	1	0 (0.0)	0 (0.0)	1 (100.0)	21	0 (0.0)	9 (42.9)	12 (57.1)
Wks. 9 – 10	0	0 (0.0)	0 (0.0)	0	17	2 (11.8)	7 (41.1)	8 (47.1)
Wks., 11 – 12	0	0 (0.0)	0 90.0)	0	15	2 (13.3)	6 (40.0)	7 (46.7)
Wks. 13+	0	0 (0.0)	0 (0.0)	0	11	2 (18.2)	4 (36.4)	5 (45.4)
I Month F/U	2	0 (0.0)	1 (50.0)	1 (50.0)	21	6 (28.6)	9 (42.8)	6 (28.6)
2 Month F/U	1	0 (0.0)	0	1	13	2 (15.4)	4 (30.8)	7 (53.8)

Platelets

Twenty- three (72%) patients developed new or worsening thrombocytopenia of at least one grade while on study or within one month of study completion. Seventeen (53%) patients had new or worsening Grade 3 or 4 thrombocytopenia. Table 005-18 presents information about the changes in platelet count by NCI grade over the course of study and follow-up for all thirty-two patients. About 9% of the study population were reported with new grade 4 thrombocytopenia during each two-week interval during the first eight weeks of study.

Table 005-18: Changes in Platelet Count from Baseline: All Patients (N =32)

Weeks on Study	No. Patients	Improved N (%)	No Change N (%)	Worse by ≥ Gr. 1 N (%)	No. % with New Gr. 4 Thrombocytopenia
Weeks 1 – 2	32	0 (0.0)	16 (50.0)	16 (50.0)	3 (9.4)
Weeks 3 – 4	32	3 (9.4)	17 (53.1)	12 (37.5)	3 (9.4)
Weeks 5 – 6	31	4 (12.9)	20 (64.5)	7 (22.6)	3 (9.7)
Weeks 7 - 8	24	8 (33.3)	11 (45.8)	5 (20.9)	2 (8.3)
Weeks 9 – 10	18	5 (27.7)	11 (61.1)	2 (11.1)	0 (0.0)
Weeks 11 – 12	16	7 (43.8)	7 (43.8)	2 (12.5)	0 (0.0)
Weeks 13+	11	3 (27.3)	6 (54.5)	2 (18.2)	0 (0.0)
1 Month F/U	24	12 (50.0)	12 (50.0)	0 (0.0)	0 (0.0)
2 Month F/U	16	8 (50.0)	8 (50.0)	0 (0.0)	0 (0.0)

Decreases in platelet counts are noted early in study with declines from baseline in platelet counts rare after week nine. Note that at one and two month follow-up, 50% of the patients are reported to have a one grade or more improvement in platelet count. Declines in the platelet count grade were noted for both responders and non-responders in the first eight weeks of study as shown in the Table 005-19.

Table 005-19: Changes in Platelet Count from Baseline: Responders (N = 9) vs. Non-Responders (N = 23)

Weeks on Study	No. Responders	Improved N (%)	No Change N (%)	Worse N (%)	No. Non-Responders	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	9	0 (0.0)	6 (66.7)	3 (33.3)	23	0 (0.0)	10 (43.5)	13 (56.5)
Wks. 3 - 4	9	1 (11.2)	4 (44.4)	4 (44.4)	23	2 (8.7)	13 (56.5)	8 (34.8)
Wks. 5 - 6	8	1 (12.5)	6 (75.01	1 (12.5)	23	3 (13.0)	14 (60.9)	1 (12.5)
Wks. 7 – 8	8	3 (37.5)	2 (25.0)	3 (37.5)	16	5 (31.2)	9 (56.3)	2 (12.5)
Wks. 9– 10	7	2 (28.6)	3 (42.8)	2 (28.6)	11	3 (27.3)	8 (72.7)	0 (0.0)
Wks., 11 – 12	7	3 (42.8)	2 (28.6)	2 (28.6)	9	3 (33.5)	4 (44,4)	2 (22.2)
Wks., 13+	6	2 (33.3)	2 (33.3)	2 (33.3)	5	1 (20.0)	4 (80.0)	0 (0.0)
1 Month F/U	8	6 (75.0)	2 (25.0)	0 (0.0)	16	6 (37.5)	10 (62.5)	0 (0.0)
2 Month F/U	7	5 (71.4)	2 (28.6)	0 (0.0)	9	3 (33.3)	6 (66.7)	0 (0.0)

On this study eleven patients were transfused with platelets more than ninety-five times. Ten of the platelet recipients had a history of prior platelet transfusion. Declines of one or more grades in platelet counts were noted more often in non-transfused patients compared to transfused patients over the course of study.

Table 009-20: Changes in Platelet Count from Baseline: Transfused (N=11) vs. Non-Transfused Patients (N = 21)

Week on Study	Transfused (N = 11)				Non-Transfused (N =21)			
	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)	No. Patients	Improved N (%)	No Change N (%)	Worse N (%)
Wks. 1 – 2	11	0 (0.0)	6 (54.5)	5 (45.5)	21	0 (0.0)	10 (47.6)	11 (53.4)
Wks. 3 – 4	11	2 (18.2)	5 (45.5)	4 (36.3)	21	1 (4.8)	12 (57.1)	8 (30.1)
Wks. 5 – 6	11	3 (27.3)	5 (45.5)	3 (27.3)	20	1 (5.0)	15 (75.0)	4 (20.0)
Wks. 7 – 8	7	4 (57.1)	1 (14.3)	2 (28.6)	17	4 (23.5)	10 (58.8)	3 (17.6)
Wks. 9 - 10	5	2 (40.0)	3 (60.0)	0 (0.0)	13	3 (23.1)	8 (61.5)	2 (15.4)
Wks., 11 – 12	4	3 (75.0)	1 (25.0)	0 (0.0)	12	4 (33.3)	6 9550.0)	2 (16.7)
Wks. 13+	2	1 (50.0)	1 (50.0)	0 (0.0)	9	2 (22.2)	5 (55.6)	2 (22.2)
I Month F/U	6	6 (100.0)	0 (0.0)	0 (0.0)	18	6 (33.3)	12 (66.7)	0 (0.0)
2 Month F/U	4	3 (75.0)	1 (25.0)	0 (0.0)	12	5 (41.7)	7 (58.3)	0 (0.0)

