A phase I study of dacetuzumab (SGN-40, a humanized anti-CD40 monoclonal antibody) in patients with chronic lymphocytic leukemia

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Abstract
Despite advances in therapy, chronic lymphocytic leukemia remains an incurable disease and novel, effective therapies are needed. In this open-label, dose-escalation, phase I study, dacetuzumab (IgG1 humanized monoclonal antibody) was administered to 12 adults, all of whom had received several prior systemic therapies (median, 4; range, 2–11). Intrapatient dose escalation (maximum weekly doses of 3–8 mg/kg) was used to diminish first-dose-related inflammatory symptoms. No dose-limiting toxicities or dose-dependent trends in adverse events (AEs) were observed. The most common AEs (in ≥2 patients) were fatigue, headache, anorexia, conjunctivitis, hyperhidrosis, and night sweats, all of which were mild or moderate. No deaths, serious AEs, or discontinuations due to AEs occurred. Although no patient achieved an objective response, five patients demonstrated stable disease after 1 cycle of therapy, with no discernable correlation between dacetuzumab dose and outcome. This modest single-agent activity may warrant further testing of dacetuzumab in combination with other chronic lymphocytic leukemia therapies.

Keywords: Chronic lymphocytic leukemia, CD40, monoclonal antibody, SGN-40, dacetuzumab, clinical trial

Introduction
Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the United States, with 15 110 new cases and 4390 deaths estimated for 2008 [1,2]. CLL cells demonstrate a mature B-cell phenotype with low surface expression of CD20 and immunoglobulin and coexpression of CD5 [3]. While the initial clinical course of CLL tends to be indolent, most patients eventually require therapy and many die of their disease [4].

Although complete remission has been observed with initial therapy in 50–70% of patients with CLL, relapses are inevitable and salvage options are limited [5–7]. Fludarabine (with or without cyclophosphamide) and chlorambucil are the standard initial regimens for CLL, but they are associated with myelosuppression, immunosuppression, and increased risk of infections [8–10]. Recently approved therapies for CLL, including alemtuzumab and bendamustine, continue to demonstrate these toxicities [11,12]. As a single agent, rituximab is better tolerated, possibly because of its ability to target only B lymphocytes, but it has limited efficacy, perhaps as a result of the low CD20 expression found on CLL lymphocytes [13]. When combined with chemotherapy (e.g., fludarabine with or without cyclophosphamide), rituximab enhances survival and response rates compared with chemotherapy alone [5,14]. However, patients who have relapsed or are refractory to fludarabine-containing therapies have a survival of less than 12 months [7,15]. Thus, CLL remains incurable, underscoring the need for developing additional targeted therapies.
CD40 is a type-1 transmembrane protein of the tumor necrosis factor receptor superfamily and is expressed on the vast majority of CLL cells, making it an attractive potential tumor target for antibody-based cancer therapy [16]. Dacetuzumab (previously SGN-40) is an IgG1 humanized monoclonal antibody that targets CD40. Dacetuzumab has multiple mechanisms of action, including induction of immune effector functions and partial agonistic signaling properties. Dacetuzumab induces both antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) through interaction with Fc receptors on T cells, natural killer cells, and monocytes/macrophages [17]. Dacetuzumab signaling occurs upon binding to and crosslinking CD40. Although CD40 cross-linking is known to activate normal B cells, leading to increased cell survival and proliferation (especially in the presence of certain cytokines; e.g., interleukin-4), dacetuzumab induces apoptosis of several non-Hodgkin lymphoma cell lines in vitro [17] and has proven effective in multiple xenograft models of lymphoma and multiple myeloma in vivo [17]. In addition, signaling via CD40 may augment CLL immunogenicity in vivo [18].

The objectives of this phase I study were to determine the safety profile, maximum tolerated dose (MTD), pharmacokinetic (PK) properties, and preliminary antitumor activity of single-agent dacetuzumab in patients with CLL.

