

Phase I study of Roneparstat (SST0001), an innovative heparanase (HPSE) inhibitor for multiple myeloma (MM) therapy

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Background: HPSE is an endo- β -d-glucuronidase that trims the heparan sulfate chains of proteoglycans, impacting cell signaling, gene expression and promoting extracellular matrix remodeling within the tumor microenvironment. High HPSE expression is associated with enhanced tumor growth, angiogenesis, metastasis and chemoresistance in several cancer types. As a result of its tumor promoting activities, HPSE is a promising new and unexploited target for anti-cancer therapy.

In MM preclinical models HPSE was shown to be a master regulator of aggressive tumor behavior and bortezomib or melphalan were found to enhance HPSE expression and secretion. High HPSE expressing MM cells were less susceptible to the cytotoxic effects of those drugs. A very significant increase in HPSE gene expression following chemotherapy was observed in patient-derived tumor samples, indicating a potential role for HPSE in regulating myeloma response to therapy.

Roneparstat, a 100% N-acetylated and glycol split heparin, is a potent HPSE inhibitor. In an in vivo model of disseminated myeloma, increased tumor killing was observed when melphalan or bortezomib were used in combination with Roneparstat.

Patients and Methods: A multicenter phase I study is ongoing in advanced heavily pre-treated refractory MM patients (pts) who have exhausted all available anti-MM therapies. Flat dose Roneparstat is administered subcutaneously DX5W1,W2 Q28D. Each cohort plans 3 + 3 pts. A direct fluorescence method (Heparin Red assay) and an indirect measurement (aPTT and TT based) of Roneparstat plasma concentration are used in pharmacokinetic (PK) studies and for assessing patient's exposure to the drug.

Results: To date, 17 pts have been enrolled, with 5 cohorts (doses ranging from 25 to 200 mg/day) evaluated and 400 mg cohort ongoing, with a total of 43 cycles administered. Roneparstat was safe and well tolerated systemically and locally, with only minor reactions (redness, bruising) at the injection site (in 6 pts, all grade 1). Preliminary PK data show measurable plasma levels at 200 and 400 mg/day (LOQ 1 μ g/mL). Systemic exposure appears linear but slightly over-proportional with the dose. A partial response as per a decrease 50% in the serum monoclonal component, lasting for 6 cycles, was observed in one patient; stable disease was observed in another patient who received 9 cycles of therapy.

Conclusions: Roneparstat was found to be safe with only minimal local side effects and showed early signs of efficacy in some patients. Based on these results, Roneparstat, at a defined dose and in combination with other anti-myeloma agents, will be evaluated in relapsed/resistant MM pts.