Protocol 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

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Name of Sponsor/Company

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
ILEX Oncology, Inc., San Antonio, Texas 78229 (ILEX Oncology, Inc. was acquired by Genzyme Corporation December 2004)

Investigators and Study Center(s)

This was a multicenter study conducted at 11 sites in the United States and 11 sites in Europe.

Studied Period

Date first patient enrolled: 31 March 1998
Date last patient enrolled: 31 July 1998
(Date of data cut-off for survival analysis: 19 February 2002)

Phase of Development

Phase II

Objectives

The primary objective of this study was to determine the response rate (complete response + partial response) with CAMPATH® in patients with B-CLL who had received an alkylating agent and failed fludarabine therapy. The secondary objective of this study was to evaluate the safety profile of CAMPATH® in this population and to evaluate the clinical benefit of CAMPATH® in this population.

Methodology

This was a multicenter, open-label, Phase II study of CAMPATH® 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 complete response (CR) or partial response (PR) or had disease progression (PD) while on fludarabine, or had relapsed within 6 months following treatment with fludarabine.

Formal assessments of disease response to CAMPATH® 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 (Cheson BD et al. Blood 1996). 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 (e.g., to confirm a CR). If a patient met all laboratory and clinical criteria for a CR by week 4 or 8 of treatment, CAMPATH® was to be discontinued and the patient followed. Patients with 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-month intervals thereafter until alternate treatment was administered or death.

The safety of CAMPATH® was evaluated after the first and subsequent doses by closely monitoring patients throughout the study for adverse events (AEs), including hematologic and chemistry laboratory assessments.

Number of Patients (Planned and Analyzed)

The study was designed to enroll 75 patients. In total, 94 patients were enrolled due to very rapid enrollment. One patient was enrolled but discontinued from the study prior to treatment; therefore, 93 patients were treated with CAMPATH® and were analyzed for safety and efficacy.

Diagnosis and Main Criteria For Inclusion:

The main criteria for inclusion were: confirmation of B-CLL diagnosis within 4 weeks prior to study entry, defined as peripheral lymphocyte count >5 X 10^9/L, and 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 PD while on fludarabine treatment, or relapse within 6 months of the last dose of fludarabine.

Test Product, Dose, and Mode of Administration

CAMPATH® was administered intravenously (IV) 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® were 30 mg administered three times per week IV, diluted in 100 mL of normal saline, and infused over 2 hours.

Patients were to be premedicated with 50 mg diphenhydramine and 650 mg acetaminophen 30 minutes prior to the first CAMPATH® infusion, each time the dose of CAMPATH® 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® therapy.

Duration of Treatment

The CAMPATH® 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.

Reference Therapy, Dose and Mode of Administration

No reference therapy was used in this study.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Efficacy

Response evaluation was performed by the investigators every 4 weeks while a patient was on study treatment. In addition to the investigators' assessments, an Independent Response Review Panel (IRRP) used the 1996 NCIWG response criteria to assess response to CAMPATH® for 93 patients. The efficacy of CAMPATH® was determined by disease assessment of patients at the time of enrollment and at weeks 4, 8, and 12 while receiving CAMPATH® or at the end of treatment and in follow-up, as appropriate. These assessments included physical examination to measure the size of lymph nodes, liver (measured below the right costal margin in the mid-clavicular line) and spleen (recorded as the longest length palpable), as well as hematologic assessments and bone marrow examinations.

Hematology: Complete blood cell counts with differential white cell counts were to be obtained weekly during treatment.

Bone marrow aspirate and biopsies: Bone marrow trephine biopsy and aspirate samples were to be collected prior to the first dose of CAMPATH® for assessment of disease involvement in the marrow and analysis by flow cytometry for clonal and lymphocyte subset markers. Repeat bone marrow samples were to be obtained at weeks 4 and 8 of treatment if the patient had complete resolution of peripheral lymphocytosis, lymphadenopathy, and/or hepatosplenomegaly. If the bone marrow was normal at weeks 4 or 8, then CAMPATH® therapy was to be discontinued, and a repeat bone marrow biopsy was to be performed 2 months later to confirm response.

Symptom assessments: Constitutional B-symptoms were to be assessed prior to the first dose of CAMPATH®, every 4 weeks during treatment, and upon completion of treatment and during follow-up, as appropriate. Additionally, any other disease-related symptoms were to be recorded and graded as mild, moderate, severe, or life-threatening based on National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (published 1984).

