Protocol CAM307: A Phase 3 Study to Evaluate the Efficacy and Safety of Front-line Therapy with Alemtuzumab (Campath®) vs Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia

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NAME OF SPONSOR/COMPANY

Genzyme Corporation
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INVESTIGATORS AND STUDY CENTER(S)

This was a multi-center study conducted at 44 study centers. There were 9 centers in the United States and 35 centers in Europe.

STUDIED PERIOD

Date of first patient randomized: 05 DEC 2001
Date of last patient randomized: 15 JUL 2004
Date last patient completed study drug: 04 MAY 2005
Date of data cut off: 01 JUN 2006

PHASE OF DEVELOPMENT

Phase 3

OBJECTIVES

The primary objective of this study was to demonstrate that Campath is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS).

The secondary objectives of this study were to evaluate:

- Complete response (CR) and overall response rate (ORR) using the 1996 National Cancer Institute Working Group (NCIWG) criteria
- Duration of response
- Survival
- Time to treatment failure
- Time to alternative treatment
- Safety

METHODOLOGY

This was a Phase 3, open-label, multicenter, randomized, comparative study of Campath versus chlorambucil as front line therapy in patients with progressive B-CLL. Eligible patients were to have previously untreated, Rai stage I-IV disease, and be experiencing progression of their B-CLL requiring treatment. Patients were randomized on a 1:1 basis to either the Campath or chlorambucil treatment group. Patients enrolled in the Campath treatment group received a maximum of 12 weeks of Campath. Patients enrolled in the chlorambucil treatment group received a maximum of 12 months of chlorambucil. Response to treatment was to be determined by the investigator based on the 1996 NCIWG criteria. The investigator was to determine the date of progression for each patient based on the definitions provided in the protocol. An independent response review panel (IRRP) was to determine response to treatment and the date of progressive disease (PD) for each patient using the same assessment criteria. The IRRP members were to be blinded to the treatment assignment in order to provide an unbiased assessment.

During the post-treatment follow-up period, all patients were to be evaluated for the assessment of disease status, safety, and survival. All patients were to be followed on a monthly basis until the time of disease progression, administration of alternative therapy, or through 18 months following the first dose of study medication, whichever was soonest. For those patients who had not progressed as of the 18-month post-first dose time point, follow up was to continue every 3 months until the time of progression or requirement for alternative therapy. Patients who progressed on study were to be followed every 3 months for survival.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)

The planned sample size of this study was 284 patients (142 per treatment arm). Patients were to be randomized on a 1:1 basis to receive either Campath (Arm A) or chlorambucil (Arm B).

The total enrollment in the study was 297 patients (213 male; 84 female); 149 (50%) of patients were randomized to Campath arm and 148 (50%) of patients were randomized to chlorambucil arm.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

After signing a written informed consent, patients who met the following criteria were eligible to participate in the study:

- Histopathologically confirmed diagnosis of B-CLL with CD5, CD19, or CD23 positive clone
- Rai stage I through IV disease with evidence of progression as evidenced by the presence of one or more of the following:

− Disease-related B symptoms (fever of greater than 38°C [100.5°F] for ≥2 weeks without evidence of infection, night sweats without evidence of infection, weight loss >10% within previous 6 months).

− Evidence of progressive marrow failure as manifested by:

o a decrease in hemoglobin to <11 g/dL, or

o a decrease in platelet count to $<100 \times 10^9$/L within the previous 6 months, or

o a decrease in absolute neutrophil count (ANC) to $<1.0 \times 10^9$/L within the previous 6 months.

− Progressive splenomegaly to >2 cm below the left costal margin or other organomegaly with progressive increase over 2 consecutive clinic visits ≥2 weeks apart.

− Progressive lymphadenopathy with at least 5 sites of involvement with either two nodes at least 2 cm in longest

diameter or one node ≥5 cm in longest diameter with progressive increase over 2 consecutive clinic visits ≥2 weeks apart.

− Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of <6 months.