### Materials and methods

#### Patients

Eligible patients were ≥18 years old with a diagnosis of CLL as defined by the World Health Organization criteria [19] and requiring treatment as defined by the National Cancer Institute Working Group (NCI-WG) on CLL [20]. Patients had to have relapsed after receiving at least one purine analog-containing regimen and were to be at least 6 weeks or five half-lives (whichever was greater) from prior chemotherapy, radiation, investigational agents, and antibody therapy, and at least 6 months from autologous stem cell transplant. Minimum blood counts required for inclusion were an absolute neutrophil count (ANC) ≥1000/μL, platelets ≥50,000/μL, and hemoglobin ≥7.5 gm/dL; ANC, platelets, and hemoglobin values could be maintained with transfusions or growth factor support as appropriate. Patients had adequate kidney and liver function and an Eastern Cooperative Oncology Group performance status ≤2, with a life expectancy >3 months. Patients were excluded if they had received an allogeneic stem cell transplant, had been treated previously with any anti-CD40 therapy, or had a systemic infection that required antibiotic therapy within 4 weeks of enrollment.

#### Study design and schedule

This was an open-label, dose-escalation, phase I study in patients with CLL. The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practices, and the applicable U.S. Food and Drug Administration regulations. Local Institutional Review Boards approved the study for each site and patients provided written informed consent prior to any study procedure.

In this study, four cohorts of patients (three patients per cohort) received six intravenous (IV) infusions of dacetuzumab up to a maximum dose of 3, 4, 6, or 8 mg/kg over 5 weeks; the dose levels chosen for the study were supported by results from previous preclinical toxicology, PK, and antitumor studies. In a separate phase I study of patients with multiple myeloma, observations of first-dose toxicity (Grade 3 or 4 headaches and aseptic meningitis) [21] were considered a manifestation of cytokine release syndrome (CRS). Based on these observations, an intrapatient dose-escalation schedule was adopted in this study (Cycle 1, see Table I). Patients who

### Table I. Dose escalation schedule, Cycles 1 and 2.

<table>
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<tr>
<th>Dacetuzumab dose (mg/kg)</th>
<th>Cycle 1</th>
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<tr>
<td></td>
<td>Week 1</td>
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<tr>
<td>Cohort (n)</td>
<td>Day 1</td>
<td>Day 4*</td>
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<tr>
<td>I (n = 3)</td>
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<tr>
<td>II (n = 3)</td>
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<td>III (n = 3)</td>
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<tr>
<td>IV (n = 3)</td>
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<td>2</td>
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Day 4 dose could be administered on Day 3 or Day 5 if required for scheduling.
responded to treatment or had no evidence of disease progression were eligible to receive four additional infusions every other week at the cohort-specific maximum dose (Cycle 2, see Table I). After completing treatment, all patients were monitored until disease progression or until study closure.

All patients received allopurinol daily as tumor lysis syndrome prophylaxis for 3 days before the first infusion of dacetuzumab and continuing through Day 14 or until the white blood count was $< 20,000/\mu$L with creatinine and lactic dehydrogenase $< 1.5$ times the upper limit of normal. Patients also received acyclovir (or equivalent antiviral) and trimethoprim/sulfamethoxazole (or equivalent antibiotic) as anti-infective prophylaxis beginning 1 day before dacetuzumab infusion and continuing until the end-of-treatment evaluation. On the days of infusions, patients received diphenhydramine (25–50 mg) and acetaminophen (650 mg) 30–60 min before infusion and 4 h after completion of infusion. Symptoms suggestive of CRS developing within 24 h of dacetuzumab infusion (e.g., headache, fever, muscle aches) were treated with a 24-h course of prednisone (40 mg immediately, 40 mg 12 h later, and 20 mg at 24 h).

Study endpoints

Safety, dose-limiting toxicity, and maximum tolerated dose. Safety assessments included adverse event (AE) monitoring, clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis), vital signs, weight, and concomitant medications. Severity of AEs and clinical laboratory values were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Relationship to study drug (unrelated, unlikely, possibly, probably, or definitely) was determined by the investigator and was reviewed by the medical monitor.

