

**A phase Ib trial of Atacicept (TACI-Ig) to neutralize APRIL and BLYS in patients with refractory or relapsed B-Cell Chronic Lymphocytic Leukemia (B-CLL)**

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*Abstract:*

**Background:** B-CLL cells are resistant to apoptosis and thus exhibit prolonged survival and accumulation *in vivo*. Exogenously added soluble BLYS (B-Lymphocyte Stimulator) and APRIL (A Proliferation-Inducing Ligand) have been shown to protect B-CLL cells from apoptosis *in vitro*. Nurse-like cells derived *in vitro* from CLL patients express high levels of APRIL and BLYS and thereby support CLL cell survival. Inhibition of APRIL significantly reduces CLL viability *in vitro*, indicating an important role for APRIL in this setting.

**Methods:** This is an open-label, dose-escalation phase I trial to assess the safety, pharmacokinetics and biological effects of atacicept administered intravenously once weekly for 5 weeks to patients with refractory or relapsed B-CLL. Eligible patients are being enrolled in sequential cohorts of 3 to receive atacicept at 1, 4, 10, 15, 20 or 27 mg/kg. Evaluation of response is being assessed using NCI-WG criteria.

**Results:** Preliminary results of the first 4 cohorts of the dose-escalation study are reported. Twelve CLL patients have entered the trial. No dose limiting toxicity has been observed and no SAE related to study drug has been reported to date. One case of mild nausea is the only drug-related toxicity reported to date. Three of six patients treated with 10 mg/kg and 15 mg/kg experienced a stabilization of their disease during the treatment period; prior to start of atacicept treatment, all had rapidly increasing leukocyte counts. One of these patients (10 mg/kg cohort), who was refractory to fludarabine therapy, has had stable disease according to NCI-WG criteria for over six months and is still receiving atacicept treatment. This same patient had a slight decrease (approximately 14% change from baseline) in absolute CLL cell concentration by Day 29 before final dosing. At lower dose levels all patients demonstrated progressive disease.

**Conclusions:** Treatment with atacicept was well tolerated at the dose levels tested so far. The multiple cases of disease stabilization at higher dose levels in this heavily pre-treated patient population are promising, and support further study with atacicept in CLL. Accrual of patients at higher dose levels is ongoing.