- Received no previous chemotherapy for B-CLL
- Life expectancy of at least 12 weeks; World Health Organization (WHO) performance status of 0, 1, or 2; and 18 years of age or older
- Serum creatinine ≤2.0 × the institutional upper limit of normal (ULN) value
- Adequate liver function as indicated by a total bilirubin, aspartate transferase (AST), and alanine transferase (ALT) ≤2 × the institutional ULN value, unless directly attributable to the disease
- Female patients with childbearing potential had to have a negative serum pregnancy test within 2 weeks prior to randomization. Male and female patients had to agree to use an effective contraceptive method while on study treatment, if appropriate, and for a minimum of 6 months following study therapy

Patients who met following criteria would be excluded:

- ANC $<0.5 \times 10^9$/L or platelet count $<10 \times 10^9$/L
- Medical condition requiring chronic use of oral corticosteroids
- Autoimmune thrombocytopenia
- Previous bone marrow transplant
- Use of investigational agents within previous 30 days
- Positive for human immunodeficiency virus (HIV)
- Past history of anaphylaxis following exposure to rat or mouse-derived complementarity determining region (CDR) grafted humanized monoclonal antibodies
- Active infection
- Patients with serious cardiac or pulmonary disease that could interfere with their ability to participate in the study
- Recent documented history (within 2 years) of active tuberculosis (TB), current active TB infection, currently receiving anti-tuberculous medication (e.g., isoniazid, rifampin, streptomycin, pyrazinamide, or others).
- Active secondary malignancy
- Central nervous system (CNS) involvement with chronic lymphocytic leukemia (CLL)
- Other severe, concurrent diseases or mental disorders
- Pregnant or lactating women
- Positive quantitative cytomegalovirus (CMV) by polymerase chain reaction (PCR) assay (using the laboratory normal ranges)

Patients with a diagnosis of mantle cell lymphoma

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Campath was to be administered intravenously (IV) daily at a starting dose of 3 mg and escalated to 30 mg as tolerated. The dose was to be increased from 3 mg to 10 mg when the dose was well tolerated; the same procedure was to be

followed when the dose was increased from 10 mg to 30 mg. All subsequent doses of Campath were to be 30 mg administered three times per week (maintenance dose) for up to 12 weeks, inclusive of dose escalation period(s).

DURATION OF TREATMENT

Patients treated with Campath received thrice weekly treatment for a maximum of 12 weeks of therapy (inclusive of dose escalation period(s)). Patients treated with chlorambucil received treatment every 28 days for a maximum of 12 cycles.

Patients treated with Campath and chlorambucil were assessed for disease status every 4 weeks during therapy by physical exam, chest x-ray as clinically indicated, and analysis of blood and bone marrow by flow cytometry.

Study treatment with either Campath or chlorambucil was to stop if there was evidence of progressive disease, the investigator thought a change of therapy would be in the best interest of the patient, the patient requested discontinuation, there was an unacceptable toxicity, patient developed autoimmune anemia or autoimmune thrombocytopenia, the patient became pregnant or failed to use adequate birth control (for those patients who were able to conceive), or the patient was unable to comply with the protocol.

Treatment with Campath was also discontinued if there was no evidence of CLL by flow cytometry analysis of the bone marrow or if there was no improvement since baseline after 4 or 8 weeks of Campath treatment. Patients in the Campath arm who had evidence of progressive disease >6 months after achieving a CR or partial response (PR) could receive a second course of Campath.

Treatment with chlorambucil was also discontinued at any time if there was a complete remission, or a response that achieved a plateau, i.e., no further reduction in lymph node size, organomegaly, or lymphocyte count over 2 months of treatment.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

Chlorambucil was to be administered at a dose of 40 mg/m^2 orally once every 28 days. Treatment was to be repeated every 28 days for a maximum of 12 cycles.
Chlorambucil for oral administration was commercially available.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Efficacy
Response evaluation was performed every 4 weeks for all patients while on study therapy and at the completion of therapy or at the time of early discontinuation. The investigators were to use the 1996 NCIWG response criteria to assess response to study treatment. In addition, the IRRP assessed response using the 1996 NCIWG response criteria.

Criteria for Evaluation – Safety
The safety was assessed by monitoring the incidence, severity, and relationship of adverse events (AEs) on the basis of clinical laboratory evaluations, physical examinations, and vital signs. Adverse events were to be graded by the investigator using National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0, 30 April 1999. The laboratory result parameters were analyzed using the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 3.0). A Data and Safety Monitoring Board (DSMB) was convened to review formally the safety and efficacy of study treatment. Procedures governing the convening and execution of the responsibilities of the DSMB were specified in a separate DSMB Charter document.