Nonhematologic dose-limiting toxicities (DLTs) were defined as any event related to study drug (possibly, probably, or definitely) and Grade 3, including CRS and acute infusion-related reactions (e.g., bronchospasm, severe hypotension). Specific events excluded from the definition of DLT included hypersensitivity reactions, fatigue, and alopecia. Laboratory abnormalities that were considered DLTs included any Grade 4 elevation in liver function tests (aspartate aminotransferase [AST]; alanine aminotransferase [ALT]) or a Grade 3 AST/ALT elevation that did not resolve to Grade 1 within 14 days. Hematologic DLTs were defined as any study drug-related Grade 4 event lasting more than 7 days except for lymphopenia, because a decrease in total lymphocyte count could be expected based on the mechanism of action of dacetuzumab.

The MTD was defined as the highest dacetuzumab dose at which fewer than one-third of patients in a cohort experienced one or more DLTs.

Pharmacokinetics. During Cycle 1, venous blood samples were obtained before and after each dacetuzumab infusion and 1 and 3 weeks after the final infusion. Serum concentrations of dacetuzumab were measured using a bridging enzyme-linked immunosorbent assay (ELISA), by MDS Pharma Services (Saint-Laurent, Quebec, Canada). The maximal ($C_{\text{max}}$) and minimal ($C_{\text{min}}$) dacetuzumab concentrations were recorded directly from experimental observations.

Antitumor activity. Best clinical responses were determined based on NCI-WG criteria for CLL [20] and included complete response, partial response (PR), nodular PR, stable disease (SD), and progressive disease (PD). Evaluations were done at baseline and end of study and included physical examinations, laboratory tests, and computed tomography (CT) scans of neck, chest, abdomen, and pelvis.

Other measures of antitumor response included percent change from baseline to the smallest post-baseline tumor size (sum of the products of the greatest diameters [SPD]) and absolute lymphocyte count (ALC), obtained from peripheral blood counts.

Correlative studies. Quantitative immunoglobulins (IgG, IgA, and IgM) were measured at each institution’s laboratory. Inflammatory cytokine concentrations (interleukin-beta [IL-1$\beta$], IL-6, IL-10, interferon-gamma [IFN-$\gamma$], and tumor necrosis factor-alpha [TNF-$\alpha$]) were measured by immunofluorescent bead methodology at IBT Reference Laboratory (Lenexa, KS). Peripheral blood mononuclear cell subsets and CD40 expression were measured by flow cytometry at Roswell Park Cancer Institute (Buffalo, NY). Human anti-human antibodies (HAHA) were analyzed by ELISA at Tandem Laboratories (West Trenton, NJ).

Statistical analysis

All patients who received at least one dose of study drug were evaluated for safety, PK, and antitumor activity. All analyses of data were descriptive. Statistical analyses were performed by DataPhiles Programming LLC (Durham, NC).

Results

Patients

The study was conducted at three academic research institutions in the United States between November
2005 and October 2006. Twelve patients were enrolled (three in each of four cohorts), with a median age of 65 years; seven patients (58%) were male (Table II). Individual patient disease characteristics are provided in Table III. Patients were heavily pretreated with a median of 4 (range, 2–11) prior systemic therapies. At baseline, nine patients had Rai stage I disease and three had stage IV disease. The median baseline ALC was 10 915/µL; 5 of 12 patients had baseline ALC <5000/µL and 2 had ALC above 100 000/µL (Table III). Ten patients had adequate postbaseline imaging studies to calculate the percent change from baseline for measurable lesions. Half of these (n = 5) had baseline tumor sizes (i.e., SPD) of greater than 100 cm² and the median SPD was 87.2 cm² (Table III). Eleven of the 12 patients completed all planned infusions in Cycle 1 of the study; Patient 11 (Cohort IV) discontinued after four infusions because of disease progression as determined by the investigator. Of five patients who demonstrated SD after Cycle 1, two completed a second cycle of dacetuzumab (Table I). These two patients had marked decreased in peripheral lymphocytes during Cycle 1 and were determined by the treating physicians to have derived clinical benefit.

