#1334

sunesis

A PHASE 1 TRIAL OF SNS-032, A POTENT AND SPECIFIC CDK 2, 7 AND 9 INHIBITOR, IN CHRONIC LYMPHOCYTIC LEUKEMIA AND MULTIPLE MYELOMA

W. Wierda[1], R. Chen[1], W. Plunkett[1], D. Siegel [2], A. Badros[3], R. Sinha[4], L. Popplewell[5]; S. Coutre[6], J.A. Fox[7], U. Hoch[7] and Z. Goldberg[7]
[1]M.D. Anderson Cancer Center, Houston, TX; [2]Hackensack University Medical Center, Hackensack, NJ; [3]University of Maryland, Baltimore, MD;
[4]Emory University, Atlanta, GA; [5]City of Hope, Duarte, CA; [6]Stanford University, Palo Alto, CA; [7]Sunesis Pharmaceuticals, Inc., South San Francisco, CA

Abstract -Updated

Background: SNS-032 is a highly selective and potent inhibitor of cyclin-dependent kinases (CDK) 2, 7 and 9. CDK2 and CDK7 are involved in cell cycle regulation. CDK7, along with CDK9, regulate RNA polymerase II-dependent transcription. Temporary inhibition of RNA polymerase II-dependent transcription by SNS-032 has significant effects on short half-life transcripts and proteins, particularly survival factors, cell cycle regulatory proteins, and cytokines that are critical for the survival of malignant B-cells in chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). This is a phase 1 study in patients with advanced CLL or MM to evaluate the safety, pharmacokinetics (PK) and preliminary evidence of activity of a loading dose (LD) followed by a 6 hr infusion of SNS-032, given weekly for 3 consecutive weeks of each 28 day cycle. Dose and schedule aim to achieve and maintain for 6 hr threshold plasma concentrations equal to or greater than the in vitro concentration required to inhibit 90% of cell growth (IC90). The study incorporates an exploratory analysis of pharmacodynamic (PD) biomarkers. **Methods:** Previously treated patients with CLL or MM, measurable disease, and ECOG status 0-1 were eligible. Increasing doses of SNS-032 given as an LD followed by a 6hr infusion were evaluated. The total starting dose was 15 mg/m^2 with an LD of 5 mg/m^2 followed by 10 mg/m^2 over 6 hr. Dose escalation is by modified Fibonacci. PD studies of target modulation were performed on peripheral blood mononuclear cells (PBMC) taken pretreatment, and 2, 6 and 24 hr after the beginning of 6hr drug infusion. Immunoblotting was performed to analyse either direct target modulation or downstream effects of target inhibition: total RNA polymerase II, phospho-Ser2-RNA pol II, phospho-Ser5-RNA pol II, PARP cleavage, XIAP, Mcl-1, Bcl-2, and the loading control β-actin. Quantitative analyses were performed with changes in phosphorylation on RNA pol II normalized to total RNA pol II protein. Changes in the other proteins were normalized to β-actin. **Results:** As of May 21, 2008, 26 patients have been treated to date at total doses of 15, 22, 33, 50 and 75 mg/m^2. Median age was 63 (range 45-82). Median number of prior therapies was 4.5 (range: 1-11). At 75 mg/m^2, early evidence of biochemical TLS has been seen, although potassium levels remained stable. There has been 1 DLT at this level – inability to receive all 3 doses. PK analyses showed that predicted and measured concentrations are similar at the doses evaluated. PD analyses showed evidence of CDK9 inhibitory activity at the 75 mg/m^2 cohort with modulation of Ser 2 phosphorylation on RNA Pol II CTD detectable at 2 hours, and decreased Mcl-1 levels at completion of infusion (6 hours) in patient samples. **Conclusions:** The mechanism of action of SNS-032 supports testing this agent in B-cell malignancies such as MM and CLL. A pharmacologically-derived dose regimen that sustains concentrations of SNS-032 at 300 nM or 115 ng/mL (the in vitro IC90), for 6 hr is being studied. The predicted target levels have shown early evidence of clinical activity and PD modulation. Enrollment continues.

Study Design

- Single agent pharacologically guided dose escalation study of SNS-032 in patients with advanced MM or CLL
- Dose Regimen:
  - Loading dose (LD) by short IV infusion followed by 6 hour infusion to achieve and exceed target concentration greater than the in vitro IC90 (115 ng/mL) qweek x 3 in a 28 day cycle
  - LD 5 mg/m^2 in cohort 1, 10 mg/m^2 for subsequent cohorts
  - Total dose for cohort 1-5: 15, 22, 33, 50, 75 mg/m^2
- Cohorts of 3-6 patients; multi-center phase 1 study

Major Inclusion Criteria

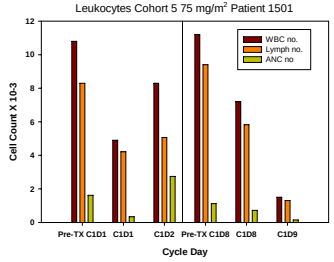
- MM – relapsed after at least 2 therapies; one of which should have included thalidomide or lenolidamide or bortezomib
- CLL – relapsed after at least one prior therapy
- Adequate hematologic, hepatic, and renal parameters; ECOG PS 0 or 1
- QTcf <500 msec

