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FDA Drug Approval Summary: Alemtuzumab as Single-Agent Treatment for B-Cell Chronic Lymphocytic Leukemia

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the results of the CAM 307 randomized trial of alemtuzumab in patients with B-cell chronic lymphocytic leukemia.
2. Describe the pretreatment and prophylactic medications recommended for patients treated with alemtuzumab.
3. Identify the most common toxicities seen with alemtuzumab treatment.

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ABSTRACT

On September 19, 2007, the U.S. Food and Drug Administration granted regular approval and expanded labeling for alemtuzumab (Campath®; Genzyme Corporation, Cambridge, MA) as single-agent treatment for B-cell chronic lymphocytic leukemia (B-CLL). Alemtuzumab was initially approved in 2001 under accelerated approval regulations. Conversion to regular approval was based on a single study submitted to verify clinical benefit. Efficacy and safety were demonstrated in an open-label, international, multicenter, randomized trial of 297 patients with previously untreated, Rai stage I–IV B-CLL experiencing progression of their disease. Patients were randomized to either alemtuzumab, 30 mg i.v. over 2 hours three times per week on alternate days for a maximum of 12 weeks, or chlorambucil, 40 mg/m^2 orally every 28 days for a maximum of 12 months. The progression-free survival time, the primary study endpoint, was significantly longer in the alemtuzumab arm than in the chlorambucil arm. Both the overall and complete response rates were also significantly higher in the alemtuzumab arm. No differences in survival were observed. There were no new safety signals identified in patients receiving alemtuzumab. The most serious, and sometimes fatal, toxicities of alemtuzumab are cytopenias, infusion reactions, and infections. *The Oncologist* 2008;13:167–174

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Introduction

Alemtuzumab (Campath®; Genzyme Corporation, Cambridge, MA) is a recombinant DNA-derived humanized IgG_1 kappa monoclonal antibody specific for the cell surface glycoprotein CD52 expressed on normal and malignant human peripheral blood B and T lymphocytes as well as natural killer cells, monocytes, macrophages, and other tissues. The mechanism of action is not completely understood, but involves a number of effects, including complement-mediated cell lysis, antibody-dependent cellular toxicity, and the induction of apoptosis. Because of its immunosuppressive properties, alemtuzumab was investigated initially for the treatment of autoimmune diseases and in transplant [1, 2]. Clinical activity was then demonstrated in a number of malignancies, including chronic lymphocytic leukemia (CLL) and T-cell prolymphocytic leukemia [3–5], which led to further investigation in these settings.

The U.S. Food and Drug Administration (FDA) granted accelerated approval for alemtuzumab on May 7, 2001, for the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL) who had been treated with alkylating agents and failed fludarabine therapy based on evidence of durable objective response rates in the range of 21%–33% across three single-arm studies. U.S. regulatory approval was contingent upon completion of a postmarketing commitment to confirm clinical benefit in the CAM 307 trial. CAM 307 was an open-label, international, multicenter, randomized trial designed to demonstrate a longer progression-free survival (PFS) duration with single-agent alemtuzumab than with single-agent chlorambucil in patients with previously untreated, Rai stage I–IV B-CLL experiencing progression of their disease requiring initiation of antileukemia treatment. The analyses of the primary (PFS) and key secondary endpoints were performed on an intent-to-treat (ITT) population of 297 patients. Conversion from accelerated to regular approval for alemtuzumab and a new labeling claim for the initial treatment of B-CLL on September 19, 2007, were supported by evidence of a significant and clinically meaningful longer PFS time, supported by higher overall and complete response rates.

Patients and Methods

The CAM 307 trial was an open-label, randomized (1:1), multicenter trial conducted in Europe and the U.S., comparing the safety and efficacy of single-agent alemtuzumab with those of single-agent chlorambucil in previously untreated patients with B-CLL who required systemic therapy for progressive disease [6]. The intended sample size of 284 patients was chosen to detect a 50% difference in the median PFS time (14 versus 21 months), with 80% power and $\alpha = 0.05$ (two-sided). Randomization was stratified with an adaptive randomization method used to achieve balance between the treatment arms for study center, Rai stage group (Rai I–II versus Rai III–IV), age (<65 years versus ≥65 years), World Health Organization (WHO) performance status score (0 or 1 versus 2), gender, and maximum lymph node size (nonpalpable or <5 cm versus ≥5 cm).