STATISTICAL METHODS

Statistical Methods – Efficacy

All randomized patients were to be evaluated for efficacy on an intent-to-treat (ITT) basis. The primary efficacy endpoint in this study was PFS, defined as the time from randomization date to first objective documentation of disease progression or death due to any cause. This study was designed to detect a 50% improvement in PFS in either the Campath or chlorambucil treatment arm (80% power, α=0.05 two-sided). Differences in PFS in the Campath versus chlorambucil arm were tested using the log-rank test, stratified by Rai stage (I-II vs III-IV). The primary analysis was to be performed on an ITT basis for all randomized patients.

The primary and secondary efficacy analyses were based on the IRRP's determination of eligibility (Rai stage and B-CLL diagnosis), response, and date of disease progression after response for all patients.

Summary statistics included sample size, mean, standard deviation, median, and range for continuous variables, where appropriate; number and percent were to be used for categorical variables.

All confidence intervals for parameters to be estimated were constructed with a significance level of alpha = 0.05. Time to event distributions of PFS, duration of response, survival, time to treatment failure, and time to alternative treatment were estimated using Kaplan-Meier method.

Statistical Methods – Safety
Toxicities, including laboratory results, were evaluated using the NCI Common Toxicity Criteria. Adverse events, serious adverse events, and infections were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 9).

SUMMARY / CONCLUSIONS

Summary / Conclusions (Patients)
A total of 297 patients with previously untreated, progressive B-CLL were enrolled in the study, 149 in the Campath arm and 148 in the chlorambucil arm; 3 patients withdrew prior to being treated with study drug (2 in the Campath arm and 1 in the chlorambucil arm). Patient enrollment was stratified by site, Rai stage (I-II vs III-IV), WHO performance status (0-1 vs 2), age (<65 years vs ≥ 65 years), sex, and maximum lymph node status (none palpable or <5 cm vs ≥ cm) (Table 1). Patient randomization was controlled by an Interactive Voice Response System (IVRS) and resulted in a very good balance across the treatment arms for stratification factors.

Characteristics	**Campath (N=149) n (%)**	**Chlorambucil (N=148) n(%)**
Rai stage group (Investigator)		
I-II	98 (65.8)	95 (64.2)
III-IV	51 (34.2)	51 (34.5)
0	.	2 (1.4)
WHO performance status		
0 or 1	143 (96.0)	143 (96.6)
2	5 (3.4)	5 (3.4)
Missing	1 (0.7)	
Age group		
<65	96 (64.4)	96 (64.9)
≥65	53 (35.6)	52 (35.1)
Sex		

Male	106 (71.1)	107 (72.3)
Female	43 (28.9)	41 (27.7)
Maximum lymph node status		
<5 cm	107 (71.8)	104 (70.3)
≥5 cm	33 (22.1)	34 (23.0)
No enlarged lymph nodes	8 (5.4)	10 (6.8)
Not reported	1 (0.7)	--

Summary / Conclusions (Efficacy)

Progression Free Survival Results

All randomized patients were evaluated for efficacy on an ITT basis. The primary objective for this protocol was to compare PFS outcome between the two treatment arms.

There were 191 events of PD or death (82 in the Campath arm and 109 in the chlorambucil arm) used for the primary analysis of PFS. The comparison between treatment arms, tested using the log-rank test stratified by Rai stage (I-II vs III-IV), is highly significant, p=0.0001 (see Figure 1). The hazard ratio of PFS estimated after adjustment by Rai stage (I-II vs III-IV) is 0.58 (95% confidence interval (CI: 0.431, 0.768), indicating that the risk of progression or death in B-CLL patients treated with Campath as first line therapy is 42% less than for those treated with chlorambucil.

The overall Kaplan-Meier median PFS was 14.6 months (95% CI: 12.3, 21.7 months) for patients in the Campath arm and 11.7 months (95% CI: 9.9, 13.2 months) for patients in the chlorambucil arm (figure 1 The estimated crude hazard ratios illustrate the separation of the 2 Kaplan-Meier curves over time (see Figure 1), suggesting a stronger benefit of Campath treatment at later time points on study compared to immediately after the start of treatment. At 6 months on study (after randomization), the estimated risk of progression or death is 9% less for Campath patients than that for chlorambucil patient. The estimated decrease in the risk of progression or death is 31% less and 70% less for Campath patients than for chlorambucil patients at 12 months and 18 months on study, respectively. Patients with Rai stage I-II disease had a longer PFS than patients with Rai stage III-IV disease. Patients with Rai stage I-II disease in the Campath arm had the best outcome of the 2 treatment arms and Rai stage groups; Kaplan-Meier median PFS was 21.7 months (95% CI: 14.0, not reached) vs 12.5 months (95% CI: 10.9, 14.8) in the chlorambucil arm. For patients with Rai stage III-IV disease, the Kaplan-Meier median PFS was 10.2 months (95% CI: 8.5, 18.1 months) for patients in the Campath arm and 8.5 months (95% CI: 4.7, 12.9 months) for patients in the chlorambucil arm.

