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# Epratuzumab

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*Humanized anti-CD22 MAb*
*Non-Hodgkin's Lymphoma Therapy*
*Treatment of Systemic Lupus Erythematosus*
*Treatment of Sjögren's Syndrome*

AMG-412
IMMU -103
IMMU-hLL2
LymphoCide™

Immunoglobulin G (human-mouse monoclonal IMMU-hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal IMMU-hLL2 κ-chain dimer

CAS: 205923-57-5
EN: 232820

**Abstract**

Monoclonal antibody (MAb) therapy has provided a major breakthrough for the treatment of B-cell malignancies and autoimmune diseases and the B-cell-specific immunoglobulin CD22 has been identified as a target for the treatment of such diseases, including non-Hodgkin's lymphoma (NHL), Sjögren's syndrome and systemic lupus erythematosus (SLE). Epratuzumab is a humanized MAb targeting CD22 that demonstrates efficacy *in vitro* in lymphoma cell lines and *in vivo* in SCID mice bearing lymphoma, with enhanced effects when administered in combination with the anti-CD20 MAbs rituximab and IMMU-106. Phase I/II clinical studies in NHL have demonstrated efficacy and objective responses with epratuzumab administered alone, in combination with rituximab or in radiolabeled form. Results from initial SLE and Sjögren's syndrome studies also demonstrated improvements in clinical signs and symptoms, and the antibody has been advanced to phase III trials for SLE, its first indication. Epratuzumab represents a versatile novel anti-CD22 MAb with promise for the treatment of B-cell diseases.

## Introduction

CD22 is a B-lymphocyte-specific 135-kD transmembrane sialoglycoprotein and a member of the immunoglobulin superfamily that is expressed on the cell surface only at mature stages of B-cell differentiation and that appears to play a critical role in B-cell development, survival and function (1-4). CD22 is postulated as a target for B-cell malignancies and its expression has been observed in up to 99% of non-Hodgkin's lymphoma (NHL) samples (5). B-cells are also known to play an important role in the pathogenesis of autoimmune diseases, including systemic lupus erythematosus (SLE) and Sjögren's syndrome, suggesting that CD22 might be a useful target for the treatment for autoimmune diseases (4, 6, 7).

The National Cancer Institute estimates that lymphoma, including Hodgkin's lymphoma and NHL, accounts for about 5% of all cases of cancer in the U.S. Whereas the mortality rate for Hodgkin's disease has decreased significantly in recent years due to treatment improvements, both the incidence and the mortality rate for the much more common NHL increased from 1975 to 2000, although they have stabilized since then (8).

SLE is a chronic inflammatory disease affecting various parts of the body, but especially the joints, skin, blood and kidneys. Like other autoimmune diseases, SLE develops when the immune system loses its ability to distinguish between foreign agents (antigens) and its own cells and tissues, and makes autoantibodies that form immune complexes with "self" antigens, which build up in tissues and can cause inflammation, injury and pain. Corticosteroids, nonsteroidal antiinflammatory drugs, immunosuppressants and antimalarials are currently used to treat symptoms, but there is no cure for this debilitating and sometimes life-threatening disease, and new treatment options are therefore needed. According to the Lupus Foundation of America, there are up to 1.5 million people in the U.S. with SLE, 90% of whom are women, most between the ages of 15 and 45. The average annual cost of medical treatment for patients with lupus has been estimated to be $6,000-10,000 (9).

Epratuzumab (IMMU-103, AMG-412, IMMU-hLL2, LymphoCid™) is a humanized MAb targeting CD22,

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designed at Immunomedics and currently being tested in phase III trials for SLE (10), as well as phase I/II studies in Waldenström's macroglobulinemia, Sjögren's syndrome and children with CD22-positive acute lymphoclastic leukemia (11). Activity has also been demonstrated in phase II studies in NHL. The MAb has received fast track designation from the FDA for SLE and Immunomedics has decided to proceed first with SLE registrational studies before those in NHL, in part due to the urgent need for new lupus treatments (11, 12).