In summary, Campath-1h therapy can result in anemia, neutropenia, and / or thrombocytopenia. Treatment delays, use of blood product support, and use of growth factors were required to manage hematological toxicity in several patients. The effect on hemoglobin and neutrophils persisted throughout study, while the toxic effect on platelets generally appears early in treatment. The effect on platelets appears to resolve over time with patients returning to baseline or improved platelet counts after completion of therapy.

Blood Product Usage on Study

Information was collected about transfusion requirements in the year prior to study. Eighteen (56.3%) patients had no prestudy transfusion requirement, while fourteen (43.8%) patients had received blood products in the year prior to study.

For the eighteen patients without a prior transfusion history, the following information is available

- Eight patients did not require transfusion of any blood products while on therapy.

- Nine patients required RBC transfusion on therapy. Seven recipients received less that three units toto, one patient seven units toto, and one an unknown number of units were transfused.
- One (the tenth) patient was transfused of single donor units of platelets on seven separate occasions.

Fourteen patients were transfused in the year prior to study.

- Prestudy, five patients had received only RBC transfusions.
  - One required no further transfusions.
  - Three continued to require RBCs only.
  - One required RBC and platelet transfusions.
- Eight patients received both RBCs and platelets in the year prior to study entry, and these eight continued to require transfusion of both products while on study.
- For the two patients who were transfused only platelets in the year prior to study,
  - One was transfused with platelets only on study.
  - One required both RBC and platelet transfusions on study.

An increase in transfusion requirement is noted for ten of the twelve previously transfused patients for whom information is available.

Twenty-one patients received in excess of 140 units of packed RBC. The average number of units that a patient received was 6.6 units (range: 1 – 22). If the three patients who required twenty, twenty-one, and twenty-two units while on study are excluded, the median number of RBCs transfused is five units (range: 1-10 units). Eleven patients were transfused platelets on more than ninety-nine occasions. The average number of times platelets were infused was nine times (range: 1 – 27 times). If the three patients who required platelet transfusions sixteen, nineteen, and twenty-one times are excluded as outliers, the median number of times platelets were transfusions for the other eight patients is four times (range: 1-9 times).

Steroid Usage on Study

Eleven patients received systemic steroid on study for a variety of reasons.

- Three patients continued to receive steroids during the entire period of study drug administration for the following reasons:
  - anti-tumor effect in one instance,
  - hemolytic anemia in one instance, and
  - thrombocytopenia in one instance.
- One additional patient was continued on maintenance steroids during the first twelve days of study.
- Seven patients received intravenuos steroids on one to eight occasions for infusion related side effects. One patient was treated with systemic steroids post therapy for interstitial pneumonitis.

In addition three patients used topical steroids to control injection site reactions associated with the subcutaneous injections of CAMPATH-1H.

CD4+ Counts

Information about lymphocyte subpopulations was not provided to Millennium when the study information was obtained from Burroughs-Wellcome.

Anti-CAMPATH-1H Antibodies

Each of nine (22.5%) study participants had three samples analyzed for anti-Campath –1h antibodies. No antibody titers were found on analysis of the twenty-seven specimens.

ANALYSIS OF CLINICAL BENEFIT

The Case Report Forms of seven partial responders were evaluated to determine the ways in which they may have benefited from Campath-1h therapy. Performance status, improvement in disease related symptomatology, improvement in organomegaly and lymphadenopathy, improvement in hematological parameters, infection profile, and adverse event profile was reviewed.

- With regard to performance status, four of seven responders reported WHO performance status 0 at study entry and are not evaluable for improvement. One responder (018-002) had no improvement in performance status. Two responders had a decrease of one grade over study. Patient 017-001's performance status decreased from 1 to 2. Patient 019-005's performance status decreased from 0 to 1.
- In terms of disease related symptoms, one of the seven responders had B-symptoms at entry. This patient (017-001, stage IV disease) reported resolution of B symptoms. Four responders reported fatigue at study entry. In one patient fatigue resolved with therapy. In three responders no assessment of fatigue was reported after baseline determination.
- Five of the seven responders had lymph node measurements reported during study. In four of these patients, lymph node decreased by >85%, the fifth patient had a 44% decrease. Two responders had splenomegaly at entry. Both patients had a marked reduction in splenomegaly (>81%, >99% respectively).
- Information about hematological parameters is as follows.
    - Four of the seven responders were eligible for improvement in hemoglobin. Two showed improvement from Gr. 2 at baseline to Gr. 0 at follow-up. One improved from Gr. 1 to Gr. 0, and the fourth from Gr. 2 to Gr. 1.
    - Four responders were eligible to show improvement in platelet count. All four patients reached normal platelet counts at completion of study (NCI CTC Gr.0). Two of the four entered study with gr. 4 thrombocytopenia, one with gr. 1 thrombocytopenia, and one with gr. 2 thrombocytopenia.
    - Three of the responders were neutropenic (one gr. 4, two gr. 2) at study entry. All reached grade 0 / 1 at follow-up.
    - At follow-up after discontinuation of therapy two responders (patient 017-001 and patient 018-002) had ceased to require platelet and RBC therapy.
- Four of the responders had infections reported during study, two of which were serious in nature.

- Patient 018-002 had Staph sepsis with grade 4 disease-related neutropenia on study.
- Patient 022-003 had interstitial pneumonitis, probably PCP, after completion of study.
- The other two responders (019-005, 019-001) had pneumonitis / bronchopneumonia and herpes simples, gr. 1.

