

**ESTYBON™ (ON 01910.Na) - a clinical stage multi kinase inhibitor:
Synthesis, structure activity relationship and biological activity**

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Cyclin D proteins are elevated in many cancer cells and targeted deletion of Cyclin D1 gene in the mammary tissues protects mice from breast cancer. Accordingly, there is an increasing awareness of this novel non-enzymatic therapeutic target for cancer. We have developed novel, non-alkylating styryl benzyl sulfones that are finding success in clinical trials in advanced cancer patients and in Myelodysplastic Syndromes (MDS), which are associated with aberrant expression of Cyclin D proteins.

Here we describe the structure function analysis of sodium (*E*)-2-(2-methoxy-5-[(2,4,6-trimethoxy-styrylsulfonyl)methyl]phenylamino)acetate (ON 01910.Na, ESTYBON™), which is in Phase 3 trials for MDS. In vitro studies with ESTYBON™ showed the inhibition of PI3K/AKT pathway, downregulation of cyclin D1, induction of NOXA and BIM and activation of JNK pathway. The fact that MDS patients bone marrow (particularly trisomy 8) over expresses cyclin D1 and in vitro studies have demonstrated the activity of ESTYBON™ against cytogenetically abnormal cells and blasts despite minimal inhibition of normal hematopoiesis provides a rationale for its use in MDS. The FDA has granted Orphan Drug Designation for the use of ESTYBON™ in MDS.

Sunday, March 27, 2011 07:00 PM

[General Poster Session \(07:00 PM - 09:00 PM\)](#)

Location: Anaheim Convention Center

Room: Hall B

Abstract #217

Potential new agent for refractory lymphomas, ON 013100 esters as a novel class of potent mitotic inhibitors: Synthesis, SAR and target identification

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Targeting components of the mitotic machinery in order to block tumor progression has been an area of intense research. This effort has resulted in several marketed anticancer agents, which provide a proof of concept for the approach. Examples include the taxanes and vinca alkaloids for which the principal target is the microtubule component of the mitotic spindle. More recently, alternate components of the mitotic machinery have been targeted in an attempt to develop novel anticancer agents.

From a screen of a small molecule compound library looking for inhibitors of mitotic cell phase, we identified a novel group of molecules with biochemical IC₅₀ in low nanomolar range. SAR analyses of this series of compounds led to ON 013100, a highly active agent arresting the tumor cells in mitotic phase. Modification of functional group in ON 013100 produced a variety of analogs with improved water solubility, bioavailability and anti-tumor activity. One of these analogs ON 013105 has entered clinical trials for refractory lymphoma (NCT01049113). In this presentation, we describe the synthesis, structure activity relationship and biotinylation of ON 013100 and its target identification by protein pull down assay using streptavidin beads.

Wednesday, 30 March 2011, 07:00 PM

[General Poster Session and Social with ORGN \(07:00 PM - 11:00 PM\)](#)

Location: Anaheim Convention Center

Room: Ballrooms C/D/E