

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103948/0**

**STATISTICAL REVIEW(S)**

## Biostatistical Review

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STN 103948

IND:

4294 / 286

CAMPATH® as front-line therapy for B-CLL  
(Chronic Lymphocytic Leukemia)

Submission dated March 16, 2001

Millenium Pharmaceuticals, Inc.

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Date:

April 2, 2001

Reviewer:

Clare Gnecco, Ph.D. 

Through:

Ghanshyam Gupta, Ph.D., Branch Chief,  
Therapeutics Group



42-01

cc:

HFM-99/Document Control Center: IND 4294 / 286

HFM-573/Dr. Schechter

HFM-588/Ms. Sickafuse

HFM-215/Dr. Lachenbruch

HFM-210/Dr. Ellenberg

HFM-210/Chron - File: CAM307.DOC

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## BACKGROUND

The current submission contains a **revised protocol for Study #CAM307**, entitled "Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with Campath (alemtuzumab) vs. Chlorambucil in Patients with Progressive B-CLL Chronic Lymphocytic Leukemia." This study is part of the Phase IV commitment for approval of BLA 99-0786.

## STUDY SUMMARY:

**Study Design:** This is a Phase III, open-label, multi-center, randomized, comparative study designed to assess the effectiveness and safety of Campath vs. chlorambucil as front-line therapy in patients who have progressive B-CLL. Eligible patients must have

previously untreated, Rai stage I-IV disease and be experiencing progression of their B-CLL requiring treatment.

**Study Objectives:** The **primary efficacy objective** is to demonstrate that Campath therapy is superior to chlorambucil therapy as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS). The **secondary objectives** are: (i) to compare the CR and overall response rate between the two treatment arms using the 1996 NCIWG criteria (ii) to compare duration of response between the two treatment arms (iii) to compare time to treatment failure (TTF) between the two treatment groups (iv) to compare the time to alternate treatment between the two treatment arms (v) to compare the survival times between the two treatment arms and (vi) to compare the safety of the two treatment arms.

**Randomization:** Patients will be randomized in a 1:1 ratio to one of the two treatments. Treatment will begin within 7 days following randomization. The procedure will be carried out centrally utilizing an adaptive randomization algorithm (Pocock and Simon, 1975) with a balancing probability of 0.80. The balancing prognostic factors are the following: (i) study center (25-30) (ii) Rai stage (I-II vs. III-IV) (iii) WHO performance status (0 vs. 1) (iv) age (< 65 vs.  $\geq$  65) (v) gender (vi) maximum lymph node size (none palpable vs. < 5 cm).

**Analysis Groups:** Patients who have a confirmed diagnosis of B-CLL and receive study drug (i.e., the all patients treated group) will be included in the efficacy analysis.

**Sample Size:** The planned sample size is 284 patients (142 per treatment arm). This sample size allows for the detection of a 50% increase (i.e., a 7-month improvement) in median PFS in either arm, with 80% power and  $\alpha = 0.05$  (2-sided). To ensure 80% power, the primary analysis will be conducted when at least 70% of the patients have progressed or died, i.e., after a total of 190 failures, regardless of treatment arm.

Assuming a 30-month accrual period, an estimated 18 months of follow-up after the last patient is enrolled will be needed to observe 190 failures. These estimates are based on a 14-month median PFS in the control arm and a 21-month PFS in the Campath arm. These estimates also assume that 5% of the patients who are randomized will not have a confirmed diagnosis of B-CLL or will not receive therapy and, therefore, will be invaluable for the PFS analysis. At the time of the second interim analysis, in which the DSMB will review efficacy, they may recommend an increase in sample size if assumptions that provide for adequate power are not being met.

**Efficacy Analysis:** The primary endpoint of PFS is defined as the time from randomization date to first objective documentation of disease progression or death due to any cause. The other time to event variables will also be measured from randomization date with the exception of response duration, which will be measured from date of documented objective response. The **primary efficacy analysis** will be based on an independent review panel's determination of eligibility and response, including date of relapse (PD after response), for all patients. The efficacy analysis will include the following: Comparisons of patient PFS, time to treatment failure (TTF), time to alternate therapy, overall survival, and duration of response between the Campath and chlorambucil arms using the logrank test, stratified by Rai stage (I-II vs. III-IV). Kaplan-Meier curves will be generated to estimate time-to-event distributions for patient PFS, overall survival, duration of response, time to alternate therapy, and TTF. For response rates, 95% confidence intervals will be provided. A chi-square will be used to compare

CR and overall response rate (CR + PR) between the treatment arms. Analyses relating PFS time to study center will be carried out using a variety of models, including Cox proportional hazards. Effects of large vs. small enrolling centers and U.S. vs. European centers on PFS will be examined. An exploratory analysis looking at outcome relative to cytogenetics at baseline will be conducted. **Analysis of Immune Responsiveness:** (i) An exploratory analysis of responsiveness of patients in the subset for specific antigen responsiveness will be conducted utilizing descriptive statistics to provide a qualitative assessment and (ii) Comparison of each patient's baseline value to follow-up values at 1, 2, and 6 months following the last dose of study drug, to evaluate reduction in immune responsiveness secondary to treatment and recovery following treatment.

**Interim Analysis:** The protocol states that *"During any planned or unplanned IA, a statistically significant increase in treatment related deaths ( $\alpha=0.05$ , two-sided, unadjusted for multiple tests) in the Campath arm will be grounds for the DSMB to recommend stopping the study. A trend in drug related deaths in the Campath arm, not yet reaching statistical significance, may be grounds for recommending changes in study procedures or closure of the study."* A formal IA to assess safety will be conducted after 50 patients per arm have reached 4 months following randomization. DSMB will primarily evaluate overall mortality and SAE rate both in absolute terms for the study as a whole and in a comparative fashion with the control arm. No formal efficacy analysis will be performed at this look. A formal IA to assess safety and efficacy is planned after 95 patients have progressed in order to detect marked differences in PFS, survival, CR rate, or toxicity. All significance tests will be performed at a level of 0.005, using O'Brien-Fleming boundaries. The final analysis will be performed at a significance level of 0.048, ensuring the overall significance of 0.05. Finally, the DSMB may recommend a readjustment of the sample size if assumptions that provide for adequate power are not being met.

#### **STATISTICAL REVIEW COMMENTS TO BE CONVEYED TO THE SPONSOR:**

- (1) The primary analysis group should be ITT, i.e., all patients as randomized.
- (2) There are a number of secondary endpoints. These should be rank ordered by clinical importance and an appropriate multiple endpoint adjustment applied if any labeling claims are anticipated for these endpoints.
- (3) The sponsor should provide estimated hazard ratios (as well as medians) for all major time to event endpoints along with 95% confidence intervals. These should be provided for both adjusted and unadjusted analyses.
- (4) The sample size calculation has been confirmed. The concern is that the hypothesized difference is too optimistic.

## Biostatistical Review

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**BLA:**

**#99-0786**

*CAMPATH for the treatment of patients with B-Cell Chronic Lymphocytic Leukemia who have received an alkylating agent and failed Fludarabine therapy*

Submission dated December 22, 1999

L & I Partners, LP

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**Date:**

*June 9, 2000*

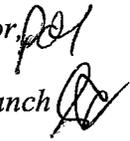
**Reviewer:**

*Clare Gnecco, Ph.D.*



**Through:**

*Peter A. Lachenbruch, Ph.D., Director*  
*Division of Biostatistics*  
*Ghanshyam Gupta, Ph.D., Acting Branch*  
*Chief, Therapeutics*



**cc:**

HFM-99/Document Control Center: BLA #99-0786  
HFM-573/Dr. Schechter  
HFM-210/Dr. Ellenberg  
HFM-210/Chron - File: CAMPATH1.DOC

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## BACKGROUND

This statistical review will only present summaries of statistical analyses based on the reviewing Medical Officer Dr. Schechter's reassessments of the major efficacy endpoints of the pivotal study and the two main supporting studies from this application. All of these studies are uncontrolled. Due to an unusually large amount of ambiguous and incomplete data, the sponsor has agreed to fully audit the entire database and will resubmit this application at a later date. Full details of the problem areas encountered and additional data to be provided can be found in Dr. Schechter's Clinical Review. Thus, this preliminary statistical review will be brief and include only the above cited analyses. A fully detailed statistical review will be undertaken when this application is resubmitted.