- No other serious adverse events were reported. Two responders did have gr.3 infusion related adverse events during CAMPATH-1H administration.

All of the responders demonstrated benefit in some disease related parameters but not in all disease related parameters.

SUMMARY

This review includes information about the efficacy including possible clinical benefit and safety for a group of thirty-two study participants with B-CLL. The study population was selected from a large single arm trial of Campath-1h conducted in patient with NHL, B-CLL, untreated B-CLL, T-CLL, PLL and multiple myeloma. Twenty-four (75%) participants had Stage III or IV disease. Eleven (34.4%) were previously treated with fludarabine. All (100%) participants had at least one regimen of alkylator therapy while fifteen (46.9%) participants had exposure to three or more alkylator containing regimens.

Fifteen (46.9%) participants completed Campath-1h therapy. Five (15.6%) participants discontinued due to disease progression. Three (9.4%) participants died on study. Six (18.8%) were discontinued for adverse events. Two (6.2%) refused further therapy. One (3.1%) discontinued to enjoy the Christmas holidays.

Seven objective (partial) responders were noted for a response rate of 21.9% [95% CI: 7.6%, 32.6%]. Median time to response was 3.9 months [95% CI: 1.4, 4.6 mos.]. Median duration of response was 7.1 months [95% CI: 4.6, 23.2 mos.]. Median progression-free survival of 4.9 months [95% CI: 2.9, 7.0 mos.] was estimated with thirty (93.8%) patients considered progressors at the time of this review. Median time to treatment failure was 3.0 months [95% CI: 1.9, 4.7 mos.]. Thirty-one patients were reported as treatment failures. Median survival for this study population was calculated as 25.8 months [95% CI: 11.7, 44.2 mos.]. Fourteen patients were censored for survival at of the September 10, 1997 cut-off however follow-up in six patients was less than one year (patients lost to follow-up).

On this study twenty-five (78.1%) patients received intravenous infusions of Campath-1h while seven received subcutaneous therapy. Two (8%) patients treated according to the recommended schedule required permanent dose reductions for treatment related side effects. The seven patients treated with subcutaneous injections did not require dose reduction. Local reactions in three patients treated subcutaneously were managed with topical steroids throughout study. Eighteen (56.8%) participants had one or more dose delays. Nine (28.1%) patients reported to have one or more dose delays $\geq$ 7 days for treatment related adverse events. Two of the three patients who missed single doses did so due to treatment related adverse events.

Three (9.4%) patients died on study. All three participants experienced fatal infections and in two cases, concomitant disease progression. In addition two patients died at > thirty days after discontinuation of study drug, one from progressive multifocal leukoencephalopathy and a second from infection. Study discontinuations for adverse events were reported in eight (25%) patients. One discontinuation was due to disease progression. Two discontinuations were for infusion-related events. One discontinuation was for drug-related grade 4 thrombocytopenia, while four were for study drug-related infections.

Fourteen serious adverse events, usually infectious in nature, were reported for ten patients. Twenty-two hospitalizations were reported during study, eighteen for to infections usually treatment related. Twenty-three (71.9%) study subjects experienced fifty infections on study or within six months of primary Campath-1h therapy. Two other infections related to study drug therapy include disseminated Zoster-Varicella (Patient 8-003) at day +225 (greater than 180 days post Campath-1h therapy) and Staph. sepsis during retreatment (Patient 6-106). Twelve infections were bacterial in nature including seven cases of bacterial sepsis. Two cases of suspected sepsis were also reported. Two fungal infections, twenty-one viral infections including seventeen episodes of H. simplex, two cases of disseminated Zoster-Varicella, one case of localized H. Zoster, and one case of CMV reactivation were also reported. One case of confirmed and one case of suspected PCP pneumonia were reported. In fifteen instances the etiology of the infection was not determined. Including in this group are two cases of interstitial pneumonitis of unknown etiology. Opportunistic infections were reported in nine (28.1%) patients.

Thirty-one (96.9%) patients were reported to have experienced one or more adverse events on study or within thirty days of study discontinuation. Nineteen (49.4%) of these adverse events were of grade 3 / 4 in nature. Adverse events can be classified as infectious, or infusion related, or hematologic in nature. Infection events have already been discussed in the previous section. Infusion related events include fever (71.9%), rigors (65.6%), hypotension (43.8%), nausea (43.8%), vomiting (34.4%), pruritis (43.8%), urticaria (32.5%), and rash or erythematous rash (40.6%). Two patients were discontinued from study for infusion related toxicity.

Hematological toxicity included new or worsening anemia in 81% of the patients with new or worsening Grade 3 or 4 hemoglobin toxicity in 28%. New or worsening neutropenia related to Campath-1h therapy were reported in 81% of the participants over the course of therapy. One or more episodes of new or worsening Grade 3 or 4 neutropenia were reported in 56% of the study participants. New or worsening thrombocytopenia of any grade was observed in 72% of participants. One or more episodes of new or worsening Grade 3 or 4 thrombocytopenia were observed in 53% of the patients. Ten patients, not transfused in the year prior to study, were transfused on study, nine receiving RBC transfusions and one multiple platelet transfusions. Ten of twelve patients transfused in the year prior to study were noted to have an increase in the number of units transfused. Median number of RBC transfusions was five units (range: 1 –10) with three patients excluded from analysis. The average number of times that

platelets were transfused was nine times (range: 1-27 times) with a median number of times estimated to be four (range: 1- 9 times. Three patients who required excessive platelets transfusions are excluded (transfused sixteen, nineteen, and twenty-four times respectively).

Steroid usage was infrequent on this study. Anti-Campath-1h antibody measurements were performed in nine patients. In the nine patients in whom antibody testing was performed, the titers were negative at baseline and on two occasions after the initiation of therapy.

