

## [Abstract 48]

### A PHASE I TRIAL OF OBLIMERSEN SODIUM FOR RELAPSED OR REFRACTORY WALDENSTROM MACROGLOBULINEMIA.

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#### Introduction

Antisense oligonucleotides are used to inhibit messenger RNA function and inhibit protein translation. Bcl-2 expression proteins have been implicated in mediating resistance to apoptotic cell death in Waldenstrom macroglobulinemia. Oblimersen sodium is a specific inhibitor of Bcl-2 expression and has shown activity in multiple myeloma and in Waldenstrom cell lines. The in vitro data led to the development of a phase I study for Waldenstrom patients with relapsed or refractory disease.

#### Materials and Methods

Eligible patients had symptomatic Waldenstrom macroglobulinemia that had failed prior cytotoxic chemotherapy and have had at least one of the following: hemoglobin  $\leq$  11 g/dL, a platelet count  $\leq$  100,000/uL, bulky lymphadenopathy, or hyperviscosity syndrome. As a phase I study, the primary end point of the study was toxicity assessment and patients are evaluated in cohorts of 3. Patients are also assessed for response using the level of the monoclonal protein. The drug was administered as a 24-hour continuous infusion for 7 days every 21 days, with escalating doses beginning at 3 mg/kg and a target of 7 mg/kg/day for 7 days to a maximum of 8 cycles.

#### Results

To date 6 patients have been accrued at dose level 1. In addition, 3 patients are currently being evaluated at dose level 2. This abstract focuses on those patients treated at the first dose level. Of these 6 patients, 5 were women, 2 had refractory disease, and 3 patients had a history of transfusion. The median age was 74.5 years, ranging from 58 to 81. The median number of prior regimens was 4 (range: 2-7). One patient had a dose-limiting toxicity on the first cycle of therapy, which was grade 3 fatigue and anorexia, and the dose for this patient was reduced. Two patients had non-hematologic grade 3 toxicity, possibly related to therapy. Five out of 6 patients on dose level had grade 3 or greater hematologic toxicity. Three patients required dose reductions in subsequent cycles. To date one patient has had a partial response with the serum M spike falling from 3.6 to 1.1 g/dL. The quantitative IgM fell from 6,000 mg/dL to 1,000 mg/dL.

#### Conclusion

Oblimersen is well tolerated in patients with Waldenstrom. Hematologic toxicity is frequent in this cohort with heavily involved bone marrows. Dose reductions with subsequent cycles are frequently required. Evaluation of the maximum tolerated dose continues, where limited data on response is promising.