The primary efficacy endpoint for the trial was the PFS duration, calculated from the date of randomization to the date of disease progression or relapse as documented by an independent response review panel (IRRP) or the date of death from any cause, whichever occurred earlier. Patients without IRRP-documented disease progression who were alive on the date of last evaluation were censored at the date of last contact. Patients with missing tumor response assessments were considered to have progressed on the date of the inevaluable response determination plus 1 day. The statistical analysis plan specified a single interim analysis of PFS after 95 events and a final analysis of PFS after 70% of the population had progressed or died (190 events). Protocol-specified exploratory analyses of PFS were planned to assess for consistency of treatment effect within the following subgroups: age (<65 years versus ≥65 years), maximum lymph node diameter (nonpalpable or <5 cm versus ≥5 cm), gender, performance status (0 or 1 versus 2), percent marrow involvement, β_2-microglobulin, and cytogenetic abnormalities. Additional study endpoints included overall survival, investigator-determined PFS, IRRP-determined overall and complete response rates, duration of response, time to treatment failure, and time to alternative treatment. Complete response (CR) and partial response (PR) were defined using the 1996 National Cancer Institute Working Group (NCIWG) criteria summarized in Table 1.

The protocol defined duration of response as the interval between the date of first documented objective response and the date of documented progressive disease or death from any cause as determined by the IRRP. The design of the case report forms, which were reviewed by the IRRP, did not clearly indicate that the intended date of response was the date of initial response. As a result, the IRRP provided the date of best response, and the duration of response analysis was performed using this time point and the censoring rules from the primary PFS analysis. Patients were evaluated for disease status response and survival monthly during treatment and at the completion of treatment or early discontinuation. Response assessments included physical examination, lymph node, liver, and spleen measurements, assessment of disease-related symptoms, and CBC with differential. In addition, at 1, 2, and 3 months after treatment had begun, flow cytometry was performed on peripheral blood and bone marrow aspirate samples, and bone

Table 1. 1996 NCIWG response criteria

Type of response
CR (duration >2 months)
Normal physical examination (including nodes, liver, spleen) and x-ray
No constitutional symptoms
Lymphocytes $\geq 4.0 \times 10^9$/l
Neutrophils $\geq 1.5 \times 10^9$/l
Platelets $>100 \times 10^9$/l
Hemoglobin >11.0 g/dl (untransfused)
Marrow normocellular for age, lymphs <30%, no nodules; if hypocellular marrow, repeat in 4 weeks
PR (duration >2 months)
Lymphocyte ≥50% decrease from baseline, and
Lymphadenopathy ≥50% decrease from baseline, and/or
Liver and/or spleen ≥50% decrease from baseline
Plus at least one of: neutrophils $\geq 1.5 \times 10^9$/l or 50% increase over baseline, platelets $>100 \times 10^9$/l or 50% increase over baseline, hemoglobin >11.0 g/dl or 50% increase over baseline (untransfused)
Otherwise CR with persistent nodules classified as nodular PR
Otherwise CR with persistent anemia or thrombocytopenia because of drug toxicity classified as PR and monitored prospectively

Abbreviations: CR, complete response; NCIWG, National Cancer Institute Working Group; PR, partial response.

marrow biopsy samples were obtained for histology if indicated (i.e., to confirm a CR at least 2 months after a patient met the NCIWG laboratory and clinical criteria for CR, and to confirm achievement of a CRm (complete response without evidence of residual disease at the molecular level) status only if peripheral blood was negative for B-CLL by flow cytometry). Patients who did not progress by 18 months after their initial dose were evaluated for disease status every 3 months until the time of progression or requirement for alternative therapy. Patients with disease progression were followed every 3 months for survival. Investigators and the IRRP used the NCIWG criteria to assess tumor response to study treatment.

Patients with previously untreated B-CLL exhibiting evidence of progressive disease were eligible to participate in the trial. Other relevant eligibility criteria are summarized in Table 2.

The dosing scheme for alemtuzumab included a dose-escalation phase to achieve the recommended dose. The dose-escalation phase consisted of an initial dose of 3 mg as a daily i.v. infusion administered over 2 hours until infusion-related side effects were tolerated followed by 10 mg as a daily 2-hour i.v. infusion until infusion-related side effects were tolerated, with final escalation to the recommended dose. The recommended dose was 30 mg as a 2-hour i.v. infusion administered three times per week on alternate days. The total course of alemtuzumab was administered over a maximum of 12 weeks, which included the dose-escalation period. Patients randomized to the alemtuzumab arm were permitted to receive a second treatment course if a CR or PR, durable for at least 6 months, was achieved with the initial treatment course. Premedication for alemtuzumab treatment, consisting of diphenhydramine and acetaminophen or paracetamol, was given. Meperidine, hydrocortisone (or equivalent), and other supportive measures were permitted as clinically indicated for alemtuzumab infusion reactions. Allopurinol was given prior to the first treatment with alemtuzumab and for 14 days thereafter. Trimethoprim/sulfamethoxazole for *Pneumocystis carinii* pneumonia prophylaxis (or therapeutic equivalent) and famciclovir (or therapeutic equivalent) for herpes prophylaxis were required for all patients receiving alemtuzumab. Prophylactic antibiotics to prevent recurrence of an infection were allowed at the investigator's discretion.