In summary treatment of B-CLL with Campath-1h therapy has resulted in an objective response of 21.9%. Median duration of response was 7.1 months in a population of B-CLL patients all of whom were pretreated with alkylator therapy and one of whom was refractory to fludarabine. Toxicities are generally infectious, infusional, or hematological in nature. This non-comparative study provides limited support for the approval of Campath-1h for use in patients previously treated with alkylators and refractory to fludarabine.

SUMMARY of INFORMATION in the CLINICAL STUDY REVIEWS

This review reports on the safety and efficacy of Campath-1h in three single arm clinical trials involving a total study population of one hundred forty-nine patients enrolled at sites in the United States and Europe. The pivotal trial, Study 211, was conducted between March 31, 1998 and July 31, 1998. Date of last follow-up for information collected about this this study for review was July 26, 2000. Study 009, with a twenty-four patient enrollment, was originally conducted as an exploratory efficacy study by Burroughs-Wellcome between February 8, 1993 and February 3, 1995 with follow-up information obtained through March 1997. The thirty-two patients who compose the study population for Study 005 were selected from a group of 125 patients with various hematological malignancies treated with CAMPATH-1H between February 12, 1993 and May 8, 1995 under the auspices of Burroughs-Wellcome. L & I Partners was able to verify 50% of the source documents prior to completion of the final study report. Last follow-up survey for survival was conducted by ILEX in March 1997.

The following table (Table S1) provides a summary of the demographic information for the three studies:

Table S1: Demographic Data for Study 211, Study 009, and Study 005

Parameter	Study 211 N = 93	Study 009 N = 24	Study 005 N = 32
Median Age in Years (Range in Years)	66 (32 – 82)	62 (44 – 77)	57 (46 – 75)
Race			
Caucasian	86 (92.5%)	24 (100%)	32 (100%)
Gender			
Male	73 (78.5%)	15 (62.5%)	22 (68.8%)
Female	20 (21.5%)	9 (37.5%)	10 (31.3%)
Rai Stage			
Stage I	5 (5.4%)	1 (4.2%)	3 (9.4%)
Stage II	16 (17.2%)	6 (25.0%)	5 (15.6%)
Stage III	18 (18.3%)	2 (12.5%)	5 (15.6%)
Stage IV	54 (58.1%)	14 (58.3%)	19 (59.4%)

A difference of nine years in the median age is noted across studies. Over 90% of the study participants are white, more than 60% are male and over half had Stage IV disease at entry into study.

Study eligibility with regard to disease histology, refractoriness to fludarabine, and prior alkylator therapy is compared across the three studies in the following table (Table S2).

Table S2: Disease Histology, Fludarabine Refractoriness, and History of Prior Alkylator Therapy for Study 211, 009, and 005

Parameter	Study 211 N = 93	Study 009 N = 24	Study 005 N = 32
B-CLL	86 (92.5%)	22 (87.5%)	32 (100.0%)
Fludarabine Refractory	87 (93.5%)	17 (70.8%)	9 (28.1%)
Alkylator Exposure	93 (100.0%)	22 (91.7%)	32 (100.0%)

More than 87.5% of the population had a diagnosis of B-CLL and over 90% had received prior therapy with alkylators. With regard to fludarabine refractoriness, eighty-six patients (over 90%) of the Study 211 population were refractory to fludarabine. On study 009 only seventeen (70.8%) participants were refractory to fludarabine, although all patients had been treated with fludarabine. On Study 005 only eleven of the thirty-two study participants had prior fludarabine therapy with nine (28.1%) of those participants considered refractory to fludarabine.

Disposition information across the three studies is shown in the following table (Table S3). About 33.3% of Study 009 participants were reported to have completed therapy, 46.9% of the Study 005 participants completed therapy, and 63.4% of the Study 211 participants completed therapy. On all three studies, a significant number of patients were discontinued for adverse events: 21.5% of the Study 211 population; 25% of the 009 population; and, 18.8% of the 005 population.

Table S3: Patient Disposition for Study 211, Study 009, and Study 005

Patient Outcome	Study 211 N = 93	Study 009 N = 24	Study 005 N = 32
Completed Therapy	59 (63.4%)	8 (33.3%)	15 (46.9%)
Died on Study	3* (3.2%)	5 (20.8%)	3 (9.4%)
Progression	5 (5.4%)	5 (20.8%)	5 (15.6%)
Discontinued due to AE	20 (21.5%)	6 (25.0%)	6 (18.8%)
Refused Therapy	6 (6.5%)	--	2 (6.2%)
Other "AE"	1 (1.1%)	--	--

*Only on-study deaths

Summary of Efficacy Information

Information about response parameters for each the three studies is presented in the Table S4. Objective response rates of 21.9% for Study 005, 29.2% for Study 009, and 33.3% for Study 211 were confirmed on review of the data. Median time to response for the three studies ranged from 1.6 months to 3.9 months. The median duration of response ranged from 6.8 months to 10.8 months. A small number of patients remained in remission for more than twelve months: seven (7.5%) patients (all refractory to fludarabine) on Study 211, three (12.5%) patients (one not refractory to fludarabine) on Study 009, and two (6.3%) patients Study 005 (neither refractory to fludarabine).

Table S4: Information about Response Parameters for Study 211, Study 009, and Study 005

Parameter	Study 211 N = 93	Study 009 N = 24	Study 005 N = 32
No. (%) Complete Responders	2 (2.2%)	-	-
No. (%) Partial Responders (%)	29 (31.2%)	7 (29.2%)	7 (21.9%)
Overall Response Rate	33.3%	29.2%	21.9%
(95% Confidence Interval)	(23.4%, 42.6%)	(11.0%, 47.4%)	(7.6%, 32.6%)
Time to Median Response	1.6 months	3.8 months	3.9 months
(95% Confidence Interval)	(1.1, 1.8 months)	(2.3, 4.0 months)	(1.4, 4.6 months)
Median Duration of Response	6.9 months	10.8 months	7.1 months
(95% Confidence Interval)	(4.6, 8.4 months)	(5.6, 18.6 months)	(4.6, 23.2 months)
No. (%) Responders Fludarabine Refractory	29 (31.2%)	5 (20.8%)	1 (3.1%)
No. (%) Duration of Response ≥ 12 Months	7 (7.5%)	3 (12.5%)	2 (6.3%)

Other efficacy information including progression (disease) free survival, time to treatment failure, and survival are summarized in Table S5.

