

# SNS-595: Preliminary Results Of Two Phase 2 Second Line

## Studies In Lung Cancer

SUNESIS

H Burris<sup>1</sup>, L Krug<sup>2</sup>, G Shapiro<sup>3</sup>, P Fidas<sup>4</sup>, J Crawford<sup>5</sup>, T Reiman<sup>6</sup>, G Michelson<sup>7</sup>, C Berman<sup>7</sup>, K Mahadocon<sup>7</sup>, U Hoch<sup>7</sup>, D Adelman<sup>7</sup>, and D Ettinger<sup>8</sup> for the SNS-595 Lung Cancer Study Group

<sup>1</sup>Sara Canon, Nashville, TN, <sup>2</sup>Memorial Sloan Kettering, NYC, <sup>3</sup>Dana Farber, Boston, MA, <sup>4</sup>Mass General Hospital, Boston, MA, <sup>5</sup>Duke University, Durham, NC, <sup>6</sup>Cross Cancer Centre, Edmonton, Canada, <sup>7</sup>Sunesis Pharmaceuticals, Inc., So. San Francisco, CA, <sup>8</sup>John Hopkins University, Baltimore, MD

### ABSTRACT (updated Sept 2007)

SNS-595 is a novel cell-cycle inhibitor that induces DNA damage responses, G2 arrest, and apoptosis. SNS-595 currently is being tested clinically in AML and ovarian cancer. **Objectives:** To assess the response rate (RR), using RECIST criteria, patient safety, and time to progression (TTP), duration of response (DOR), and overall survival (OS) in patients (pts) with refractory (Ref) and sensitive (Sen) SCLC and advanced NSCLC treated with SNS-595.

**Methods:** In both studies, SNS-595 was given q3 weekly at a dose of 48mg/m<sup>2</sup> IV bolus for up to 8 cycles. Both studies used a 2-stage Fleming design. The SCLC study had 2 strata, refractory (Ref = relapsed <90 days after end of initial therapy or never responded) and sensitive (Sen = relapse >90 days after response to initial therapy). The SCLC study was powered to detect a 18% ORR for the Ref and a 30% ORR for the Sen strata. The study enrolled 20 pts in stage 1 for both strata and required at least 1 response in the Ref and 2 responses in the Sen for continuation to stage 2 and enrollment of 20 more pts in each stratum. The NSCLC study was powered to detect a 15% ORR. The study required a minimum of 1 response in the first 25 pts for study continuation to study stage 2 with 25 more pts. **Conclusions:** SNS-595 demonstrates clinical activity as single agent 2nd-line therapy in SCLC-Sen and NSCLC. For SCLC-Sen pts, ORR was 2/22 (9%, 2 PRs), with 16/22 (73%) showing SD. For NSCLC pts, the ORR was 1/28 (4%, 1PR) with 50% (14/28) showing SD. SNS-595 is well tolerated with neutropenia being the main Grade 3 or 4 AE that occurred in 12-15% of pts. SNS-595 met the pre-determined RR in the SCLC-Sen cohort warranting expansion of this cohort to additional patients.

### BACKGROUND

SNS-595 is a replication-dependent DNA damaging agent that causes irreversible growth arrest of proliferating cells and rapid apoptosis resulting in potent anti-tumor activity. SNS-595 has a mechanism of action that includes DNA intercalation, as well as a unique inhibition of topoisomerase II that causes highly selective DNA damage. SNS-595 has demonstrated preclinical evidence of activity in several mouse lung cancer models. Patients enrolled in a Phase 1 study (q3 weekly dosing, 41 advanced solid tumor patients) were risk stratified based on prior myeloablative chemotherapy into minimally and heavily pre-treated groups (as defined by Tolcher *et al*, JCO 2001) The study results demonstrated:

- The primary dose limiting toxicity of SNS-595 observed was neutropenia
- Grade 3 or 4 neutropenia occurred in 34% of patients with 1 reported febrile neutropenia
- The MTD for heavily pre-treated patients was 48mg/m<sup>2</sup> administered q3 weekly (also the Phase 2 starting dose)
- The MTD for minimally pre-treated patients is likely to be 60mg/m<sup>2</sup> administered q3 weekly and could be considered as a dose for Phase 2 studies in this patient population

(As presented at ASCO 2006, Abstract #3062)

