**SNS-032 Exhibits Dose-dependent Mechanism-based Inhibition of CDK7 and CDK9 in Peripheral Blood Mononuclear Cells from Patients with Advanced Cancers Treated in an Ongoing Phase 1 Trial**


**SNS-032 is a selective inhibitor of CDKs 2, 7 and 9 that compares favorably to flavopiridol and seliciclib when assayed in human versus bovine serum. We successfully demonstrate mechanism-based, dose-dependent inhibition of CDKs 7 and 9 as decreased phosphorylation of pS5 and pS2 of RNA Pol II CTD. Decreased Mcl-1 suggests inhibition of survival proteins. These data indicate SNS-032 is a selective inhibitor of CDKs 2, 7 and 9 and pro-apoptotic agent than flavopiridol when assayed in human versus bovine serum.**

**Background**

It is hypothesized that targeted inhibition of CDKs 2, 7 and 9 will provide clinical benefit in hematologic cancers by inducing apoptosis of malignant cells and disrupting tumor cell proliferation. It is further hypothesized that inhibition of CDK2, 7 and 9 will disrupt the open chromatin state required for tumor establishment.

**Summary & Conclusions**

> SNS-032 is a selective inhibitor of CDKs 2, 7 and 9 that compares favorably to flavopiridol and seliciclib with respect to potency, selectivity and human plasma protein binding

> Human serum decreases the activity of flavopiridol while the activity of SNS-032 is maintained

> Inhibition of CDK activity by SNS-032 is 2X greater than flavopiridol in the presence of 10% human serum

> MM cell killing by SNS-032 is 5X greater than flavopiridol in the presence of 10% human serum

> Mechanism-based, dose-dependent target modulation of CDK7, CDK9 and down modulation of the survival signaling protein Mcl-1 is observed in PBMCs from patients treated with SNS-032.

> In contrast, target modulation has not been demonstrated in PBMCs from patients treated with flavopiridol suggesting that clinical activity observed with this drug may reflect off-target effects.

> Dose-dependent down modulation of actin was observed on Day 1, suggesting global inhibition of RNA polymerase II-mediated transcription by SNS-032.

Taken together, these observations support the ongoing Phase 1 study of SNS-032 in B-lymphoid malignancies, testing the hypothesis that inhibition of survival signaling in hematologic diseases will result in meaningful clinical benefit.

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**Abstract**

**SNS-032 is A More Potent Inhibitor of CDK9 Than Flavopiridol In 10% Human Serum**

RPMI-8226 MM Cytotoxicity Assay (MTT)

**Human Plasma PK Analysis Of SNS-032 Following 1hr Infusion**

**SNS-032 Induces Dose-dependent Target Modulation And Down-regulation Of Mcl-1**