

## SUPPRESSION OF CYCLIN D 1 (CD1) BY ON 01910.Na IS ASSOCIATED WITH DECREASED SURVIVAL OF TRISOMY 8 MYELODYPLASTIC BONE MARROW: A POTENTIAL TARGETTED THERAPY FOR TRISOMY 8 MDS

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CD34 positive cells from patients with trisomy 8 myelodysplastic syndrome (MDS) have pronounced expression of early apoptotic markers compared to normal hematopoietic cells. However, trisomy 8 clones persist in patients with bone marrow failure and expand following immunosuppression (Sloand EM et al; Blood 2005; 106(3):841). We have demonstrated up-regulation of c-myc, survivin, and CD1 in CD34 cells of patients with trisomy 8 (Sloand et al; Blood 2007; 109(6):2399). Employing siRNA mediated knockdown of the anti-apoptotic protein survivin, we demonstrated a decrease in trisomy 8 cell growth and postulated that increased Cyclin D1 caused the upregulation of survivin resulting in resistance of these cells to apoptosis.

Using fluorescent *in situ* hybridization (FISH) we showed that the novel styryl sulfone, ON 01910.Na (Vedula MS et al; European Journal of Medicinal Chemistry 2003;38:811), inhibits cyclin D1 accumulation and is selectively toxic to trisomy 8 cells while promoting maturation of diploid cells. Flow cytometry of cultured cells demonstrated increased proportions of mature CD15 positive myeloid cells and decreased number of immature CD33+ cells or CD34+ blasts (add ASH 2007 reference). These encouraging *in vitro* data led to a phase I/II trial of ON 01910.Na in MDS patients with refractory anemia with excess blasts who had IPSS => int-2. This study was designed to assess the safety and activity of escalating doses of ON 01910.Na (800 mg/m<sup>2</sup>/day x 3 days, 800 mg/m<sup>2</sup>/day x 5 days, 1500 mg/m<sup>2</sup>/day x 5 days, 1800 mg/m<sup>2</sup>/day x 5 days every 2 weeks) in MDS patients. To date five MDS patients have been treated with ON 01910.Na for 4 to 16 weeks in the first two dose cohorts. Two patients had isolated trisomy 8, two had complex cytogenetic abnormalities including trisomy 8 in all aneuploid cells, and one had monosomy 7. Four of five patients demonstrated a rapid and significant decrease in the number of blasts (from a 16% mean baseline to 6% at Day 28; p=0.02) and aneuploid cells after 4 weeks of therapy (see below), concomitantly with increases in neutrophil and/or platelet counts in four patients. All four patients exhibiting a biological effect of drug treatment had trisomy 8 in their aneuploid clone prior to therapy. One monosomy 7 patient, previously refractory to EPO became responsive to Darbopoietin and another trisomy 8 patient became platelet-transfusion independent. Infusions were well tolerated. Only two serious adverse events were reported (atrial fibrillation successfully cardioversed and unlikely related to the drug, with a prior history in one of the two patients).