- **Major DLT Criteria (CTCAE v3.0) During Cycle 1**
  - Grade 4 neutropenia ≥ 14 days
  - Thrombocytopenia (≤30k) for ≥ 14 days after last dose of cycle 1
  - Grade 3 LFTs ≥2 days
  - TLS (tumor lysis syndrome) requiring hemodialysis
  - Inability to receive all 3 doses of SNS-032 within 28 days due to drug related toxicity

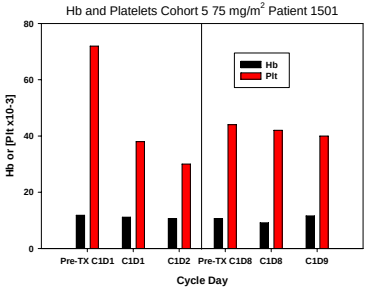
Patient Demographics

	MM N=12	CLL N=14	Total N=26
Median Age (years) (Range)	63.5 (53-72)	62 (45-82)	63 (45-82)
Male (N)	3	13	16
Female (N)	9	1	10
ECOG PS (N) 0 1 2	1 10 1	1 12 1	2 22 2
Median Prior Tx (N) (Range)	3 (3-11)	7 (1-9)	5 (1-11)

SNS-032 Decreases Leukocyte Counts



SNS-032 Decreases Platelets But Not Affect Hb



SNS-032-Related DLTs and TLS

	Cohorts 1-3 15-33 mg/m^2	Cohort 4 50 mg/m^2		Cohort 5 75 mg/m^2	
Disease	MM/CLL	MM	CLL	MM	CLL
N	15	5	3	1	5
DLT	0	0	0	0	1*
TLS	0	0	0	0	4**

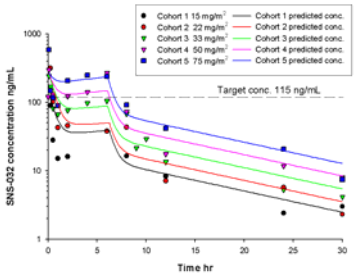
* Received only 2 of 3 Cycle 1 doses due to vascular leak syndrome
** Biochemical evidence of TLS

SNS-032-Related Biochemical TLS

	Pre-Tx	C1D1	C1D8	C1D9	C1D15	C1D16
Uric Acid mg/dL	6.1	9	4.7	11.4	4.7	7.1
ALT IU/L	34	33	32	38	38	43
LDH IU/L	777	3153	764	1450	671	941
K mEq/L	3.8	3.1	3.4	3.7	3.7	3.9
Phosphorous mg/dL	3.4	5.6	2.5	5.1	2.9	4.1
Na mEq/dL	142	135	140	139	138	136
Cr mg/dL	1.2	1.2	1.1	1.4	1.2	1.3

SNS-032 Target Concentration Exceeded in Cohort 5

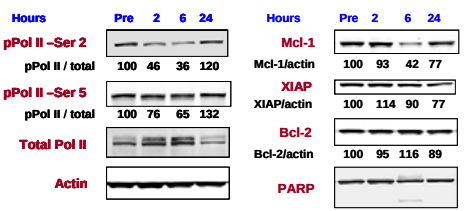
Mean Plasma Concentration-Time Profiles



- Concentrations above SNS-032 in vitro IC90 (115 ng/mL) for 6 hours are achieved in Cohort 5, 75 mg/m^2
  - SNS-032 concentrations > 200 ng/mL were observed at this dose level
  - SNS-032 concentrations of ~ 290 ng/mL are predicted for 100 mg/m^2, the dose anticipated for Cohort 6
- Observed and predicted concentrations are similar; SNS-032 PK are described by a 2 compartment pharmacokinetic model

SNS-032 Induces Mechanism-Based Target Modulation

Evaluation of PD Markers - Cohort 5 75 mg/m^2 Patient 1503 – CLL (Representative Data)



- Transcriptional inhibition demonstrated by marked down-regulation of Mcl-1 and modest down-regulation of XIAP
- Both CDK7 and CDK9 were inhibited by SNS-032 as indicated by decreased phosphorylation of Ser5 and Ser2 of RNA Pol II, respectively; the extent of CDK9 inhibition exceeded that of CDK7
- Apoptosis is detected at the completion of infusion by cleaved PARP evident at 6 hr
- Overall, over 50% of samples demonstrate evidence of target modulation by SNS-032
- These findings are consistent with those in CLL cells treated with SNS-032 in vitro (Chen et al. Proc ASH, 2007)

Summary & Conclusions

- Early evidence of SNS-032 mechanism-based activity is demonstrated in patients with advanced CLL treated at doses that maintain serum concentrations of drug above the IC90 for at least 6 hours
  - Mechanism-based target modulation is demonstrated. Data are consistent with previous reports of primary CLL cells treated with SNS-032 in vitro (Chen et al AACR 2007)
  - SNS-032 induces biochemical TLS. This is clinically manageable with standard TLS measures; 1 patient was withdrawn for drug-related vascular leak syndrome
  - SNS-032 induces decreases in leukocyte and platelet counts at 75 mg/m^2
- Trial enrollment and dose escalation continue for both MM and CLL

PDF available at: http://www.sunesis.com/science/presentations_and_publications.php