The **pivotal trial** in this submission is **Study CAM211**, “A Phase II Study of CAMPATH-1H (CAMPATH®) in Patients with B-Cell Chronic Lymphocytic Leukemia Who Have Received an Alkylating Agent and Failed Fludarabine Therapy.” The sponsor’s detailed Study Synopsis for this uncontrolled study is appended to this review. The two main **supporting studies** were **small uncontrolled Phase II trials, viz., Studies #05 and #09.**

**REVIEWER’S ANALYSIS OF MEDICAL OFFICER’S REASSMENTS FOR STUDY CAM211 (Based on data revision as of 5/18/00):**

**(a) Response Categories / Frequencies:**

<b>Response Category</b>	<b>Count</b>	<b>%</b>
<b>CR</b>	<b>2</b>	<b>2.1</b>
<b>PR</b>	<b>28</b>	<b>30.1</b>
<b>SD</b>	<b>45</b>	<b>48.4</b>
<b>PD</b>	<b>11</b>	<b>11.8</b>
<b>NE</b>	<b>7</b>	<b>7.5</b>
	<b>N = 93</b>	<b>100%</b>

**Disease Type:**            **CLL=86 pts (92.5%)**  
                                  **LYM= 5 pts**  
                                  **ACLL= 2 pts**

**(b) Estimated Objective Response Rate / 95% CI:**

**30/93 = 32.2%**            **95% CI: [22.8%, 41.6%]**

**(c) ITT Time to Response (Months):**

**# Events: 30**  
**Median: 1.63 months**  
**95% CI: [1.15, 1.84]**

**(d) ITT Duration of Response (Months):**

**#Events: 30**  
**Median: 5.88 months**  
**95% CI: [4.40, 9.66]**

**(e) Duration of Response Subgroup: CLL + RAI Stage III, IV + Fludara Refractory + IV Administration:**

**#Events: 20**  
**Median: 7.23 months**  
**95% CI: [5.32, 13.96]**

**(f) ITT Disease Free Survival (Months):**

**# Events: 88**  
**# Censored: 5 (5.4%)**  
**Median: 3.78 months**  
**95% CI: [2.82, 4.47]**

**(g) ITT Survival (Months):**

**#Events: 47**  
**#Censored: 46 (49.5%)**  
**Median: 12.42 months**  
**95% CI: [10.18, 14.16]**

**(h) ITT Time to Treatment Failure (Months):**

**#Events: 89**  
**#Censored: 4 (4.3%)**  
**Median: 2.53 months**  
**95% CI: [2.17, 3.94]**

**Note: Kaplan-Meier plots appear at the end of the results section.**

**REVIEWER'S ANALYSIS OF MEDICAL OFFICER'S REASSESSMENTS FOR STUDY #05 (Based on data revisions as of 4/11/00) :**

**(a) Response Categories / Frequencies:**

Category	Count	%
CR	0	0
PR	7	17.5%
SD	20	50.0%
PD	8	20.0%
NE	5	12.5%
	<b>N = 40</b>	<b>100%</b>

**Disease Type: CLL = 32 (80%)**  
**LYM = 4**  
**PLL = 4**

**(b) Estimated Objective Response Rate / 95% CI:**

7/40 = 17.5%                      95%CI: [7.0%, 28.0%]

**(c) ITT Time to Response (Months):**

#Events: 7  
Median: 3.91 months  
95% CI: [1.38, 4.57]

**(d) ITT Duration of Response (Months):**

#Events: 7  
Median: 6.21 months  
95% CI: [4.57, 16.26]

**(e) Duration of Response Subgroup: CLL + RAI Stage III,IV + Fludara Refractory + IV Administration:**

#Events: 0  
None of the 7 responders qualify for this subgroup

**(f) ITT Disease Free Survival (Months):**

#Events: 37  
# Censored: 3 (7.5%)  
Median: 3.58 months  
95% CI: [2.17, 7.42]

**(g) ITT Survival (Months):**

#Events: 22  
#Censored: 18 (45%)  
Median: 20.47 months  
95% CI: [11.73, 31.74]

**(h) ITT Time to Treatment Failure:**

N=39 (Note: problem with one case / questionable dates)  
#Events: 39  
#Censored: 0  
Median: 2.43 months  
95% CI: [1.64, 3.58 ]  
Note: Kaplan-Meier plots appear at the end of the results section.

**REVIEWER's ANALYSIS OF MEDICAL OFFICER's REASSESSMENTS's FOR STUDY #09 (Based on data revisions as of 4/11/00):**

**(a) Response Categories / Frequencies:**

Response Category	Count	%
CR	0	0
PR	7	29.2
SD	7	29.2
PD	5	20.8
NE	5	20.8
	N = 24	100%

**Disease Type:**      **CLL = 21 pts (87.5%)**  
                              **LYM = 1 pt**  
                              **PLL = 2 pts**