Safety, dose-limiting toxicity, and maximum tolerated dose

All 12 patients received at least one dose of dacetuzumab and are included in the safety population. Almost all dacetuzumab infusions were administered as planned: one infusion was delayed because of administration error, and dacetuzumab was discontinued for one patient (previously described disease progression); no other interruptions, dose reductions, or discontinuations of study drug occurred. Four patients received systemic steroids...
during treatment: one each for treatment-related CRS symptoms (hydrocortisone and prednisone), prophylaxis of infusion reactions (prednisone), treatment of swollen and stiff joints (prednisone), and treatment of CLL (dexamethasone); all four patients had PD as best clinical response.

No DLTs were reported during the study. However, a DLT was retrospectively identified in Patient 4 (Cohort II): Grade 4 thrombocytopenia developed 27 days after the final infusion of dacetuzumab and lasted 14 days; although the investigator considered the event related to dacetuzumab, the decision to advance to the next cohort had already occurred. Grade 4 thrombocytopenia was not observed in subsequent cohorts. The MTD of dacetuzumab was not established at the doses tested in this study.

Although 11 of 12 patients (92%) experienced at least one study drug-related AE, dacetuzumab was well tolerated and no dose-dependent trends in AEs were observed. AEs that occurred in ≥2 patients (17%) were fatigue, headache, anorexia, conjunctivitis, hyperhidrosis, and night sweats (Table IV). Most events were Grade 1 or Grade 2 in severity; however, Patient 4 (Cohort II, previously described), with Grade 1 thrombocytopenia at baseline, developed Grade 3 thrombocytopenia (considered related to study drug) that progressed to Grade 4 during follow-up. No patient died during the study, experienced a serious AE, or withdrew from the study due to an AE. No increase was observed in the severity of AEs in the two patients who received a second cycle of dacetuzumab.

Because AEs related to CRS are thought to occur primarily after the first few doses of dacetuzumab, an analysis was made of the incidence of AEs within 14 days of the first dose. Of the AEs that occurred in two or more patients, headache, anorexia, and conjunctivitis occurred exclusively within 14 days after the first dose. The incidence of fatigue, hyperhidrosis, and night sweats was comparable for the two periods (i.e., ≤14 days after vs. >14 days after the first dose).

Noninfectious ocular disorders were experienced by three patients during the study: Patient 7 had Grade 2 conjunctivitis, which resolved with antihistamine eye drops within 4 days; Patient 10 had Grade 1 conjunctivitis, which resolved with decongestant eye drops within 20 days; and Patient 9 had Grade 1 blepharitis with onset >2 weeks after the last infusion, which was treated with decongestant eye drops and was still present at the end-of-treatment evaluation.

Three patients experienced Grade 3 or Grade 4 abnormal laboratory results: Patient 4 (Cohort II) experienced Grade 4 decreased platelets, as previously described; Patient 8 (Cohort III) had Grade 3 decreased platelets at the end-of-treatment visit; and Patient 9 (Cohort III) had a transient Grade 3 decreased ANC on day 15. Grade 1 or 2 increases in AST (n = 7), ALT (n = 6), and alkaline phosphatase (n = 6) were observed during the study.

**Pharmacokinetics**

In Cycle 1, the maximum serum concentrations (C_max) of dacetuzumab increased with dose in this patient population (Figure 1). There also appears to be accumulation of trough levels throughout Cycle 1 after the completion of intrapatient dose escalation. High interpatient variability was observed in C_min values. Because of sparse sampling, exposure and terminal half-life could not be reliably calculated.