In an exploratory analysis, the Kaplan-Meier median PFS was 14.6 months (range: 12.0 to 24.4 months) for patients reporting a CMV event during therapy, which compares to the overall PFS (n=149) of 14.6 months (range: 12.3 to 21.7 months). This result suggests that the treatment efficacy as measured by PFS was not compromised in patients who experienced CMV events while on study.

Results for response rate, duration of response, overall survival, time to treatment failure, and time to alternative treatment are summarized below and presented in Table 2, Summary of Efficacy Results.

Response Rate Results

The overall response rate (ORR=CR + PR) per the IRRP assessment was significantly higher for the Campath-treated patients compared to the chlorambucil treated patients. Specifically, 83.2% of patients in the Campath arm (95% CI: 76.2%, 88.8%) had a response of either CR or PR compared to 55.4% of patients in the chlorambucil arm (95% CI: 47.0%, 63.6%), p <0.0001. Likewise, there was a significantly higher percentage of CR patients in the Campath arm compared to the chlorambucil arm, 24.2% vs 2.0%, respectively, p <0.0001.

Among the Rai stage I-II patients, a higher ORR was observed in the Campath arm, 87.1%, compared to the 63.5% ORR in the chlorambucil arm. Similarly, a higher ORR was observed among the Rai stage III-IV patients, 76%, in the Campath arm compared to 38.8% ORR in the chlorambucil arm.

Among the Rai stage I-II patients, a higher CR rate was observed in the Campath arm, 29.0%, compared to the 3.1% CR rate in the chlorambucil arm. A CR rate of 14.0% was observed for the Rai stage III-IV patients in the Campath arm compared to no CR for the Rai stage III-IV patients in the chlorambucil arm.

Elimination of minimal residual disease, (CRm-: a CR by NCIWG criteria and no evidence of disease in the bone marrow by flow cytometry analysis) occurred in 11 of 36 complete responders to alemtuzumab versus none to chlorambucil. Two CRm- patients were determined by the IRRP to be Rai Stage 0 at study entry. Among the remaining 9 patients with Rai I-IV as assessed by the IRRP, there was only 1 report of PD at the time of data cut-off, which had occurred at 24.4 months.

In patients with CMV infection, ORR was 83% with 26% CR, and in patients with CMV viremia ORR was 92% with 29% CR.

Duration Of Response Results
The Kaplan-Meier median duration of IRRP-determined best response was 16.2 months (95% CI: 11.5, 23.0 months) for patients in the Campath arm and 12.7 months (95% CI: 10.2, 14.3 months) for patients in the chlorambucil arm.

Overall Survival Results
There was no difference in overall survival with a total of 24 deaths in the Campath arm (i.e., 83.9% alive), and 24 deaths in the chlorambucil arm (i.e., 83.8% alive). There were not enough events or long enough follow-up data to be able to detect a difference in overall survival.

Time To Treatment Failure Results
The overall Kaplan-Meier median time to treatment failure was 9.8 months (95% CI: 7.8, 13.4 months) for patients in the Campath arm and 11.3 months (95% CI: 9.3, 12.9 months) for patients in the chlorambucil arm with a non-significant hazard ratio of 0.82 (95% CI: 0.624, 1.077) favoring the Campath arm.

Time To Alternative Treatment Results
The overall Kaplan-Meier median time to alternative treatment was 23.3 months (95% CI: 20.7, 31.0 months) for patients in the Campath arm and 14.7 months (95% CI: 12.6, 16.8 months) for patients in the chlorambucil arm. The difference in treatment effect on time to alternative treatment between Campath and chlorambucil was highly statistically significant (p=0.0001, stratified log-rank test). The hazard ratio is 0.54 (95% CI: 0.391, 0.742) after adjustment by Rai stage group (I-II vs III-IV), meaning that the risk of receiving alternative therapy or death for B-CLL patients treated first-line with Campath is 46% less than for those treated with chlorambucil.