**(b) Estimated Objective Response Rate / 95% CI:**

**7/24 = 29.2%**                      **95% CI: [13.1%, 45.3%]**

**(c) ITT Time to Response (Months):**

**#Events: 7**  
**Median: 3.68 months**  
**95% CI: [2.30, 4.04]**

**(d) ITT Duration of Response (Months):**

**#Events: 7**  
**Median: 10.84 months**  
**95% CI: [5.85, 18.59]**

**(e) Duration of Response Subgroup: CLL + RAI Stage III,IV + Fludara Refractory + IV Administration**

**#Events: 3**                      **No analysis given sample size**

**(f) ITT Disease Free Survival (Months):**

**#Events: 20**  
**#Censored: 4 (16.7%)**  
**Median: 7.46 months**  
**95% CI: [3.78, 13.63]**

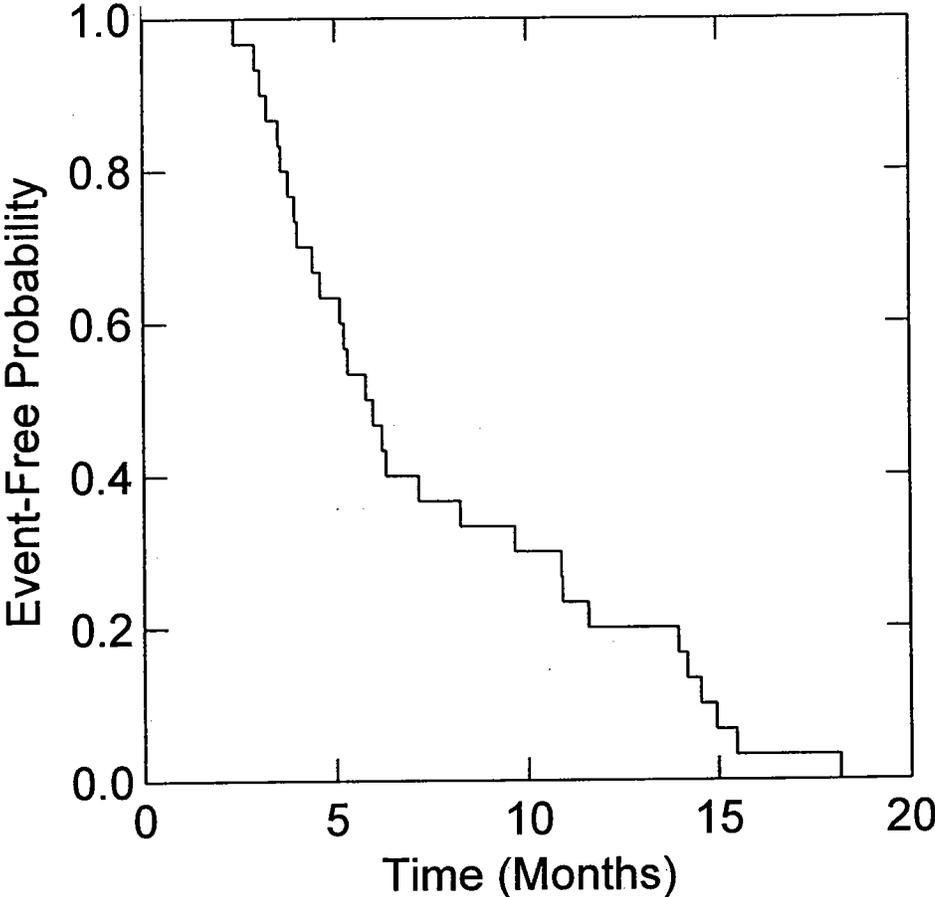
**(g) ITT Survival (Months):**

**#Events: 10**  
**#Censored: 14 (58.3%)**  
**Median: 30.26 months**  
**95% CI: [7.09, \_\_\_\_\_]**

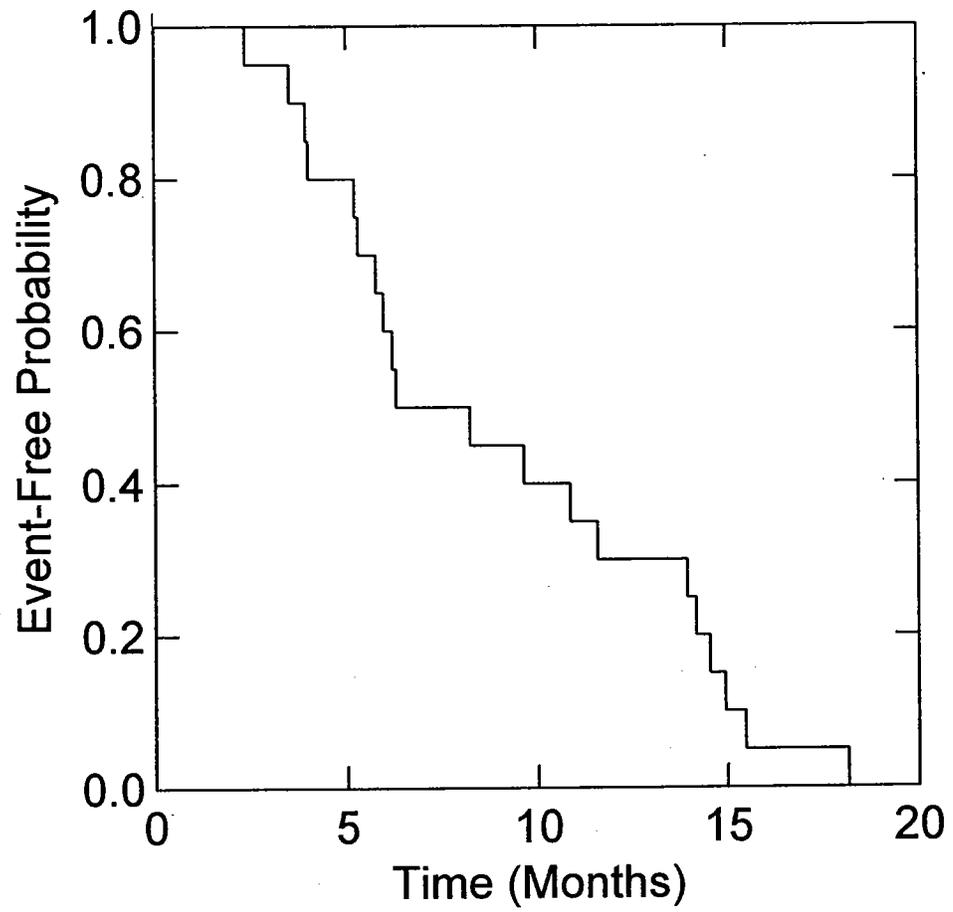
**(h) ITT Time to Treatment Failure (Months):**

**N = 23 (One case had questionable dates)**  
**#Events: 21**  
**#Censored: 2 (8.7 %)**  
**Median: 5.72 months**  
**95% CI: [1.84, 11.33]**