Table S5: Time to Event Parameters for Study 211, Study 009, and Study 005

Parameter	Study 211 N = 93	Study 009 N = 24	Study 005 N = 32
No. (%) Progressed	92 (98.9%)	22 (91.7%)	30 (93.8%)
No. (%) Censored	1 (1.1%)	2 (8.3%)	2 (6.2%)
Median Progression Free Survival	4.0 months	7.1 months	4.9 months
(95% Confidence Interval)	(3.2, 4.7 months)	(3.2, 8.7 months)	(2.9, 7.0 months)
No. Treatment Failures	92 (98.8%)	23 (95.8%)	31 (96.7%)
No. Censored	1 (1.1%)	1 (4.2%)	1 (3.1%)
Median Time to Treatment Failure	3.0 months	3.8 months	3.0 months
(95% Confidence Interval)	(2.4, 4.3 months)	(1.6, 8.6 months)	(1.9, 4.7 months)
No. Dead	51 (54.8%)	18 (75.0%)	18 (56.3%)
No. Alive (Censored)	42 (45.2%)	6 (25.0%)	14 (43.7%)
Median Survival	15.9 months	27.5 months	25.8 months
(95% Confidence Interval)	(11.8, + months)	(7.1, 32.6 months)	(11.7, 44.3 months)

At the time of this review almost the entire population of each study had progressed. The median progression free survival for Study 211 is 4.0 months, for Study 005 is 4.9 months and for Study 009 is 7.3 months. In all studies median time to treatment failure is shorter than progression free survival due to the number of study discontinuations for adverse events and, in Study 211, refusal to continue therapy. Median survival on Study 211 is ten months, on Study 005 about twenty-six months, and on Study 009 about twenty-eight months. Stage of disease, number of prior treatments, number of deaths due to infectious complications, the size of the study population, amount of follow-up, and use of therapies such as bone marrow transplant post Campath-1h therapy help to explain the differences in survival among the three studies.

Summary of Safety Data

Information about dose omissions of less than five days and dose delays $\geq$ seven days is presented in Table S6. The major reason for a missed dose was hematological, infusional, or infectious toxicity. Note that the reason for the missed single doses is unknown over 50% of the time on Study 009 due to failure to collect this information. On Study 211, 32.3% about one-third of the study population missed seven or more consecutive days due usually to hematologic or infectious toxicity. For Study 009 half of the missed doses were due to drug related toxicity while in the other 50% the reason could not be determined. On Study 005, 50% of patients missed seven or more consecutive days of therapy usually for Campath-1h related toxicity, usually infectious in nature. Note that on Study 005 patients could be "rested" during therapy at the investigator's discretion, which may provide the reason for some of the longer treatment delays.

Table S6: Treatment Delays on Study 211, Study 009, and Study 005

	Study 211 (N = 93)	Study 009 (N = 24)	Study 005 (N = 32)
Treatment Delays < 5 Days			
No. of Patients	20 (21.5%)	13 (54.2%)	3 (9.4%)
No. of Delays	31	31	3
Reason for Delay			
Hematologic Toxicity	15	10	1
Infectious	1	2	1
Infusion Toxicity	6	-	-
Other	9	2	-
Unknown		17	1
Treatment Delays ≥ 7 Days			
No. of Patients	30 (32.3%)	12 (50.0%)	15 (46.9%)
No. of Delays	37	19	24
Reason for Delay			
Hematological Toxicity	20	5	9
Infection	14	11	3
Infusion Related	-	-	2
Other	3	3	10
Unknown	-	-	-

On all three studies, deaths were reported on study and within 180 days of completion of study drug therapy. Follow-up for six month post therapy for mortality on these studies is related to the fact that delayed recovery from marrow toxicity and the prolonged suppression of the immune system secondary to Campath-1h therapy have been reported. The following table (Table S9) provides information about the mortality across the three studies.

Table S9: Mortality and CAMPATH-1H-Related Mortality on Study 211, 009, and 005

	Study 211 (N=93)	Study 009 (N=24)	Study 005 (N=32)
Deaths on Study	9	3	3
Campath-1h Related	4* (44.4%)	1 (33.3%)	3 (100.0%)
Deaths with 180 Days of Therapy	15	4	2
Campath-1h Related	9 (60.0%)	2 (50%)	2 (100.0%)

*One additional death may be due to Campath therapy.

As noted previously, a significant number of deaths reported on these studies are related Campath-1h. The cause of death was usually of an infectious etiology, sometimes opportunistic in nature, and often associated with Camapth-1h incuded myelotoxicity in particular neutropenia.

An overview of the serious adverse events for each of the three studies is included in the following table. More than 65% of the patients on each study had one or more serious adverse events on study or within 180 days of Campath-1h discontinuation. The majority of these serious adverse events were related to Campath-1h therapy. Note that in Table S10 febrile neutropenia is reported as an infection.