	Campath (N=149)	**Chlorambucil (N=148)**	**P value**
Median Progression Free Survival (months) (95% CI) †	14.6 (12.3, 21.7)	11.7 (9.9, 13.2)	0.0001*
Hazard Ratio (95% CI)	0.58 (0.431, 0.768)		
Overall Response Rate (%)	83.2	55.4	<0.0001**
Complete Response (%)	24.2	2.0	<0.0001***
MRD Negative (CRm Negative) (%)	7.4†††	0	0.0008***
Partial Response (%)	59.1	53.4	Not Applicable
Median Duration of Best Response (CR or PR) (months) (95% CI)	16.2 (11.5, 23.0)	12.7 (10.2, 14.3)	Not Applicable
Overall Survival (% Censored) ††	83.9	83.8	Not Significant
Median Time to Treatment Failure	9.8 (7.8, 13.4)	11.3 (9.3, 12.9)	Not Significant

(months) (95% CI) †			
Hazard Ratio (95% CI)	0.82 (0.624, 1.077)		
Median Time to Alternative Treatment (months) (95% CI) †	23.3 (20.7, 31.0)	14.7 (12.6, 16.8)	0.0001*
Hazard Ratio (95% CI)	0.54 (0.391, 0.742)		

* Stratified log-rank test
**Pearson's chi-square test
***Fisher's exact test
† Hazard ratio less than 1 indicates benefit for Campath patient relative to chlorambucil patient, smaller values indicate a stronger benefit for Campath relative to chlorambucil.
†† There was no difference in the number of deaths in the Campath and chlorambucil treatment groups (24 deaths in each group).
††† Includes 2 patients who were Rai Stage 0 by IRRP.

Summary / Conclusions (Safety)
There were 147 patients in the Campath arm and 147 patients in the chlorambucil arm who received at least one administration of study drug. The median duration of exposure to Campath was 11.7 weeks with a median cumulative dose of 956 mg. The median duration of exposure to chlorambucil was 28.3 weeks with a median cumulative dose of 515 mg.

Adverse Events
Overall, the incidence of reported adverse events was higher for patients in the Campath arm than for patients in the chlorambucil arm.

Most Frequently Reported (≥10%) AEs Regardless of Causality
The most frequently reported (≥10%) AEs regardless of causality noted for Campath-treated patients during the on-treatment period were pyrexia (102; 69.4%), CMV viremia (81; 55.1%), chills (77; 52.4%), nausea (25; 17.0%), hypotension (24; 16.3%), CMV infection (23; 15.6%), urticaria (23; 15.6%), headache (21; 14.3%), dyspnea (19; 12.9%), hypertension (19; 12.9%), rash (19; 12.9%), fatigue (17; 11.6%), vomiting (16; 10.9%), diarrhea (15; 10.2%), insomnia (15; 10.2%), and neutropenia (15; 10.2%). Many of the events were consistent with Campath infusion reactions and occurred during the initial infusions, were mild or moderate in severity, and decreased in frequency with subsequent doses. Premedication with diphenhydramine and acetaminophen appear to have been helpful in reducing the incidence and severity of subsequent infusion reactions. The most frequently reported AEs regardless of causality for chlorambucil-treated patients during the on-treatment period were nausea (54; 36.7%), vomiting (27; 18.4%), fatigue (18; 12.2%), and pyrexia (16; 10.9%).

Most Frequently Reported (≥10%) Study Drug Related AEs
The most frequently reported (≥10%) study drug related AEs noted for Campath-treated patients during the on-treatment period were pyrexia (94; 63.9%), CMV viremia (78; 53.1%), chills (73; 49.7%), urticaria (22; 15.0%), hypotension (21; 14.3%), CMV infection (19; 12.9%), nausea (19; 12.9%), and rash (18; 12.2%). The most frequently reported (≥10%) study drug related AEs for chlorambucil-treated patients during the on-treatment period were nausea (51; 34.7%) and vomiting (27; 18.4%).