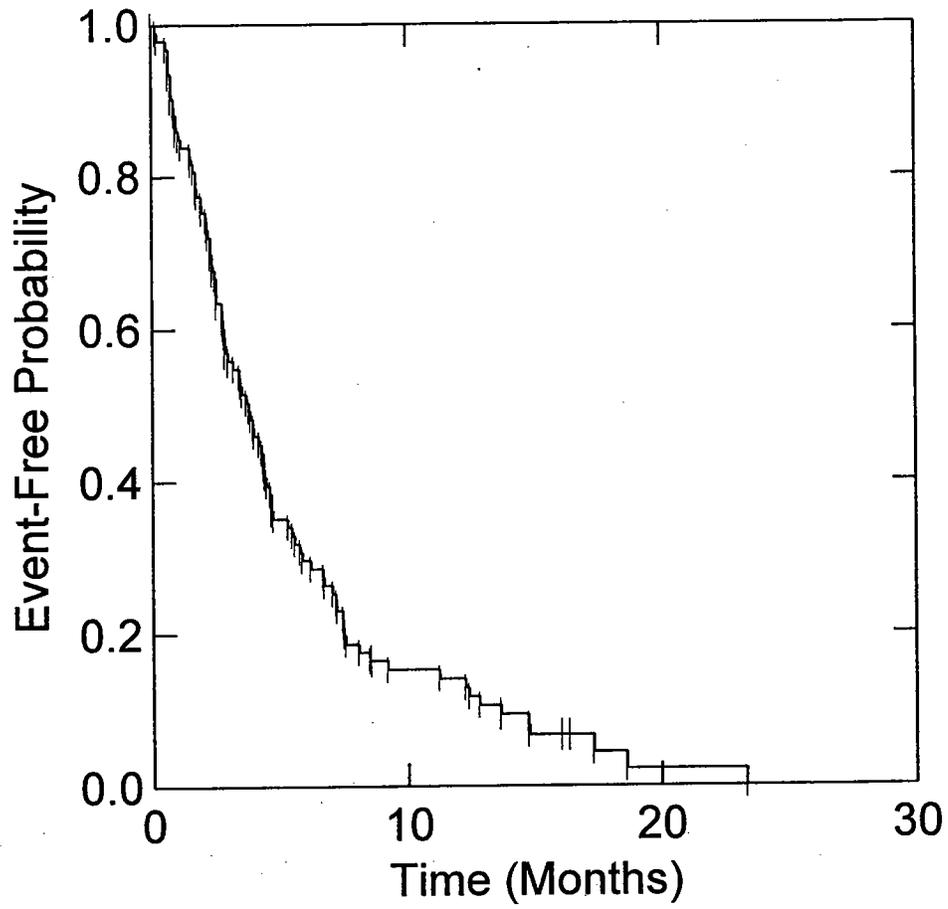
# #211/ Response Duration



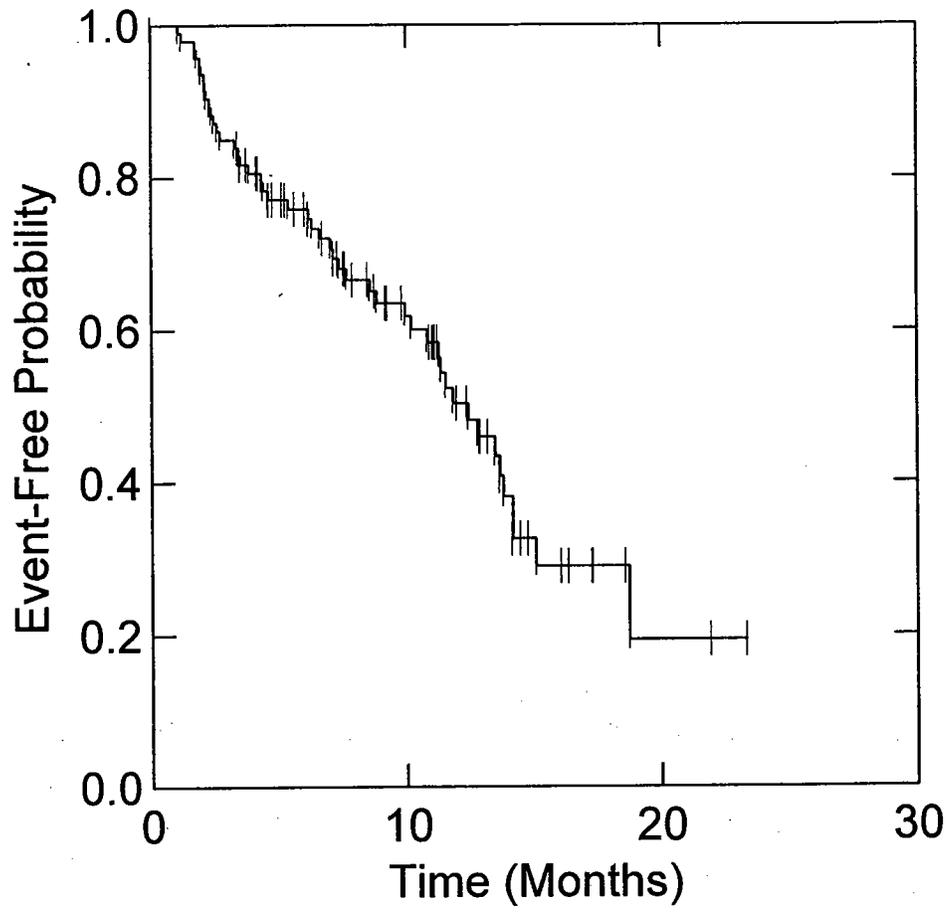
# #211 / Subgroup / Response Duration



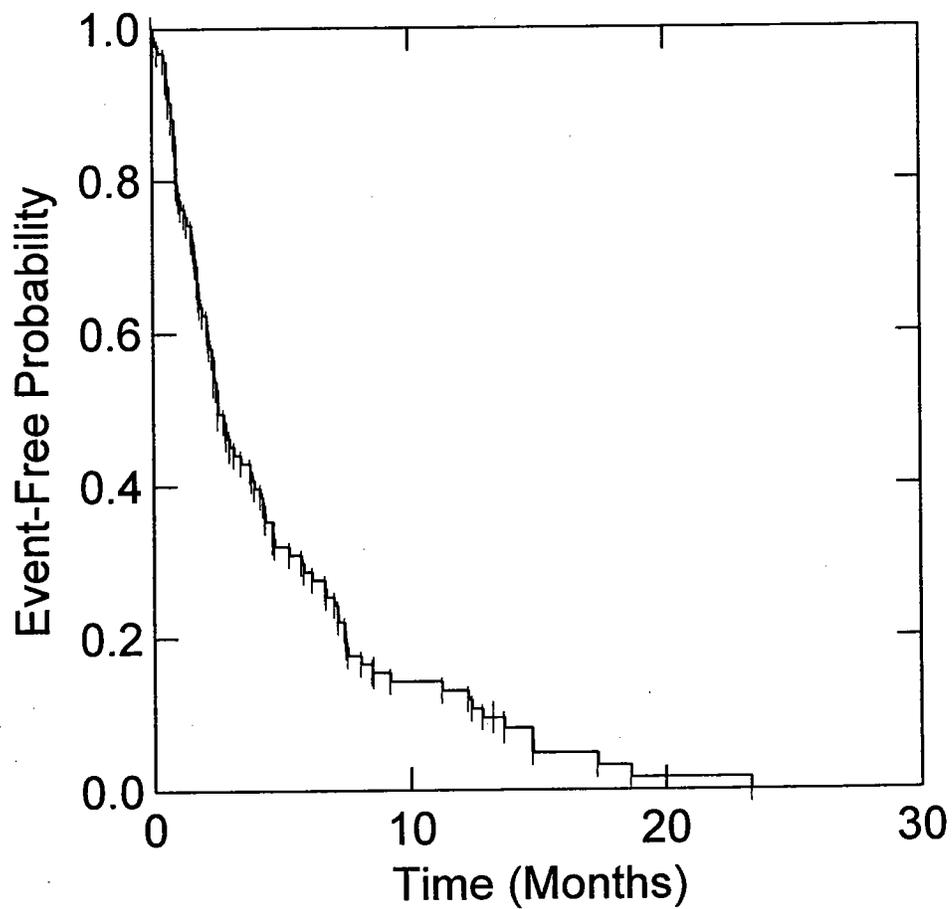
# #211 / Disease Free Survival



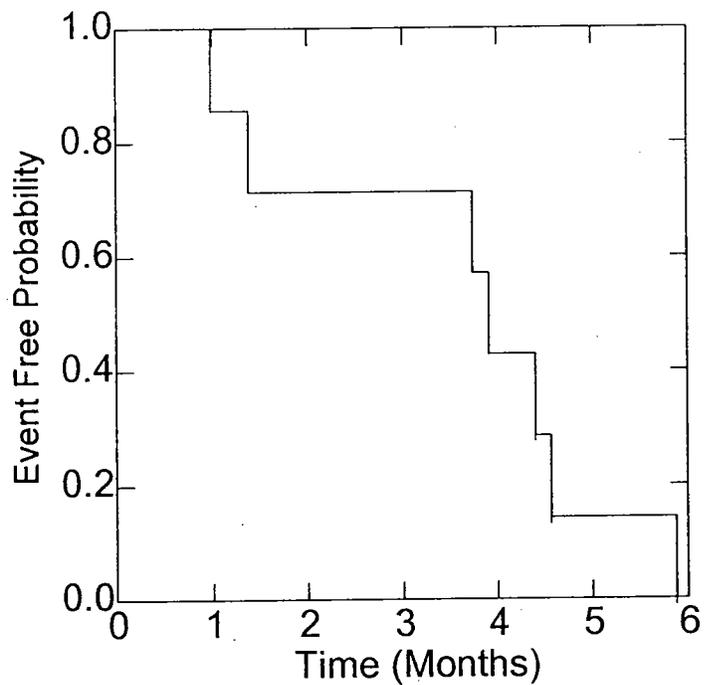
# #211 / Survival



# #211 / Time to Treatment Failure

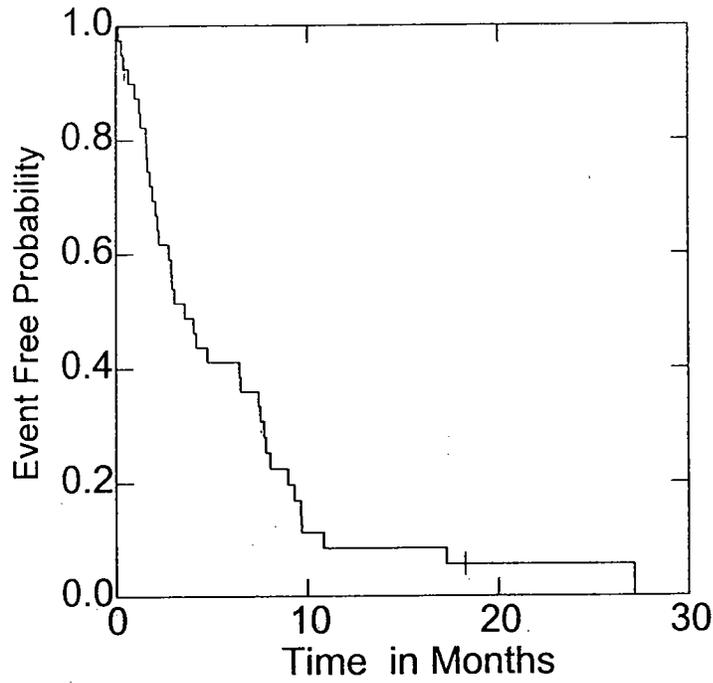


# #05 / RESPONSE DURATION

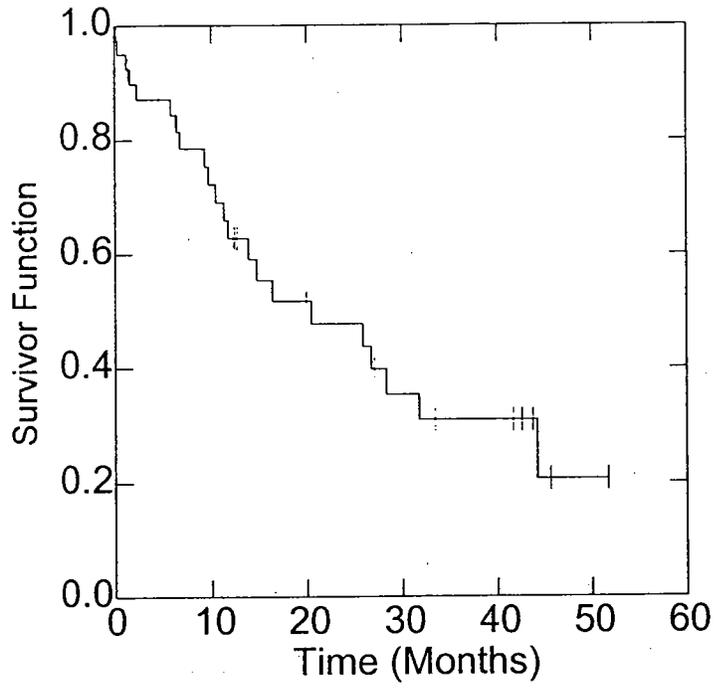


# STUDY 05 / TIME TO PROGRESSION

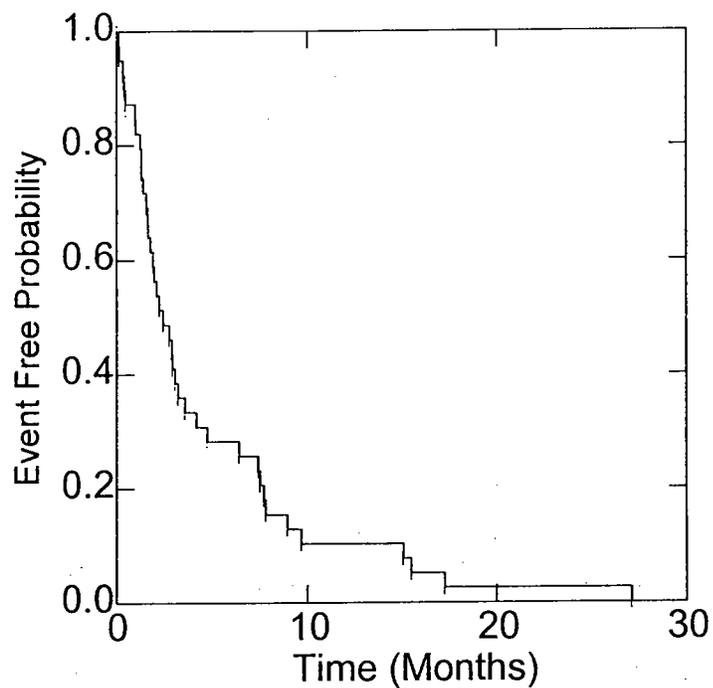
(Really Disease Free Survival)



# #05 / SURVIVAL PLOT



# #05 / TIME TO TREATMENT FAILURE



## 2. STUDY SYNOPSIS

<b>Name of Company:</b> L&I Partners, LP	<b>Name of Finished Product:</b> CAMPATH-1H	<b>Name of Active Ingredient:</b> CAMPATH-1H
<b>Title of Study:</b> A Phase II Study of CAMPATH-1H in Patients With B-Cell Chronic Lymphocytic Leukemia Who Have Received an Alkylating Agent and Failed Fludarabine Therapy		
<b>Investigators and/or Study Centers:</b> This multicenter study included 22 study centers in the United States and Europe.		
<b>Publication (reference):</b> Keating M, Rai K, Flinn I, Jain V, Binet JL, Bolin R, Hillmen P, Hutchinson M, and the CAMPATH-1H collaborative study group. Multicentre study of Campath-1H in patients with chronic lymphocytic leukemia (B-CLL) refractory to fludarabine. <i>Hematologica</i> 1999; 84: 259, SS-1094 (abstr.) (see Appendix 16.1.11)		
<b>Studied Period (years):</b> 1 year (Date of first patient enrollment): 31 March 1998 (Date of last patient enrollment): 31 July 1998 (Status/Data Cut-off): Ongoing for follow-up assessments/31 January 1999		<b>Phase of development:</b> Phase II
<b>Objectives:</b> <u>Primary:</u> To determine the response rate (CR + PR) with CAMPATH-1H in patients with B-cell chronic lymphocytic leukemia (B-CLL) who had received an alkylating agent and failed fludarabine therapy. <u>Secondary:</u> To evaluate the safety profile of CAMPATH-1H in this population and to evaluate the clinical benefit of CAMPATH-1H in this population.		