Table S10: Serious Adverse Events Reported on Study or Within 180 Days of Discontinuation of Study Drug Therapy for Study 211, Study 009, and Study 005

	Study 211 (N=93)	Study 009 (N=24)	Study 005 (N=32)
No. of Patients with Serious Adverse Events	62 (66.7%)	19 (79.2%)	21 (65.6%)
No. of Episodes of Serious Adverse Events,	115 (100.0%)	36 (100.0%)	32 (!00.0%)
Primary Infectious, CAMPATH-1H Related (With Neutropenia)	62 (53.9%) (46)	23 (63.8%) (8)	22 (68.8%) (4)
Hematologic, CAMPATH-1H Related	12 (10.4%)	1 (4.3%)	3 (13.6%)
CAMPATH-1H Infusion Related	10 (8.7%)	6 (26.1%)	4 (18.2%)
Other Non-Related Serious Adverse Events	31 (26.9%)	6 (26.1%)	3 (13.6%)

Most serious adverse events were infectious in nature and the infection was often accompanied by neutropenia. As noted in the study reports infections related to study drug therapy were responsible for at least ten deaths on Study 211, for four deaths on Study 009, and five deaths on Study 005.

Eight patients (8.6%) on Study 211 and two (8.3%) patients on Study 009 were reported to undergo transformation to a more aggressive lymphoma or develop a new malignancy. None of the patients on Study 005 are known to have developed a second malignancy or transformed to a higher grade malignancy, however the patient follow-up was not as complete on Study 005 as on the other two studies. This finding is a matter of concern should Campath-1 be used in earlier stage CLL or in other disease settings.

With regard to opportunistic infections secondary to therapy, Table S11 includes information from each of the three studies about the number of patients who received PCP and antiviral prophylaxis. As the number of patients who were prophylaxed increased, CMV and other fungal infections appear to become more common and PCP / interstitial pneumonitis less common.

Table S11: Opportunistic Infections on Study 211, Study 009, and Study 005

	Study 211 N = 93	Study 009 N = 24	Study 005 N = 32
No. (%) Patients with Opportunistic Infections	27 (29.0%)	10 (41.7%)	9 (28.1%)
No. (%) Patients Prophylaxed	82* (88.2%)	14** (58.3%)	18 ** (56.3%)
No. of Opportunistic Infections	47 (100.0%)	27 (100.0%)	25 (100.0%)
No. of Serious Opportunistic Infections	23 (48.9%)	15 (55.5%)	13 (52.0%)

*Two patients did not receive either PCP or antiviral prophylaxis

** The duration of prophylaxis and the amount / type of prophylaxis varies.

Hematological toxicity was observed on all three studies. Pancytopenia was noted in eight (8.6%) patients on Study 211 and associated with three fatalities. Three patients on Study 009 were identified as having suppression in all three cell lines with partial or complete recovery reported in all three patients. On Study 005 no cases of pancytopenia were clearly identified, however one patient had anemia, neutropenia, and thrombocytopenia at the time that interstitial pneumonitis was diagnosed. Autoimmune complications were noted in five patients in Study 211, four had autoimmune thrombocytopenia, and one had autoimmune hemolytic anemia. One death is reported in a patient with autoimmune thrombocytopenia. No autoimmune hematologic phenomena

were observed in the study population on Study 009 or Study 005. One case of interstitial pneumonitis on Study 009 appears to be related to Campath-1h.

The number (%) of patients with changes in the NCI CTC hemoglobin, neutrophil, and platelet grade from baseline over the course of study were reviewed over each two week interval on study as well as at one month, two months, and four months of follow-up. The same information was reviewed for responders as compared to non-responders and for transfused and / or growth factor treated patients to determine the influence of response and transfusion on the the grade of toxicity. With regard to hemoglobin toxicity (defined as one grade or greater change in hemoglobin grade) declines were noted during the first eight weeks of study in each two week intervals on all three studies populations. A 6 - 31.6% incidence of grade 3 / 4 toxicity as shown in Table S12.

Table S12: Decline in Hemoglobin Grade from Baseline with New Grade 3 / 4 Hemoglobin Toxicity – All Studies

	Study 211 (N =90)		Study 009 (N = 19)		Study 005 (N=32)	
Weeks on Study	Decline ≥ Gr. 1 N (%)	New Gr. 3 / 4 (%)	Decline ≥ Gr. 1 N (%)	New Gr. 3 / 4 N (%)	Decline ≥ Gr. 1 N (%)	New Gr. 3 / 4 N (%)
Weeks 1 – 2	43 (47.8)	13 (14.4)	8 (42.1)	6 (31.6)	18 (56.2)	3 (9.3)
Weeks 3 – 4	50 (56.8)	18 (20.4)	6 (33.3)	1 (5.5)	18 (56.2)	2 (6.2)
Weeks 5 – 6	42 (57.8)	14 (18.9)	3 (18.8)	0 (0.0)	18 (58.0)	4 (12.5)
Weeks 7 - 8	38 (56.7)	12 (17.9)	2 (20.0)	0 (0.0)	11 (45.8)	1 (4.2)
Weeks 9 – 10	14 (32.6)	0 (0.0)	4 (33.3)	1 (8.3)	7 (38.9)	2 (11.1)
Weeks 11 – 12	11 (26.8)	1 (1.1)	3 (30.0)	1 (10.0)	7 (43.8)	2 (12.5)
Weeks 13+	4 (26.6)	0 (0.0)	4 (40.0)	0 (0.0)	5 (45.4)	0 (0.0)
1 Month F/U	15 (18.3)	1 (1.1)	4 (22.2)	0 (0.0)	4 (16.7)	1 (4.2)
2 Month F/U	8 (13.1)	1 (1.6)	1 (7.7)	1 (7.7)	2 (12.5)	0 (0.0)

In looking at erythrocyte toxicity, response or non-response did not appear to play in development of toxicity. Recovery to baseline is noted in about half of the patients, while about one-third have improvement over baseline hemoglobin values in the 50-60% of study population for whom information is available.