**Antitumor response**

Five patients (three in Cohort I, one in Cohort II, and one in Cohort IV) completed Cycle 1 with SD, but no patient in the study achieved an objective response. Although seven patients demonstrated PD, no patient experienced tumor flare during treatment, in the opinion of the investigators. No relationship between antitumor activity and dose was apparent (Table III). Ten of 12 patients (83%) had decreased peripheral lymphocytes at some point during treatment, and 3 of 10 patients (30%) with measurable postbaseline lesions had decreased tumor area (SPD) upon restaging (range, −7% to −15%; Table III).

Of the five patients with SD, two (Patient 3 in Cohort I and Patient 10 in Cohort IV) received a second cycle of dacetuzumab (four infusions every other week at the cohort-specific maximum dose [3 and 8 mg/kg, respectively]). Of note, these two patients, who had some of the highest baseline lymphocyte counts, also had the greatest reductions in circulating lymphocyte counts. At the end of Cycle 2, Patient 3 (Cohort I), who had a 74% drop in peripheral lymphocytes during Cycle 1 (Table III), had a 53% increase, compared with end of Cycle 1. Patient 10 (Cohort IV) had decreased peripheral

<table>
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<th>Table IV. Adverse events occurring in two or more patients.</th>
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<td>Preferred term</td>
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lymphocyte counts from 100,000/μL at baseline to 7000/μL after Cycle 1 and further decreased to 4000/μL after Cycle 2. However, this individual had increased adenopathy after treatment, meeting criteria for disease progression.

Correlative studies

Quantitative immunoglobulin levels were available for 7 of the 12 patients. Overall, slight decreases in IgG and IgA and no change in IgM concentrations were observed; however, the number of patients was small and substantial variability was observed.

Serum cytokine concentrations were available pre- and postinfusion for 11 of the 12 patients. Three of the 11 patients (27%) had increases in IL-6 (n = 3), IL-10 (n = 2), or TNF-α (n = 3) that were ≥4-fold higher than predose, suggesting that an increase in serum cytokine concentration may be a consequence of dacetuzumab administration. Patient 3 in Cohort I had increases in IL-6, IL-10, and TNF-α throughout Cycle 1 and Cycle 2; Patients 10 and 11 in Cohort IV had transient (Day 1 only) increases in IL-6 and TNF-α (and IL-10 in Patient 11) following the first infusion of Cycle 1. Of note, two of the three patients with ≥4-fold higher increases (Patient 3 in Cohort I and Patient 10 in Cohort IV) had significant decreases in circulating lymphocytes and were the only two patients to receive a second cycle of dacetuzumab.

In the available mononuclear cell subsets (7/12 patients), no clear patterns of changes were noted for T-cell subsets (CD3+, CD3+CD4+, and CD3+CD8+ cells), natural killer cells (CD15+ or CD56+), or monocytes (CD14+).

Peripheral blood cells were analyzed by flow cytometry for CD40 expression at baseline. Although all patients had detectable CD40+ CLL cells, the surface staining was low intensity, and 6 of 12 patients had CD40 coexpressed on less than 40% of CD19+ cells.

No evidence for human anti-human antibodies was observed in the 10 patients with available post-baseline data. However, interference from dacetuzumab in the serum may decrease the sensitivity of this assay.

Discussion

In this open-label, dose-escalation, phase I study, dacetuzumab was well tolerated in heavily pretreated patients with CLL. Using an intrapatient dose-escalation schedule of doses up to 8 mg/kg/week, the MTD of dacetuzumab was not reached with the use of acetaminophen and diphenhydramine premedication. Although no objective responses were reported, 5 of 12 patients had SD, with no apparent relationship to dacetuzumab dose level.