<b>Methodology:</b> This was a multicenter, open-label, Phase II study of CAMPATH-1H in patients with B-CLL who had received at least one alkylating agent-containing regimen and had documented failure to fludarabine. Patients were eligible if they had failed to achieve a CR or PR or had disease progression while on fludarabine, or had relapsed within 6 months following treatment with fludarabine. Seventy-five patients were required to confirm the target 20% response rate with a lower end of the 95% confidence interval of at least 10%, as agreed upon with the Food and Drug Administration (FDA). The dose of CAMPATH-1H was increased daily during week 1 from an initial dose of 3 mg to 10 mg until a dose of 30 mg IV over 2 hours could be administered without unacceptable side effects (ie, $\leq$ grade 2). All subsequent doses were to be 30 mg IV three times a week for a maximum of 12 weeks. If a patient experienced unacceptable infusion-related events after the first dose or during escalation, the dose escalation could be delayed until the current dose was well tolerated. Patients were to be premedicated with 50 mg diphenhydramine and 650 mg acetaminophen 30 minutes prior to the first CAMPATH-1H infusion, each time the dose of CAMPATH-1H was increased, and thereafter if clinically indicated. Prophylaxis with trimethoprim/sulfamethoxazole DS and famciclovir (or equivalents) was to be administered starting on Day 8 of treatment and continued for a minimum of 2 months following the discontinuation of CAMPATH-1H therapy. The safety of CAMPATH-1H was evaluated after the first and subsequent doses by closely monitoring patients throughout the study for adverse events (AEs), including hematological and clinical chemistry assessments. Formal assessments of disease response were performed by the investigators at weeks 4, 8 and 12. The investigator was to assess response to therapy according to the 1996 NCI Working Group (NCIWG) response guidelines. A bone marrow aspirate and/or trephine biopsy sample were to be obtained 2 months after the clinical and laboratory criteria for a response were met, if appropriate (eg, to confirm a CR). If a patient met all laboratory and clinical criteria for a complete response (CR) by week 4 or 8 of treatment, CAMPATH-1H was to be discontinued and the patient followed. Patients with partial response (PR) or stable disease (SD) by week 8 and who had not improved further since week 4, were to discontinue therapy. All patients were to be followed off therapy at monthly intervals for 6 months and at 3-		