Neutrophil counts were noted to decline over the course of therapy in up to 60.2% of the patients in Study 211, 67.3% in Study 009, and 61.3% in Study 005. New grade 4 neutropenia is noted in up to 21.6% of the study population of Study 211, in up to 27.2% of the population of Study 009, and in up to 12.9% of the population of Study 005. Declines in neutrophil counts occurred over the course of study regardless of response to therapy. Persistent neutropenia is noted with recovery delayed for several months after discontinuation of Campath-1h therapy in responders as well as non-responders and in the face of growth factor administration. Growth factor administration was reported in 35.5% of the Study 211 population, 20.8% of the 009 study population, and only 9.4% of the 005 population.

Table S13: Decline in Neutrophil Counts from Baseline with New Grade 4 Neutropenia – All Studies

	Study 211 (N = 92)		Study 009 (N = 24)		Study 005 (N=32)	
Weeks on Study	Decline ≥ Gr. 1 N (%)	New Gr. 4 N (%)	Decline ≥ Gr. 1 N (%)	New Gr. 4 N (%)	Decline ≥ Gr. 1 N (%)	New Gr. 4 N (%)
Weeks 1 – 2	45 (48.9)	13 (14.1)	13 (54.2)	3 (12.5)	18 (58.1)	4 (12.9)
Weeks 3 – 4	53 (60.2)	16 (18.2)	14 (67.3)	6 (27.2)	19 (61.3)	4 (12.9)
Weeks 5 – 6	42 (56.8)	16 (21.6)	10 (55.5)	4 (22.2)	16 (53.3)	4 (6.7)
Weeks 7 - 8	35 (52.2)	12 (17.9)	9 52.9)	1 (5.9)	13 (59.1)	2 (9.1)
Weeks 9 – 10	21 (48.8)	7 (16.3)	6 (42.9)	0 (0.0)	8 (47.1)	1 (5.9)
Weeks 11 – 12	17 (43.6)	3 (7.7)	8 (72.7)	1 (9.1)	7 (46.7)	1 (6.7)
Weeks 13+	6 (46.0)	3 (20.0)	8 (66.7)	1 (8.3)	5 (45.4)	0 (0.0)
1 Month F/U	38 (46.9)	10 (11.0)	9 (37.4)	0 (0.0)	7 (30.4)	0 (0.0)
2 Month F/U	20 (37.8)	5 (8.2)	5 (38.5)	0 (0.0)	8 (53.4)	0 (0.0)
4 Month F/U	17 (25.8)	3 (4.5)	-	-	-	-

The highest number of patients reporting a decline in platelet counts is noted in the first weeks of therapy. The high incidence in the first two weeks on study is probably related to acute thrombocytopenia associated with Campath-1h infusion. The overall incidence of grade 4 thrombocytopenia was < than 10% during any two week period on each of the three studies. The persistent decrease in the platelet count from baseline over the course of study appears more likely due to disease progression than to Campath-1h therapy. Rarely patients have had suppression of platelet production for prolonged periods post therapy. Most patients have recovery to baseline or better after discontinuation of therapy.

Table S14: Decline in Platelet Counts from Baseline with New Grade 4 Thrombocytopenia – All Studies

	Study 211 (N = 92)		Study 009 (N = 24)		Study 005 (N=32)	
Weeks on Study	Decline ≥ Gr. 1 N (%)	New Gr. 4 N (%)	Decline ≥ Gr. 1 N (%)	New Gr. 4 N (%)	Decline ≥ Gr. 1 N (%)	New Gr. 4 N (%)
Weeks 1 – 2	65 (70.7)	8 (8.7)	65 (70.7)	8 (8.7)	16 (50.0)	3 (9.4)
Weeks 3 – 4	43 (48.9)	8 (9.1)	43 (48.9)	8 (9.1)	12 (37.5)	3 (9.4)
Weeks 5 – 6	31 (41.9)	2 (2.7)	31 (41.9)	2 (2.7)	7 (22.6)	3 (9.7)
Weeks 7 - 8	20 (29.9)	3 (4.5)	20 (29.9)	3 (4.5)	5 (20.9)	2 (8.3)
Weeks 9 – 10	16 (37.2)	2 (4.7)	16 (37.2)	2 (4.7)	2 (11.1)	0 (0.0)
Weeks 11 – 12	9 (21.9)	0 (0.0)	9 (21.9)	0 (0.0)	2 (12.5)	0 (0.0)
Weeks 13+	5 (33.3)	1 (6.7)	5 (33.3)	1 (6.7)	2 (18.2)	0 (0.0)
1 Month F/U	16 (19.5)	4 (4.9)	16 (19.5)	4 (4.9)	0 (0.0)	0 (0.0)
2 Month F/U	7 (11.5)	2 (3.3)	7 (11.5)	2 (3.3)	0 (0.0)	0 (0.0)

In summary, review of the CBC data for all participants provided the following information about the overall incidence of hematological toxicity on study or within thirty days of discontinuation of Campath-1h therapy. For the entire study population of one-hundred forty nine patients, one-hundred nineteen (80%) experienced new or worsening grade 1 to 4 anemia and 38% experienced grade 3 or 4 NCI CTC anemia at least once while on study or within thirty days of study completion. One hundred twenty-seven (72%) patients experienced new or worsening grade 1 to 4 neutropenia and ninety-six (64%) patients had at least one episode of grade 3 or 4 neutropenia while on study. Grade one or greater thrombocytopenia was reported for one hundred seven (72%) of the study participants with seventy-four (50%) patients experiencing at least one episode of grade 3 or 4 thrombocytopenia.

Information about use of blood products on each of the studies in included in the following table. Sixty-seven (72%) participants on Study 211 required RBC transfusion. The median RBC transfusion requirement was six units (range: 3 –10). The median number of times platelets were transfused on Study 211 was three (range: 1- 10). Nineteen (79%) of the Study 009 population required transfusion. The median number of RBC units transfused was six (range: 2 – 16). The median number of times that platelets were transfused on Study 009 was six (range: 1 –10). Twenty-four (67%) of the 005 study population required transfusion. Median number of RBC transfusion was 5 units (range: 1- 10). Median number of times platelets were transfused on this study was 4 (range: 1 –9).