Criteria for Evaluation – Safety

The safety of CAMPATH® was assessed by monitoring the incidence, severity, and relationship of adverse events, particularly the incidence of infection and bone marrow toxicity; and changes in physical examination results, vital signs, and clinical laboratory results.

STATISTICAL METHODS

Data from all patients who received at least one dose of CAMPATH® (Intent-to-Treat population) were included in the safety and efficacy analyses.

Statistical Methods – Efficacy

The overall response rate (including 95% confidence interval) was defined as the proportion of patients with CR+PR over the total number of patients treated and was the primary efficacy endpoint in this study. All confidence intervals for parameters to be estimated were constructed using Exact method with a significance level of alpha=0.05. All time-to-event variables, including time to response, duration of response, time to disease progression, time to treatment failure, time to alternate treatment and survival were estimated using the Kaplan-Meier method. Disease response was further characterized by descriptively presenting 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).

Statistical Methods – Safety

On-study and post-study AEs and serious adverse events (SAEs) were coded using a modified World Health Organization Adverse Reaction Terminology (WHOART) and tabulated by body system and preferred term; infections were tabulated by infection type (e.g., bacterial, viral). The occurrence of hematological toxicities was evaluated using NCI CTC 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 and IgG results.

SUMMARY – CONCLUSIONS

Patient Characteristics at Study Entry

The 93 patients diagnosed with CLL entered in this study represented a severely ill patient population. The median age at study entry was 66 years old. Median time since the initial diagnosis of CLL was 6.1 years. The median number of prior chemotherapy regimens was 3 (range: 2-7). All patients had been previously treated with alkylating agent(s), all except one had failed at least one fludarabine-containing regimen, and 48.4% had never responded to a nucleoside analog. All enrolled patients except one had either Rai stage III/IV disease or stage 0-II with clear indicators of advanced disease status. Among the patients with baseline bone marrow biopsy results (n=85), all had bone marrow involvement, 73 of the 85 (85.9%) had >50% of the bone marrow occupied by tumor. The majority of patients had enlarged lymph nodes, 49.5% had at least one lymph node measuring >2 cm. Splenomegaly and hepatomegaly were present at baseline in 54.8% and 36.6% of patients, respectively. At baseline, 42% of patients had B-symptoms present plus 34.4% with asthenia, 9.7% with pain, and 20.4% with other CLL-related symptoms.

Summary – Conclusions (Efficacy)

Response Rate: The overall response rate (CR + PR) for the 93 patients was 33.3% (95% CI: 24%, 44%) as determined by the independent response review panel; 2 of the 31 responding patients achieved CR and 29 had PR. Fifty patients (53.8%) had SD, and 12 (12.9%) had either PD (n=8) or could not be evaluated due to early discontinuation or lack of follow-up (n=4). The rate of response to CAMPATH® in patients who had never responded to any nucleoside analog was 28.9% (13/45) versus 37.5% (18/48) in patients who had responded to at least one previous nucleoside analog regimen. In addition, 10/29 patients (34.5%) who had received a nucleoside analog in combination with another chemotherapeutic agent and 5/15 patients (33%) for whom that additional agent was cyclophosphamide achieved objective responses to CAMPATH®.

Time to event variables: The median time to response following initiation of CAMPATH® therapy was 1.5 months with a median duration of response of 8.7 months. Median time to progression for all patients was 4.7 months with the median time to progression for responding patients of 9.5 months. The median time to alternate therapy was 6.4 months for all patients and 14.5 months for responding patients.

Survival data updated in an addendum to the original report (dated 15 May 2002):
The addendum reported on the overall survival data obtained from the long-term follow-up of the 93 patients reported in the original CAM211 clinical study report dated 29 November 1999. The data cut-off date of 19 February 2002 was used for the updated survival analysis.