## Pharmacological Actions

Initial *in vitro* studies investigated epratuzumab's mechanism of action in cell-based assays. In Chinese hamster ovary (CHO) cells, epratuzumab bound to the CD22 extracellular domain with high affinity ($K_D$ = 0.7 nM). In Burkitt lymphoma cell lines and primary B-cells, epratuzumab induced a significant increase in CD22 phosphorylation. Confocal microscopy also revealed a rapid and direct internalization of epratuzumab after binding to CD22, with a reduction in the number of cell-surface CD22 binding sites. Maximum internalization was comparable among B-cell populations, including samples from patients with B-cell malignancies, after several hours of treatment and appeared to reach saturation at antibody concentrations of 1-5 μg/ml (13).

In experiments in NHL cell lines, the antitumor activity of epratuzumab appeared to be mainly due to antibody-dependent cellular cytotoxicity (ADCC), whereas no significant activity was observed in assays for complement-mediated cell lysis, apoptosis or growth inhibition. *In vivo* studies in tumor-bearing SCID mice demonstrated an increase in survival compared to placebo-treated animals, particularly in animals with intact natural killer (NK) cells and neutrophils (14, 15). *In vitro* and *in vivo* experiments also demonstrated enhanced antitumor activity when epratuzumab was combined with MAbs targeting distinct antigens, such as the anti-CD20 MAbs rituximab and IMMU-106 (15, 16).

Studies in cynomolgus monkeys were carried out to investigate the effect of epratuzumab on normal CD22-expressing peripheral blood B-cells. Once-weekly administration of escalating doses of the compound (300, 900 or 2000 mg/m$^2$), given over a period of 4 weeks, resulted in partial inhibition (70%) of circulating B-cells compared to baseline at all doses. The serum exposure of epratuzumab increased dose-dependently, with mean $C_{max}$ values of 594, 1500 and 3530 μg/ml, respectively. Following the final treatment, a half-life of 4.4-6.3 days was observed, with B-cell levels recovering 7 weeks following the end of treatment (17).

## Pharmacokinetics

The pharmacokinetics of epratuzumab alone (360 mg/m$^2$ i.v. over 1 h weekly x 4 weeks) or in combination with rituximab (375 mg/m$^2$ i.v. over 3-6 h weekly x 4 weeks) were investigated in patients with B-cell NHL. The $C_{max}$ (336 μg/ml alone and 316 μg/ml in combination with rituximab) and AUC (46.6 μg/ml alone and 39.4 μg/ml with rituximab) of epratuzumab were similar in both groups and the $t_{1/2}$ was 19-25 days. The data suggest that the pharmacokinetics of epratuzumab are unaffected by the concomitant administration of rituximab (18), and these findings were corroborated in another similar study (19).

## Clinical Studies

Phase I/II clinical trial results demonstrated good tolerance and activity for epratuzumab in patients with relapsed/refractory indolent and aggressive NHL receiving 4 weekly infusions of 120-1000 mg/m$^2$. No serious or dose-limiting toxicity was observed. Response rates ranged from 10% in patients with aggressive NHL to 29% in subjects with diffuse large B-cell NHL at doses of 240 mg/m$^2$ or above, and durable responses (34+ months) were obtained (20-23).

Retreatment was assessed in 13 patients with disease progression following epratuzumab monotherapy. A second 4-week course of treatment was given 9-104 weeks following the start of their initial course at doses ranging from 240 to 1000 mg/m$^2$/week. Retreatment was well tolerated and achieved a second partial response in 2 of 6 patients who had had an initial response (24).

The feasibility of combination therapy with epratuzumab (360 mg/m$^2$) followed by rituximab (375 mg/m$^2$) and standard-dose CHOP chemotherapy administered once every 3 weeks was tested in newly diagnosed patients with diffuse large B-cell lymphoma. Grade 4 neutropenia was evident in all 11 patients evaluable for toxicity at various stages of the treatment and the incidence following 20 cycles was 29%. Three patients developed fever or infection and 9 patients required dose reductions. Grade 3 or 4 anemia (3 patients), thrombocytopenia (1 patient), cardiac (1 patient), neurological (2 patients) and pulmonary toxicity (1 patient) were also seen (25).