Dose modifications (delay or discontinuation of alemtuzumab) were required for serious infection, disease progression, Common Toxicity Criteria (CTC) grade ≥3 pulmonary, renal, or hepatic toxicity, a positive qualitative polymerase chain reaction assay for cytomegalovirus (CMV), autoimmune anemia, or autoimmune thrombocytopenia, an absolute neutrophil count $\leq 0.25 \times 10^9$/l, a platelet count ≤50% of the baseline value in patients with a baseline value $\leq 0.25 \times 10^9$/l; if alemtuzumab dosing was held for >4 weeks, treatment was terminated.

Table 2. CAM 307 eligibility criteria

Inclusion criteria	Exclusion criteria
B-CLL (histopathologically confirmed)	ANC $<0.5 \times 10^9$/l
Rai stage I–IV	Platelet count $<10 \times 10^9$/l
$CD5^+$, $CD19^+$, or $CD23^+$	Chronic use of oral corticosteroids
No prior systemic chemotherapy	Autoimmune thrombocytopenia
Adequate renal function (serum creatinine ≤2.0× ULN)	Prior bone marrow transplant
Adequate hepatic function (total bilirubin, AST, ALT ≤2.0× ULN)	Investigational agent in past 30 days
WHO performance status score of 0, 1, or 2	HIV positive
Progressive disease (one or more of):	History of anaphylaxis to rat- or mouse-derived humanized monoclonal antibodies
Disease-related B symptoms	Active infection
Marrow failure (manifested by decreased hemoglobin to <11 g/dl, or platelet count $<100 \times 10^9$/l within prior 6 months, or ANC $<1.0 \times 10^9$/l within prior 6 months)	Serious cardiac or pulmonary disease
Progressive splenomegaly (>2 cm below left costal margin or other organomegaly with progressive increase over two clinic visits ≥2 wks apart)	Active TB in past 2 yrs or current antibiotics for TB
Progressive lymphadenopathy (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 two consecutive clinic visits ≥2 wks apart)	Active secondary malignancy
Progressive lymphocytosis (increase of >50% over a 2-month period or anticipated doubling time <6 months)	Central nervous system CLL
	Other severe, concurrent diseases or mental disorders
	Pregnant or lactating
	Quantitative PCR positive for CMV
	diagnosis of mantle cell lymphoma

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; B-CLL, B-cell chronic lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; PCR, polymerase chain reaction; TB, tuberculosis; ULN, upper limit of normal; WHO, World Health Organization.

Chlorambucil was administered at a dose of 40 mg/m^2 orally once every 28 days for a maximum of 12 months. Chlorambucil was interrupted or discontinued for disease progression, CTC grade ≥3 pulmonary, renal, hepatic, or nonhematologic toxicity, serious infection, autoimmune anemia or autoimmune thrombocytopenia, complete remission, and a response plateau. Allopurinol was given prior to the first day of chlorambucil treatment and for 8 days thereafter for the first three treatment cycles.

Results

Two hundred ninety-seven patients were enrolled and randomized from December 2001 to July 2004, which constituted the ITT population for analyses of efficacy endpoints. The last patient received drug in May 2005; the data cutoff for efficacy analyses was June 1, 2006. Of these 297 patients, 149 were randomized to alemtuzumab and 148 to chlorambucil. The majority (273/297) were enrolled at sites outside the U.S. There were 294 patients who received the assigned treatment with alemtuzumab ($n = 147$) or chlorambucil ($n = 147$) for which adverse drug reaction data were analyzed.

The baseline characteristics for the ITT population, by treatment arm, are shown in Table 3. The treatment arms were balanced for major demographic and prognostic factors. Gender stratification was similar to that seen in B-CLL, where there is a 2:1 male-to-female ratio. Ninety-nine percent of patients were white, and 65% were <65 years of age. The majority of patients enrolled in the study were IRRP-confirmed RAI stage I–II (63%), had a WHO performance status score of 0 or 1 (96%), and had a maximal lymph node diameter of <5 cm (77%).

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