The median survival time for all patients by intent-to-treat analysis is 16.0 months with a range of 1.1 to 45.6 months and with the lower limit of the 95% confidence interval at 11.8 months. The median survival time for responding (CR + PR) patients is 33.3 months with a range of 4.4 to 45.6 months and with the lower limit of the 95% confidence interval at 25.7 months. At the time of data cut-off (19 February 2002), 16 patients (17.2%) remained with censored data; 13 patients were known to be alive and 3 were lost to follow-up, the remaining 77 (82.8%) patients had died as of the cut-off date. Of the 13 patients (13/93, 14.0%) that were alive and being followed at the time of the data cutoff date for the analysis, 1 had a CR, 10 had a PR, and 2 had SD following treatment with CAMPATH®.

Individual Parameters of Response: Overall, 65/67 (97.0%) patients with lymphocytosis at baseline (defined as an absolute lymphocyte count (ALC) >5 X 10^9/L) and who also had follow-up information, including all of the responding patients with data available and all but one of the stable disease patients, had resolution of the peripheral blood lymphocytosis (ALC <4 X 10^9/L) at the last on treatment assessment. Disease reduction in the bone marrow was substantial with 61.3% of patients with baseline and follow-up data showing complete (22 patients, 35.5%) or >50% (16 patients, 25.8%) resolution of disease infiltration. Lymphadenopathy completely resolved in 27.3% of patients and an additional 47.0% had ≥ 50% reduction in lymph node 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 74.2% of the patients at end of treatment. Twenty-five (43.9%) of 57 patients with hemoglobin levels ≤ 11 g/dL at baseline improved to >11 g/dL or had a >50% improvement over baseline at the time of the two-month follow-up. Twelve (50.0%) of 24 patients with an absolute neutrophil count (ANC) <1.5 X 10^9/L at baseline improved to ≥ 1.5 X 10^9/L or had a >50% improvement over baseline. Fifty-four patients had platelet counts ≤ 100.0 X 10^9/L at baseline and 21 of these patients (38.9%) improved to >100.0 X 10^9/L or had a >50% improvement compared to their baseline value.

Clinical Benefit: An analysis of clinical benefit occurring in responding patients was conducted. Overall, 6 separate categories of clinical benefit were identified including 1) an increase in chemotherapy-free time following CAMPATH® therapy compared with the period prior to CAMPATH®, 2) resolution of disease related B and other symptoms, 3) improvement of performance status (PS), 4) resolution of symptomatic bulky disease such as massive splenomegaly or hepatomegaly, 5) substantial improvement in markedly abnormal hematological parameters and 6) survival >18 months. All patients who qualified as responding patients according to the NCIWG criteria experienced at least one of the benefits shown above; most patients experienced more than one of these benefits. Twenty-five of the 31 responding patients experienced a longer chemotherapy free period following CAMPATH® than following their prior chemotherapy. Seventeen of the 31 responding patients entered the study with B symptoms or fatigue. All 17 experienced resolution of these symptoms. Eight of the responding patients who enrolled with a PS of 1 improved to 0. Eleven of 12 (91.7%) patients among the responding patients with massive (>6 cm below costal margin) splenomegaly or hepatomegaly at baseline had complete resolution of the organomegaly. Eleven (73.3%) of the 15 responding patients who had baseline hemoglobin <11 g/dL had improvements in hemoglobin of >2g/dL to >11g/dL with a maximal increase which ranged from 2.2 to 6.4 g/dL, a level of increase which has been associated with quality of life improvements in epoetin alpha studies (Glaspy J, et al. J Clin Oncol 1997; Demetri GD, et al. J Clin Oncol 1998). Two patients entered the study with grade 4 thrombocytopenia and/or grade 4 neutropenia. One entered the study with an ANC of 0 and achieved a normal ANC on study and the other entered the study with ANC of 0.4 X 10^9/L and platelet count of 4 X 10^9/L and a heavy requirement for platelet transfusions and RBCs. This patient improved to ANC >1.0 X 10^9/L and platelet count >50.0 X 10^9/L and was transfusion free for over 7 months. The median number of benefits experienced by the responding patients was 3 with a range of 1 to 6. This is an overall reflection of the activity of CAMPATH® in this disease and suggests that achieving an objective response with this agent is associated with real and important clinical benefits for patients. In addition, at least 16 patients with stable disease also experienced a median of 3 (range: 1-6) benefits.

Summary – Conclusions (Safety)

CAMPATH® therapy was administered as planned to the majority of the enrolled patients. Most (84, 90.3%) patients were escalated to the target dose (30 mg) within the 5 days. There were 84 (90.3%) patients treated with 10 or more doses of CAMPATH® 30 mg and 51 patients (54.8%) treated with >20 doses of CAMPATH® 30 mg. Only one patient was discontinued from study participation due to an AE (grade 4 dyspnea and bronchospasm) during the first CAMPATH® infusion.