The patient population in this study had advanced disease and was heavily pretreated (median of four
prior systemic therapies), often with aggressive combination chemotherapy regimens. At baseline, all patients had significant adenopathy, and many had elevated $\beta_2$-microglobulin levels and relatively low levels of circulating CLL cells (Table III). Elevated $\beta_2$-microglobulin levels are associated with increasing tumor mass and worse prognosis [22,23]. Presence of bulky lymphadenopathy (greater than 3–5 cm in diameter) has been associated with failure to respond to mAb therapy in previous studies [24,25]. Of interest, two of the three patients with the highest circulating lymphocyte counts at baseline (75 000 and 100 000 cells/µL) were the patients with the greatest reductions in circulating lymphocyte counts and those who received a second cycle of therapy.

Overall, the baseline expression of CD40 on CLL cells was of low intensity and not uniform. Although the study comprised a limited number of patients, these data differ from those previously reported [26] in which >75% of CLL cells expressed CD40. It is noteworthy that CD20 is not highly expressed on CLL cells, but rituximab has proven to be a very active therapy when used in combination with chemotherapy [5,15]. In this study, the lack of DLT and modest antitumor activity of dacetuzumab suggest that further evaluation of this antibody in combination with other therapies may be feasible.

The dominant mechanism of action for dacetuzumab in CLL has not been determined. Immune effector functions (ADCC and ADCP) may be involved in depleting CLL cells, in which case the antitumor activity could be related to the status of the innate immune system. Hence, the modest activity observed in this small study could have been partially attributable to significant immunosuppression associated with prior therapies, and greater antitumor activity might be observed in patients with less advanced disease. Additionally, dacetuzumab may signal via crosslinking CD40 on the surface of CLL cells, which might induce apoptosis, sensitize the cells for other agents, or result in greater immune recognition of CLL cells via the upregulation of immune costimulatory molecules [18,27,28]. It is also possible that multiple mechanisms of actions may work differently in different patients, depending upon the characteristics of their CLL cells and residual immune cell function. Because of the partial agonistic signaling properties of dacetuzumab, it is possible that exposure could lead to an increased proliferative rate. It is noteworthy that, in the opinion of the investigators, no patients experienced tumor flare during treatment.

Although the study was limited by the small sample size, no dose-response relationship for safety or antitumor activity was apparent. The maximum dose of dacetuzumab tested in this study (8 mg/kg/week) was considered adequate to deplete B cells in preclinical testing and is similar to or higher than most approved therapeutic monoclonal antibodies. Nonetheless, it is possible that the $C_{\text{min}}$ values and exposures were not adequate to provide maximum therapeutic effect and that higher levels would be associated with better responses. It is also noteworthy that Cycle 2 dosing was administered every 14 days, which could have resulted in longer intervals of subtherapeutic plasma levels.

In this population with advanced CLL, one DLT was recognized after cohort advancement (study drug-related Grade 4 thrombocytopenia lasting more than 7 days); however, no other drug-related Grade 3 or 4 AEs were identified during treatment with dacetuzumab. Furthermore, no dose-dependent trends were observed in AEs, vital signs, or laboratory values, including hematologic effects.

Some AEs did appear to be drug-related even in this small patient population. These include headache (as a manifestation of CRS), noninfectious ocular inflammation, and asymptomatic elevations in hepatic enzymes (ALT and AST). Although none of these events were serious or reached Grade 3 severity, they were each reported in more than one patient, generally within 2 weeks of the first infusion. It is possible that each of these events is related to the partial agonistic signaling of dacetuzumab. CD40 is expressed on monocytes and macrophages (including Kupffer cells in the liver) and conjunctiva, which may explain some of the AEs observed, and a first-dose effect could result from transient inflammatory effects [29]. It should be noted that these drug-related events also have been observed in other single-agent dacetuzumab trials, including those for multiple myeloma and non-Hodgkin lymphoma [30,31].

A planned phase II portion of the study was not conducted due to the decision by investigators and sponsor that a single-arm, single-agent study of dacetuzumab was not an optimal use of resources in this patient population. The observed safety profile and modest single-agent activity suggest that future trials testing dacetuzumab in combination with other CLL therapies may be worthy of consideration.

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