Serious Adverse Events (SAEs)
The overall incidence of serious adverse events (SAEs) was higher in the Campath arm than in the chlorambucil arm. The most frequently reported (≥2%) SAEs regardless of causality for Campath-treated patients during the on-treatment period were CMV viremia (16; 10.9%), CMV infection (8; 5.4%), and pyrexia (5; 3.4%). The most frequently (≥2%) reported SAEs regardless of causality for chlorambucil-treated patients during the on-treatment period was pneumonia (5; 3.4%).

Most Frequently Reported SAE

The most frequently reported SAE in the Campath arm was CMV viremia. In many European countries, CMV viremia was reported as a SAE because standard medical practice required hospital admission for treatment with IV ganciclovir, which was the treatment recommended in the protocol for confirmed CMV viremia or infection. These hospitalizations, by definition an SAE, contributed to the increase in the overall incidence of SAEs in the Campath arm.

Infection Events

The incidence of CMV viremia and infections was greater for the Campath arm compared to the chlorambucil arm; 81 patients (55.1%) in the Campath arm vs 11 patients (7.5%) in the chlorambucil arm experienced viremia and 23 patients (15.6%) in the Campath arm and 0 (0%) patients in the chlorambucil arm experienced infection. The increased incidence of CMV viremia/infection may have been due to the greater frequency in the sampling schedule for quantitative CMV by PCR (weekly for Campath arm vs monthly for chlorambucil arm). While receiving study therapy, patients in the Campath arm were monitored on a fixed, weekly schedule and when clinically indicated for detection of CMV whereas patients in the chlorambucil arm were tested once a month and when clinically indicated. The majority of CMV viremia/infection events occurred during the on-treatment period, such events were mild to moderate in severity, and they were readily managed. Thus, because of the increased incidence of CMV viremia/infection in the Campath arm, the overall incidence of infections was greater in the Campath arm than in the chlorambucil arm. The incidence of non-CMV infections was similar between treatment arms.

Hematologic Toxicities

Although hematologic toxicity was common, recovery was seen during study, or shortly thereafter for most patients. Except for neutropenia and lymphopenia, the incidence of treatment-emergent grade 3 and 4 hematological toxicities including anemia and thrombocytopenia were similar between the two treatment arms. Among the patients with ANC results at both baseline and post-baseline, 60/146 patients (41.1%) in the Campath arm had grade 3 or worse ANC values as compared to the 36/144 patients (25.0%) in the chlorambucil arm. Among the patients with hemoglobin results at both baseline and post-baseline, 16/146 patients (11.0%) in the Campath arm had grade 3 or worse hemoglobin values as compared to the 26/145 patients (17.9%) in the chlorambucil arm. Among the patients with platelet results at both baseline and post-baseline, 18/147 patients (12.2%) in the Campath arm had grade 3 or worse platelet values as compared to the 17/147 patients (11.6%) in the chlorambucil arm. The median time to recovery of CD4+ counts to ≥200/mL occurred by 6 months post-treatment, median value 251.0 × 10^6/L, for patients treated with Campath.

No patients in the Campath arm developed autoimmune thrombocytopenia, and 2 patients developed autoimmune thrombocytopenia in the chlorambucil arm. One patient in the Campath arm and 2 patients in the chlorambucil arm developed hemolytic anemia, and one patient in the Campath arm developed pure red cell aplasia during the post-treatment follow-up period. The observed hematologic events in both treatment arms were consistent with recognized complications of B-CLL.

Discontinuations Due to Adverse Events

More patients in the Campath arm than in the chlorambucil arm discontinued study due to an adverse event. In the Campath arm, infusion reactions and CMV were the most frequent adverse events leading to study discontinuation. Fifty patients (50/294, 17.0%) were discontinued from study treatment due to an AE, 33/147 patients (22.4%) in the Campath arm and 17/147 patients (11.6%) in the chlorambucil arm. Drug related AEs that led to study drug discontinuation were reported for 29/147 patients (19.7%) in the Campath arm and 6/147 patients (4.1%) in the chlorambucil arm.

Deaths on Study

Four patients (one in the Campath arm and 3 in the chlorambucil arm) died during treatment or within 30 days of the last dose of study drug. The one patient in the Campath arm entered the study with Rai stage III and the investigator attributed the death to underlying disease. The causes of death for the 3 patients in the chlorambucil arm were Listeria monocytogenes encephalitis, cardiac insufficiency, and sudden death (cause unknown). The only death considered by the investigator to be likely related to study drug was the patient with the Listeria monocytogenes encephalitis infection.

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