All 93 patients experienced at least one AE on study. The most frequently reported events regardless of severity grade were acute infusion-related events including rigors (90.3%), fever (84.9%), nausea (52.7%), vomiting (37.6%), and rash (33.3%). There was a substantial decrease in the incidence of these infusion-related events from Week 1 to Weeks 2 to 4 with a further decrease reported for treatment beyond 4 weeks. The majority of AEs, regardless of relationship to study drug, had a maximum severity grade 1 or 2. The most commonly reported grade 3 or 4 AEs were fever (20.4%), rigors (14.0%), 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, with 11.8% and 9.7% reported as grade 3 or 4, respectively.

In this study, infections were reported separately. During the study, 51 (54.8%) of the 93 patients experienced at least one infection; which had a maximum severity of grade 1 or 2 for 26/93 patients (28.0%). Grade 3 or 4 infections were reported in 25/93 patients (26.9%). The most commonly reported grade 3 or 4 infections were pulmonary infections, including pneumonia and pneumonitis (13 patients, 14.0%) and sepsis (9 patients, 9.7%). Opportunistic infections (OIs) were uncommon, with only 11 patients (11.8%) experiencing OIs during treatment or within 30 days of the last dose of CAMPATH®, signifying the effectiveness of the prescribed anti-infective prophylaxis. The most common on-study OI was cytomegalovirus (CMV) infection (n=7). OIs were uncommon in the follow-up period (a total of 7 infections).

Forty-six patients (49.5%) experienced SAEs on-study; in 42 patients (45.2%) these events had a maximum severity of grade 3 or 4. SAEs reported in >5% of the patients included fever (29.0%), pneumonia (12.9%), sepsis (11.8%), dyspnea (9.7%), granulocytopenia (9.7%), anemia (7.5%), neutropenic fever (7.5%), asthenia (6.5%), CMV infection (6.5%), thrombocytopenia (6.5%), and rigors (5.4%). Nine deaths (9.7%) occurred during treatment or within 30 days of the last dose of CAMPATH®. Five (5.4%) were associated with infection and considered likely related to CAMPATH®. As of the last available follow-up information (15 February 2000), 44 patients had died >30 days after their last dose of CAMPATH®, including 19 deaths that occurred from 30 to 180 days post-treatment and 25 that occurred >180 days post-treatment. The causes of death in the 44 patients were progressive CLL (n=24), infection (n=11), and one each due to inanition, CLL-related thrombocytopenia with GI bleeding, autoimmune hemolytic anemia, respiratory distress, idiopathic thrombocytopenic purpura (ITP), cerebrovascular accident, disease progression with infection and heart failure with infection; and one case for which cause was not reported. Four of the deaths were considered related to CAMPATH®.

Although hematologic toxicity was common, recovery occurred at the end of treatment or shortly thereafter in most patients. Hemoglobin levels recovered at the end of treatment with further improvement noted at the 1- and 2-month post-treatment follow-up, when 81.7% and 86.9% of patients with available data, respectively, had hemoglobin grades that were equal to or improved over their baseline grade. Thrombocytopenia was common during study, with recovery noted at study end and the 1- and 2-month post-treatment follow-up. All patients developed lymphopenia during treatment as a direct effect of the pharmacologic action of CAMPATH®. The median absolute CD3+/CD4+ lymphocyte count reached its nadir at week 4 but increased significantly by the week 12 assessment. Further recovery was observed 2, 4, and 6 months after the end of treatment.

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 observed in studies with fludarabine and other nucleoside analogs in this disease. A higher rate of moderate and severe adverse events and infections were seen in patients who had been more intensively treated prior to study entry, had Rai stage III/IV disease and poorer performance status. This is consistent with the experience reported in the literature in patients with relapsed/ refractory CLL and suggests that the toxicity of any agent in the treatment of this disease is related to the interaction between the stage of disease and consequent hematological compromise and the cumulative toxic effects of prior therapy. The safety results in the present study compare favorably with previous CAMPATH® studies in which premedication and prophylactic anti-infectives were not routinely prescribed.

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