Single-Cell Network Profiling (SCNP) to Evaluate the Protemic Profiles Associated with ON 01910.Na Treatment of MDS Patients

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ABSTRACT

Background: Single-Cell Network Profiling (SCNP) is used to measure simultaneously the effects of multiple modulations (including drugs) on intracellular signaling cascades at the single cell level. ON 01910.Na has been reported to target the kinase 1, 2, 3, PI3K, and Akt pathways. In an ongoing phase II study in late-stage (Falotak and the Janssen Krasian (JAK) signal transducers and activators of transcription (STAT) pathway) to identify specific proteomic profiles associated with the biological activity of ON 01910.Na in MDS pts.

Methods: MDS patient bone marrow samples were collected at baseline and after treatment cycles 1, 2 or high risk MDS pts refractory to hypomethylating agents. Bone marrow mononuclear cells (BMMCs) were stimulated with SCF, or granulocyte colony stimulating factor (GMSF), or a combination of these factors, and were assessed for several intracellular signaling cascades at the single cell level. ON 01910.Na was used in combination with SCF or on its own to test for the functional effects on intracellular signaling cascades at the single cell level. ON 01910.Na induced differentiation of CD34+ cells increased during the course of the clinical trial.

Results: SCNP analysis in PI 01910.Na (progressed to AML, after completion of trial) showed that frequency of CD34+cells increased during the course of the clinical trial, while when stimulated with either SCF or GMSF, compared to baseline findings, CD34+ cells exhibited increased p-S6 and p-Akt responsiveness with treatment; and interestingly, CD34+ cell responsiveness to G-CSF decreased (p-stat) and p-stat) while no signaling was observed in response to GM-CSF. In contrast, SCNP analysis in PI 01910.Na (stable disease), showed that frequency of CD34+ cells was maintained throughout; when stimulated with either SCF or G-CSF, the CD34+ cells exhibited decreased p-S6, p-Akt, p-ERK (right) and while CD34+ cell responsiveness to G-CSF increased (p-stat), a robust p-STAT5 response was observed which increased during the course of the clinical trial.

Conclusions: SCNP analysis of BMSC samples from 2 MDS patients, one of whom progressed to AML, restituted that measurement of signaling events was feasible in these situations. During the course of treatment, increased CD34+ cell counts correlated with progression to AML. The analysis of patient samples in this longitudinal study, under therapeutic pressure of treatment with ON 01910.Na, identified aberrant cellular signaling that contributed to the progression to AML. The approach could also be used to determine the mechanism of action of other drugs in other disease settings.

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