<b>Name of Company:</b> L&I Partners, LP	<b>Name of Finished Product:</b> CAMPATH-1H	<b>Name of Active Ingredient:</b> CAMPATH-1H
month intervals thereafter until alternative treatment was administered or death. A central pathology review panel examined all bone marrow specimens in this study. An independent response review panel determined the response to CAMPATH-1H for each patient according to the 1996 NCIWG response guidelines.		
<b>Number of Patients (planned and analyzed):</b> The study was designed to enroll a total of 75 patients. Ninety-four patients were enrolled in the study and 93 of these patients (73 male; 20 female) were treated with CAMPATH-1H. The increased number of patients over the planned sample size was due to a very rapid enrollment, in particular at the US sites (European sites usually required more time to obtain regulatory approval) and the desire of the Sponsor to enroll at least 25 patients at European sites.		
<b>Diagnosis and Main Criteria for Inclusion:</b> The main criteria for inclusion were: confirmation of B-CLL within 4 weeks prior to study entry, defined as peripheral lymphocyte count $> 5 \times 10^9/L$ , and/or clonal CD5+/CD19+ lymphocytes; and previous therapy with an alkylating agent and documentation of failure to fludarabine therapy. Fludarabine failure was defined as failure to achieve a CR or PR to at least one fludarabine-containing regimen, or disease progression (PD) while on fludarabine treatment, or relapse within 6 months of the last dose of fludarabine. Additional criteria were age 18 years or older; written informed consent; $\leq 5$ previous therapy regimens; WHO performance status of 0, 1, or 2; and creatinine and conjugated bilirubin $\leq 2 \times$ the upper limit of normal unless secondary to infiltration of the liver with CLL. Patients were to require treatment for CLL according to the following criteria: Rai stage III or IV or Rai stage 0-II with at least <u>one</u> of the following: evidence of progressive marrow failure as manifested by the development, or worsening of, anemia and/or thrombocytopenia; autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy; massive (ie, $> 6$ cm below the left costal margin) or progressive splenomegaly; progressive lymphocytosis with an increase of $> 50\%$ over a 2-month period or an anticipated doubling time of less than 6 months; lymphocyte count $> 100,000 \text{ mm}^3$ ; or B symptoms.		
<b>Test Product, Dose and Mode of Administration, Batch Number(s):</b> CAMPATH-1H was administered intravenously at a daily starting dose of 3 mg. The dose was increased to 10 mg when any infusion-related AEs were within acceptable limits; the same procedure was followed when the dose was increased from 10 mg to 30 mg. All subsequent doses of CAMPATH-1H were 30 mg administered three times per week IV diluted in 100 mL of normal saline, infused over 2 hours. Batch numbers: 711077, 711215, 711216		
<b>Reference Therapy, Dose and Mode of Administration, Batch Number(s):</b> Not applicable.		
<b>Duration of Treatment:</b> The CAMPATH-1H dose was increased from 3 mg to 10 mg to 30 mg during week 1, then continued at 30 mg three times weekly for a maximum of 12 weeks.		
<b>Criteria for Evaluation:</b> <b>Efficacy:</b> Response evaluation was performed every 4 weeks while on study. All 93 treated patients were evaluated for response. The 1996 NCI Working Group response criteria were used by an Independent Review Panel to assess the response to CAMPATH-1H in each of the 93 patients. <b>Safety:</b> The safety of CAMPATH-1H was assessed by monitoring the incidence, severity, and relationship of AEs, particularly the incidence of infection and bone marrow toxicity; and changes in physical examination results, vital signs, and clinical laboratory results.		

<b>Name of Company:</b> L&I Partners, LP	<b>Name of Finished Product:</b> CAMPATH-1H	<b>Name of Active Ingredient:</b> CAMPATH-1H
<p><b>Statistical Methods:</b></p> <p>Efficacy analyses are based on an intent-to-treat population: data from all patients who received at least one dose of CAMPATH-1H (N = 93) are included. Safety analyses were also conducted on the population of patients who received at least one dose of study drug.</p> <p>Summary statistics including sample sizes, means, standard deviations, medians, and ranges are provided, where appropriate for continuous variables; frequency and percents are provided for categorical variables.</p> <p>The major response rate (including 95% confidence interval), defined as the proportion of patients with CR+PR over the total number of patients treated, was the primary efficacy endpoint in this study. All confidence intervals for parameters to be estimated were constructed with a significance level of alpha = 0.05. All time-to-event variables, including duration of response, time to disease progression, and survival were analyzed using Kaplan-Meier product-limit survival estimates as implemented in the SAS LIFETEST procedure.</p> <p>Disease response was further characterized by presenting descriptively resolution or improvement in each of the individual 1996 NCIWG response parameters that were present at enrollment (lymphocytosis, malignant infiltration in the bone marrow, lymphadenopathy, splenomegaly, hepatomegaly, anemia, thrombocytopenia and neutropenia).</p> <p>Potential evidence of clinical benefit, including resolution of B-symptoms and other disease-related symptoms, change from baseline in WHO performance status, improvement of 1 or 2 g/dL over baseline in hemoglobin, improvement in patients with grade 3 or 4 thrombocytopenia or neutropenia at enrollment, improvement in patients with bulky lymph nodes (&gt; 5 cm) or massive splenomegaly (&gt; 6 cm) at baseline, and improvement in transfusion requirements from enrollment, were evaluated descriptively.</p> <p>On-study and post-study AEs and SAEs are tabulated by WHOART body system and preferred term. Infections are tabulated by infection type (eg, bacterial, viral) and WHOART preferred term (eg, pneumonia, sepsis). Discontinuations due to AEs are tabulated from study termination data. The occurrence of hematological toxicities was evaluated using NCI Common Toxicity Criteria and the NCIWG grading scale of hematological toxicity for patients with CLL. Descriptive statistics for lymphocyte count across time on study are presented as well as shifts from baseline for Coombs test results and IgG.</p>		
<p><b>Summary and Conclusions:</b></p> <p><b>Patient Characteristics at Study Entry:</b></p> <p>The 93 CLL patients entered in this study represented a severely ill patient population. The median age was 66 years. Median time since initial CLL diagnosis was 6.1 years. The median number of prior chemotherapy regimens was 3 (range: 2 to 7). All patients had been previously treated with alkylating agent(s) and all but one had failed at least one fludarabine-containing regimen (48.4% had never responded to any nucleoside analog). Median time since last CLL therapy was 4.1 months. All patients except one had either Rai stage III/IV (76.3%) or stage 0-II with clear indicators of advanced disease status. In addition, 75 patients (80.6%) were enrolled with other co-morbid conditions. Infections had been reported in the past medical history of 49 patients (52.7%; median 2, range: 1-6) and 31 of the patients (33.3%) had experienced infections in the month prior to study entry. Other cancers had been recorded in 20 (21.5%) of the 93 patients (13 skin cancers, 9 solid tumors). All patients with baseline bone marrow biopsies available (n = 85) presented with bone marrow involvement, most with extensive involvement. More than 50% of the bone marrow was occupied by tumor in 73 (85.9%) of these 85 patients. The majority of patients had enlarged lymph nodes, and 49.5% of the patients had at least one node &gt; 2 cm. Splenomegaly and hepatomegaly were present at baseline in 54.8% and 36.6% of the patients, respectively. Massive (&gt; 6 cm) splenomegaly was present in 29 (37.7%) of 77 patients with spleens (16 patients had prior splenectomy). Forty-one percent of the patients had B-symptoms, 34.4% had asthenia, 9.7% had pain, and 20.4% had other CLL-related symptoms at baseline. Overall, 62 patients (66.7%) were symptomatic due to their CLL at study entry.</p>		