Table S15: Use of Blood Products on Study 211, Study 009, and Study 005

	Study 211 (N = 93) N %	Study 009 (N = 24) N %	Study 005 (N = 32) N %
No. (%) No Prior Transfusion History	75 (80.6)	12 (50.0)	18 (56.3)
No. (%) Transfusion Free During Study	25 (26.8)	5 (20.8)	8 (25.0)
No. (%) RBC Transfusion Only	27 (29.0)	5 (20.8)	9 (28.2)
No. (%) RBC, Platelet Transfusions	20 (21.5)	2 (8.3)	--
No. (%) Platelets Only	3 (3.2)	0 (0.0)	1 (3.1)
Pre-Study Transfusions	18 (19.4)	12 (50.0)	14 (43.8)
No. (%) Increase in Blood Product Use	12 (12.9)	9 (37.5)	9 (28.1)
No. (%) No Change in Blood Product Use	5 (5.4)	1 (4.2)	4 (12.5)
No. (%) Decrease in Blood Product Use	1 (1.1)	2 (8.3)	1 (3.1)
Median* No. RBC Units Transfused (Range in Units)	6 (3 –10)	6 (2 –16)	5 (1 –10)
Median* No. of Times Platelets Transfused (Range of Times)	3 (1 – 10)	6 (2 –10)	4 (1 –9)

*Outliers excluded

The above information demonstrates that Campath-1h has a significant degree of hematological toxicity, toxicity that was associated with fatal or serious infection in most cases.

Information about CD3+/4+ counts from Study 211 and 009 shows that nadir counts are observed approximately 4 weeks after initiation of therapy and begin rise after therapy is discontinued. Nadir CD3+/4+ count on Study 211 was 2 (two)/ul. At two months post therapy the median CD3+/4+ count is approximately 200/ul. As late as six months post study median CD3+/4+ counts were continuing to increased but had did not achieve the baseline median count reported for the study group.

Suggestions of clinical (patient) benefit were demonstrated retrospectively in the following ways for some responders on each of the three studies. Improvement in clinical symptoms, improvement in organomegaly and lymphadenopathy, rise in hemoglobin, improvement in platelet counts and neutrophil counts are noted. For a few patients, response was not always coupled with clinical benefit as, for example, the partial responder who died from autoimmune thrombocytopenia secondary to Campath-1h.

In summary, Campath-1h therapy does have efficacy as demonstrated by a response rate ranging from 21 – 33.3% with a median duration of response ranging from 6.9 to 10.8 months in these single arm studies. The true measure of net clinical benefit (sustained

improvement in symptoms without adverse impact on survival) is unknown as no comparator arm exists in these trials. Patient benefit in terms of improvement in symptomatology, improvement in uncomfortable organomegaly / lymphadenopathy, and improvement in blood counts were noted for responders. However, the toxicity profile of this drug is of concern.

A significant number of serious, sometimes fatal, adverse events have been reported with Campath-1h therapy. The lack of a comparator arm prevents comparisons of the incidence and severity of these serious adverse events as compared to best supportive care or alternative experimental therapy. Also, the adverse event information for the supporting studies 005 and 009 is probably incomplete due to the loss of some source data. The majority of toxicities associated with Campath-1h therapy are infectious in nature, often with a hematological component. Hematologic toxicities including pancytopenia, autoimmune cytopenias, and prolonged marrow from drug related neutropenia have been reported with Campath-1h therapy. In addition all patients experience some degree of acute infusion related toxicities.

The question then, based on the information at hand, is whether the benefits of objective tumor response with Campath-1h therapy outweigh the risks of infection including fatal infections and the risks of significant hematological toxicity including fatal marrow hypoplasia or immune cytopenia.

RECOMMENDED ACTION:

Based on the information presented in these reviews and after a discussion at ODAC on December 14, 2001 Campath® is recommended for accelerated approval. A comparative clinical trial must be performed to further delineate of efficacy and safety of Campath® and provide evidence of clinical benefit.

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BLA 99-0786: Campath®(alemtuzumab)
REVIEW OF FINANCIAL DISCLOSURE STATEMENTS

Ninety-four investigators for twenty-seven sites in the United States, Great Britain, France, and Germany completed the financial disclosure statement. Ten investigators failed to complete the financial disclosure form. Six non-responders were in Britain and four were in the United States. In one instance the non-responding investigator was reported to have left the university. In other nine instances the sponsor reports that there was "no response to requests, either verbal or written" to complete the forms. None of these ten investigators enrolled patients on study.

Two investigators owned shares of ILEX and / or Leukocyte (Millennium) stock. _____ reported ownership of forty shares of ILEX stock. This site enrolled ___ patients four of whom were responders. Review of the records revealed no evidence of any irregularities with regard to the conduct of the study or the results obtained at this center.

_____ reported ownership of 3000 shares ILEX and 2000 shares of Leukocyte (Millennium). Sixteen subinvestigators working with ___ at various locations throughout the state of ___ enrolled ___ patients. None of these subinvestigators had any financial interests in either ILEX or Leukocyte. Clinical information for Study ___ was collected from all sites and filed at the central office of _____. This clinical information was inspected by the FDA ___ Field Office with guidance from the BIMO ___ ___. Discrepancies and missing information noted by the FDA reviewer were remedied by collection of the original hospital records and physician notes. The efficacy and safety data was verified by the BLA clinical reviewer. Differences were noted in some efficacy assessments. The FDA reviewer discussed these differences with the sponsor and the differences were resolved. ___ received an untitled letter dated ___ ___ regarding the conduct of Study ___ While ___ did own a large number of shares (value > $25,000) in ILEX and Leukocyte (Millennium), no evidence of fraudulent conduct was observed on FDA inspection.

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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