The safety and efficacy of epratuzumab in combination with rituximab were also assessed in a phase II study in NHL.. Four weekly infusions of epratuzumab (360 mg/m$^2$ i.v. over 60 min) plus rituximab (375 mg/m$^2$ i.v. over 4-6 h) were administered to rituximab-naive patients. Treatment-related adverse events occurred during the first week of infusion and were classified as grade 1-2. The most frequent adverse events included chills/rigors (42%), fever (34%), and nausea and flushing (25%). Preliminary efficacy data revealed 5 complete responses (26).

A multicenter, open-label clinical trial evaluated the efficacy of combining epratuzumab with rituximab in the management of relapsed/refractory NHL. Sixty-five patients with indolent or aggressive histology were treated with epratuzumab (360 mg/m$^2$ i.v.) plus rituximab (375 mg/m$^2$ i.v.) once weekly for 4 weeks. A total of 57%

of evaluable patients with indolent histology and 46% of patients with aggressive diffuse large B-cell lymphoma had a complete or partial response to treatment. After a follow-up of 15 months, disease progression was seen in 31% of patients with indolent disease and 69% of those with aggressive disease. The most common adverse events with this combination were rigors, fever, hypotension and nausea (27, 28).

Another multicenter, open-label study of this combination was carried out in patients with recurring low-grade NHL. Weekly infusions over 4 consecutive weeks were well tolerated in the 49 patients included in the study and were not associated with toxicity. Adverse events were reported by 88% of patients and included rigors (43%), nausea (24%), pyrexia (24%), vomiting (22%) and fatigue (22%). Peripheral B-cell counts decreased rapidly with the first infusion, lasting 6-9 months posttreatment. An objective response was obtained in 58% of patients (28% complete and 30% partial responses). Furthermore, patients who had previously received rituximab treatment more frequently achieved objective responses (75% compared to 48% of rituximab-naive patients) (29).

Phase I/II trials have also evaluated the utility and safety of radioimmunotherapy with labeled epratuzumab in patients with relapsed/refractory NHL. Both $^{90}$Y-labeled epratuzumab (30-32) and $^{186}$Re-labeled antibody (33) have demonstrated promising antitumor activity and no major toxicity.

An initial open-label, nonrandomized study was conducted to assess the feasibility, safety and efficacy of epratuzumab in SLE. In 11 of 14 patients who completed treatment (360 mg/m$^2$ every 2 weeks for 4 cycles), infusions administered over 23-86 min were well tolerated. B-cell levels decreased immediately after treatment and for up to 4 weeks, during which time measurable epratuzumab levels were evident in serum. SLE assessments showed consistent clinical improvement and BILAG (British Isles Lupus Assessment Group) global disease activity was decreased in all patients immediately following treatment, with 73% reaching over a 50% reduction compared to baseline. This attenuated activity was still evident for 10 weeks following treatment in all patients, and in 78% 18 weeks later (11, 34, 35). The current pivotal phase III trials known as ALLEVIATE (Alleviate Lupus Affliction with Epratuzumab and Validate its Autoimmune Safety and Efficacy), one in SLE patients with severe flares and the other in patients with moderately active SLE, were subsequently initiated (10).

An open-label, nonrandomized trial has been performed in 15 patients with primary Sjögren's syndrome to assess feasibility, safety and efficacy. Patients received 360 mg/m$^2$ of epratuzumab every 2 weeks for a total of 4 doses. Fourteen patients received all 4 infusions without reactions, with a median infusion time of 50 min. B-cell levels decreased posttreatment, with no significant change in T-cells or immunoglobulins. Epratuzumab serum levels ranged from 67 to 245 μg/ml and half-life ranged from 7 to 10 days following the fourth infusion. Patients reported improvements in their clinical signs and symptoms, including dry/irritated eyes (58%), dry mouth (36%), fatigue (64%), tender joints (100%) and tender points (67%). These improved responses were still evident at assessment points 4 and 12 weeks later (36).

## Source

Immunomedics, Inc. (US).

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