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<p><b>Summary of Efficacy:</b></p> <p><u>Primary endpoint: (Response rate):</u> The overall major response rate (CR + PR) for the 93 patients was 33.3% (95% CI: 24%, 44%) as determined by the independent review panel; two of the 31 responders achieved CR and 29 had PR. This response rate significantly exceeded the target 20% (95% CI: 10%-30%) response rate for demonstration of efficacy as previously agreed to with the FDA. Nine of the PRs had CR with persistent nodules (n = 5) and/or CR with persistent anemia/ thrombocytopenia (n = 6). Fifty-five patients (59.1%) had SD, and seven ( 7.5%) had PD (n = 4) or early discontinuation (n = 3), the latter included in the denominator by the sponsor for determining overall response rate. The rate of response to CAMPATH-1H in patients who had never responded to any nucleoside analog was 31.1% (14/45) versus 35.4% (17/48) in patients who had responded to at least one previous nucleoside analog regimen.</p> <p><u>Time to event variables:</u> The median time to response following initiation of CAMPATH-1H therapy was 1.2 months. Since follow-up is still ongoing, the current data may be too immature to give a reliable estimate of median duration of response. However, the Kaplan-Meier median duration of response is currently 6.7 months (Lower 95% CI: 6.4 ) with 22 (71.0%) of the 31 responders still in remission at the time of the data cut-off. Median time to progression for all patients was 5.8 months (95% CI: 4.3, 7.6); the median time to progression for the responders had not yet been reached. The median survival time for all patients had not yet been reached; 67 (72.0%) of the 93 patients were alive at the data cut-off.</p> <p><u>Individual Parameters of Response:</u> Overall, 66 (98.5%) of the 67 patients with lymphocytosis at baseline (defined as an ALC &gt; 5 × 10<sup>9</sup>/L) and who also had follow-up information, including all of the responders with data available and all but one of the stable disease patients, had resolution of the peripheral blood lymphocytosis (ALC &lt; 4 × 10<sup>9</sup>/L) at the last on treatment assessment. Disease reduction in the bone marrow was substantial with 46.0% of patients with baseline and follow-up data showing complete or &gt; 50% resolution of disease infiltration. Lymphadenopathy completely resolved in 26.2% of patients and an additional 47.7% had ≥ 50% reduction in nodal size at end of treatment. Splenomegaly resolved in 54.3% patients and an additional 28.3% showed ≥ 50% reduction in the spleen size at end of treatment. Hepatomegaly resolved or improved by ≥ 50% in 73.3% of the patients at end of treatment. Twenty-three (39.0%) of 59 patients with abnormal hemoglobin &lt; 11 g/dL at baseline met the 1996 NCIWG response criteria, ie, improved to &gt; 11g/dL or had a &gt; 50% improvement over baseline at the two month follow-up. Twelve (46.2%) of 26 patients with ANC &lt; 1500/μL at baseline met the NCIWG response criteria for ANC response at the 2 month follow-up, ie, improved to ≥ 1500/μL or had a &gt; 50% improvement over baseline. Fifty-three patients had platelet counts &lt; 100,000/μL at baseline. Eighteen patients (34.0%) met the criteria for platelet response by the NCIWG response criteria at the 2 month follow-up, ie, improved to &gt; 100,000/μL or had a &gt; 50% improvement over baseline.</p> <p><u>Clinical benefit:</u></p> <p><u>Disease-related symptoms:</u> B-symptoms resolved entirely in 27 (71.1%) of 38 patients with baseline symptoms. Asthenia completely resolved in 11 (34.4%) of the 32 patients with baseline asthenia, and pain resolved in 4 (44.4%) of 9 patients with pain at baseline. Overall, 29 (46.8%) of the 62 patients with B-symptoms and/or other CLL-related symptoms had resolution of all CLL-related symptomatology with CAMPATH-1H therapy.</p> <p><u>WHO performance status:</u> Performance status (PS) was maintained in the majority of patients during study and follow-up. At study end, 14 (28.0%) of 50 patients with baseline PS 1 had improved to PS 0, and 3 (15.8%) of 19 patients with PS 2 improved to PS 1.</p> <p><u>Hematologic improvements leading to clinical benefit:</u> Among the 37 patients who did not receive RBC transfusions or erythropoietin on treatment, 19 (51.4%) had a ≥ 1 g/dL increase in hemoglobin; nine of these patients (24.3%) had increases ≥ 2 g/dL. Of the 9 patients with grade 4 thrombocytopenia at baseline (platelet count &lt; 25 × 10<sup>9</sup>/L), 4 of 5 with data available improved to a platelet count &gt; 25 × 10<sup>9</sup>/L and 3 of these had a platelet count &gt; 50 × 10<sup>9</sup>/L at the 2 month follow-up. Of the 10 patients with grade 3 thrombocytopenia at</p>		

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<p>baseline (platelet count <math>\geq 25</math> and <math>&lt; 50 \times 10^9/L</math>), 4 of 8 with data available improved to <math>\geq 50 \times 10^9/L</math> and one of these improved to <math>\geq 100 \times 10^9/L</math> at the 2 month follow-up. Of the 10 patients with grade 4 neutropenia (ANC <math>&lt; 0.5 \times 10^9/L</math>) at baseline, 7 of 9 with data available improved to <math>\geq 1.0 \times 10^9/L</math> at the 2 month follow-up, and 6 of those improved to <math>\geq 1.5 \times 10^9/L</math>. Of the 7 patients with grade 3 neutropenia (<math>0.5 \leq \text{ANC} &lt; 1.0</math>), 4 of 5 with data available improved to <math>\geq 1.0 \times 10^9/L</math> and 2 of those improved to <math>\geq 1.5 \times 10^9/L</math>.</p> <p>Improvements in bulky lymphadenopathy: Seven (50.0%) of 14 patients with lymphadenopathy <math>&gt; 5</math> cm had a <math>\geq 50\%</math> reduction in the length of the largest node at the end of treatment assessment, and 9 (64.3%) of the 14 patients had a <math>\geq 50\%</math> improvement in the overall sum of the measurements of all nodes.</p> <p>Improvement in massive splenomegaly: Of the 29 patients with spleen <math>&gt; 6</math> cm at baseline, 21 (72.4%) had a <math>\geq 50\%</math> improvement including 10 patients (34.5%) with complete resolution of massive splenomegaly.</p>		
<p><b>Safety Results:</b></p> <p>CAMPATH-1H was administered as planned in the majority of patients. The target 30 mg dose was reached within the first 5 days in approximately 90% of the patients. In addition, ~90% of the patients (n = 84) were treated with 10 or more 30 mg doses of CAMPATH-1H, and 50 patients (53.8%) were treated with 21 to <math>&gt; 30</math> doses of study drug. Only one patient discontinued the study due to an AE (grade 4 dyspnea and bronchospasm) during the first CAMPATH-1H infusion.</p> <p>All 93 patients had at least one AE on study. In 32 patients (34.4%), all reported events had a maximum severity of grade 1 or 2. Thirty-two patients (34.4%) had at least one grade 3 event and 29 (31.2%) had at least one event of grade 4 severity. The most frequently reported events regardless of severity grade were acute, infusion related events including rigors (89.2%), fever (83.9%), nausea (50.5%), vomiting (36.6%), and rash (33.3%). There was a substantial decrease in the incidence of these infusion-related events from Week 1 to Week 2 with a further decrease reported for treatment beyond 2 weeks. This decrease in the reported rate of events was also observed for grade 3 or 4 acute infusion-related events, although these severe events were infrequent at all times.</p> <p>The majority of AEs, regardless of relationship to study drug, had a maximum severity grade 1 or 2. The most commonly reported events of grade 3 or 4 severity were fever (19.4%), rigors (12.9%), dyspnea (11.8%), and pneumonia (11.8%). The majority of the most commonly reported drug-related events also had a maximum severity of grade 1 or 2 except for pneumonia and sepsis, for which grade 3 or 4 events were reported in 11 patients (11.8%) and 9 patients (9.7%), respectively.</p> <p>Forty-four patients (47.3%) experienced SAEs on-study, in 41 patients (44.1%) these events had a maximum severity of grade 3 or 4. No serious, unexpected and drug-related events occurred during this study. SAEs reported in more than 5% of the patients included fever, pneumonia, sepsis, dyspnea, granulocytopenia, anemia, neutropenic fever, asthenia, CMV infection, thrombocytopenia, and rigors.</p> <p>As of the data cut-off, a total of 23 (24.7%) of the 93 patients had discontinued the study in association with adverse events including 20 patients (21.5%) who were discontinued due to events likely related to CAMPATH-1H. The most common reason for discontinuation was infection reported as leading to study termination in 7 patients (7.5%) and as a terminal event in 3 (3.2%). Other reasons for treatment termination included fever or fatigue in 4 patients (4.3%); thrombocytopenia, pancytopenia or immunosuppression in 4 patients (4.3%); infusion-related events in 3 patients (3.2%); and death due to disease progression and pulmonary embolism in one patient each.</p> <p>Not unexpectedly in a patient population with advanced stage CLL and multiple prior therapies, infections were reported during this study. During study, 50 (53.8%) of the 93 patients experienced at least one infection, which had a maximum severity of grade 1 or 2 in 26 of the patients (28.0%). Grade 3 or 4 infections were reported in 24 patients (25.8%). The most commonly reported grade 3 or 4 infections on study were pulmonary infections including pneumonia and pneumonitis (12 patients, 12.9%) and sepsis (9 patients, 9.7%). Except for the first</p>		

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<p>month of CAMPATH-1H therapy, monthly incidence of all infections regardless of severity grade was consistently lower than that recorded in the one month prior to entry. Only 10 patients (10.8%) had grade 3 or 4 infections in the first month on study. The incidence of these major infections was similar in Month 2 (8.2%) and then decreased to 2.3% at Month 3. A sustained decrease in the number of patients with major infections was observed post-study. At months 5 and 6 in follow-up, only 1 and 2 patients, respectively, had a severe infection.</p> <p>Opportunistic infections were uncommon, with only 10 patients (10.8%) experiencing OIs during treatment (grade 2 in 3 patients), demonstrating the effectiveness of the prescribed prophylaxis. The most common OI was CMV infection (n = 7). Four of these CMV infections were grade 3 in severity; no grade 4 CMV infections were reported. One patient experienced PCP pneumonia, one, <i>Aspergillus</i> pneumonia, and one, rhinocerebral mucormycosis on study. Seven OIs were grade 3 or 4 in severity; one patient died as a result of the infection (rhinocerebral mucormycosis). The patient who developed and recovered from PCP on study had not received prophylaxis with trimethoprim/sulfamethoxazole. Two of the patients who developed CMV infection had not received antiviral prophylaxis as mandated by the protocol. OIs were also uncommon in the follow-up period (total of 6 infections in 6 patients). Two of these OIs (PCP, <i>Aspergillus</i> pneumonia) were fatal. The PCP occurred in an elderly patient with Rai stage IV B-CLL at baseline in whom prophylactic trimethoprim/sulfamethoxazole was discontinued 2 days (instead of 2 months as per protocol) after the last CAMPATH-1H dose.</p> <p>Nine deaths (9.7%) occurred during treatment or within 30 days of the last dose of CAMPATH-1H. Five (5.4%) were associated with infection and considered likely related to CAMPATH-1H. Seventeen patients died more than 30 days after their last dose of CAMPATH-1H. Four of these deaths were considered related to CAMPATH-1H. Thus, at the data cut-off date, 26 patients (28.0%) had died during study or follow-up, with 9 (9.7%) related deaths. Twenty-three of the 26 patients who died had failed to respond to CAMPATH-1H.</p> <p>Transient decreases in hemoglobin were noted during the study. Hemoglobin grades equal to or better than baseline grade were reported for 65.1%, 49.4%, and 40.3% of patients at weeks 1 to 2, 3 to 4 and 5 to 8, respectively. Hemoglobin levels recovered at the end of treatment with further improvement noted at the 2 month post-treatment follow-up, when 72.7% and 90.1% of patients with data available, respectively, had hemoglobin grades that were equal to or had improved over their baseline grade. Transfusion requirements were related to baseline hemoglobin levels. Forty-one percent of patients with hemoglobin levels of grade of 0 to 1 required transfusions on study compared to 91.2% of patients with baseline grade of 2 or 3.</p> <p>Although thrombocytopenia was common during study, recovery was noted at study end and 2-months post-treatment. Platelet count grades equal to or better than baseline grade were reported for 33.3%, 59.3%, 61.4% and 68.2% of patients at weeks 1 to 2, 3 to 4, 5 to 8 and 9 to last infusion, respectively. Further improvement was noted at the 2 month post-treatment follow-up when 84.5% of patients had platelet count grades equal to or better than their baseline grade. The overall percentage of patients with grade 3 or 4 thrombocytopenia was 12.7% at the 2 month follow-up compared to 20.4% at baseline. Requirement for platelet transfusions was markedly less for patients with baseline platelet count grade 0 or 1 as compared to patients with grade 2, 3 or 4 (14.8% compared to 51.3%).</p> <p>All patients developed lymphopenia during the study as a direct effect of the pharmacologic effect of CAMPATH-1H. The median absolute CD3+/CD4+ lymphocyte count reached its nadir at week 4 (<math>0.002 \times 10^9/L</math>) but increased significantly (<math>0.072 \times 10^9/L</math>) by the week 12 assessment. Further recovery was noted 2 and 4 months post-treatment, at which time the median values were <math>0.212 \times 10^9/L</math> and <math>0.286 \times 10^9/L</math>, respectively. Similar results were observed for the CD3+/CD8+ cell population.</p> <p>No significant changes of clinical relevance were observed in the clinical biochemistry parameters during this study.</p>		

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<p>In summary, CAMPATH-1H therapy was delivered as planned to the majority of the 93 severely ill patients with advanced, refractory CLL in this study. Most adverse events were mild or moderate, occurred in association with the first few infusions, and their incidence markedly diminished after the first week of therapy. Although hematologic toxicity was common, nadirs recovered during study or shortly thereafter in most patients. Similarly, lymphocyte recovery started to occur at the end of study. The incidence of infections and the number of deaths associated with infection in these advanced-stage, fludarabine-refractory CLL patients are not dissimilar from those in studies with fludarabine and other nucleoside analogs in this disease. The safety results in the present study compare favorably with previous CAMPATH-1H studies in which premedication and prophylactic anti-infectives were not routinely prescribed.</p>		
<p><b>Conclusions:</b>            CAMPATH therapy was associated with a substantial objective response rate of 33% which significantly exceeded the 20% target set forth in the protocol. In addition, consistent tumor burden reduction was seen in the majority of the patients including both responders and stable disease patients which was associated with improvement or resolution of disease-related organ involvement, hematologic abnormalities and disease-related B-symptoms and other symptoms. This was accomplished with a reasonably well-tolerated therapy considering the severely ill condition of this patient population at baseline. Most of the reported events occurred during the initial infusions and were mild or moderate in severity. The incidence of infections was not dissimilar to that seen with nucleoside analogs. In addition, the incidence of OIs in this study was low and appears to be less than that observed in previous studies with CAMPATH-1H in patients with B-CLL and NHL (125-005-C92 and 125-009-C92). It is concluded that CAMPATH-1H showed a favorable benefit to risk ratio in these heavily pretreated patients with advanced B-CLL, having failed fludarabine and without any effective therapy currently available.</p>		
<p><b>Date of the report:</b> 27 November 1999</p>		