### METHODS AND SCHEMA

- Primary Endpoint: ORR using RECIST criteria
- Secondary Endpoints: Safety, TTP, DOR, PFS, OS
- Treatment: SNS-595 48 mg/m<sup>2</sup> IV q3 weekly for up to 8 cycles
- Patient population: lung cancer patients that have failed 1<sup>st</sup> line platinum based therapy
- Phase 2, 2-stage design
  - NSCLC: 25 pts/stage, powered to detect a 15% ORR
  - SCLC Sensitive: 20 pts/stage; powered to detect a 30% ORR
  - SCLC Refractory: 20 pts/stage; powered to detect an 18% ORR

### PATIENTS

Table 1: Patient Demographics

	SCLC-Sen N = 26	SCLC-Ref N = 25	NSCLC N = 31
<b>Age (yrs)</b>			
Median	59	59.7	62.6
Range	46-82	46-81	35-76
<b>Sex</b>			
Male	12 (46%)	16 (64%)	20 (65%)
Female	14 (54%)	9 (36%)	11 (35%)
<b>Race</b>			
African-American	1 (4%)	0 (0%)	3 (10%)
Caucasian	25 (96%)	25 (100%)	28 (90%)

Table 2: Patient Baseline Characteristics

	SCLC-Sen N = 26	SCLC-Ref N = 25	NSCLC N = 31
<b>ECOG Performance Status</b>			
0	8 (31%)	4 (16%)	8 (26%)
1	16 (62%)	17 (68%)	23 (74%)
2	2 (8%)	2 (8%)	0 (0%)
Not done	0 (0%)	2 (8%)	0 (0%)
<b>Stage at Diagnosis</b>			
Limited	12 (46%)	2 (8%)	I 1
Extensive	14 (54%)	23 (92%)	II 1
			III 7
			IV 22
<b>Metastases at Entry?</b>			
Yes	16 (62%)	21 (84%)	26 (84%)
No	10 (38%)	4 (16%)	5 (16%)

### SAFETY DATA

SNS-595 is generally well tolerated with a clinically manageable adverse event profile

- Primary Grade 3/4 adverse event was neutropenia
- Incidence of febrile neutropenia was lowest for SCLC sensitive cohort
- Incidence of Grade 3/4 neutropenia (15%) was much lower than observed in the Phase 1 dose escalation study (34%)

Table 3: Frequent (>5% pts) NCI CTCAE Grade 3 or 4 Adverse Events

	SCLC-Sen N=26	SCLC-Ref N=25	NSCLC N=31
<b>Blood &amp; Lymphatic Systems Disorders</b>			
Neutropenia	<b>4 (15%)</b>	3 (12%)	4 (13%)
Febrile neutropenia	1 (4%)	<b>3 (12%)</b>	4 (13%)
Leukopenia	1 (4%)	1 (4%)	3 (10%)
<b>General Disorders</b>			
Fatigue	1 (2%)	2 (8%)	<b>7 (23%)</b>
<b>Infections</b>			
Pneumonia	1 (2%)	2 (8%)	2 (7%)
<b>Musculoskeletal</b>			
Arthralgia	-	-	2 (7%)

Bold – Most frequent AE

Table 4: Number of Patients with Dose Delays and/or Reductions due to Neutropenia

	SCLC-Sen N=26	SCLC-Ref N=25	NSCLC N=31
Delay	4 (15%)	0	3 (10%)
Reduction	0	2 (8%)*	2 (6%)*
Both	2 (8%)	2 (8%)	0

\* one of the two patients had febrile neutropenia

### PHARMACOKINETICS

SNS-595 demonstrates highly reproducible pharmacokinetics

- Low inter-patient variability in SCLC patient population consistent with Phase 1 population

Table 5: SNS-595 Pharmacokinetics

	Dose (mg/m <sup>2</sup> )	n	T <sub>1/2</sub> (hr)	AUC (µg·hr/mL)	CL (L/hr/m <sup>2</sup> )	V <sub>ss</sub> (L/m <sup>2</sup> )
Phase 2 SCLC	48	8	18±3	28±7	1.8±0.4	45±12
Phase 1	3-75	40	22±11	29±11*	2±0.7	53±11

\*n=11 @48 mg/m<sup>2</sup>

### DRUG EXPOSURE

Table 6: Exposure to SNS-595

# Cycles Completed	SCLC-Sen N = 26	SCLC-Ref N = 25	NSCLC N = 31
0	0	1	0
1	6	7	5
<b>2</b>	<b>8</b>	<b>12</b>	<b>18</b>
3	2	2	0
4	5	1	2
5	2	0	0
6	2	2	5
7	0	0	0
8	1	0	1

Bold - Median

### EFFICACY RESULTS

SNS-595 shows evidence of clinical activity in lung cancer (A=SCLC Sensitive; B=SCLC Refractory; C=NSCLC)

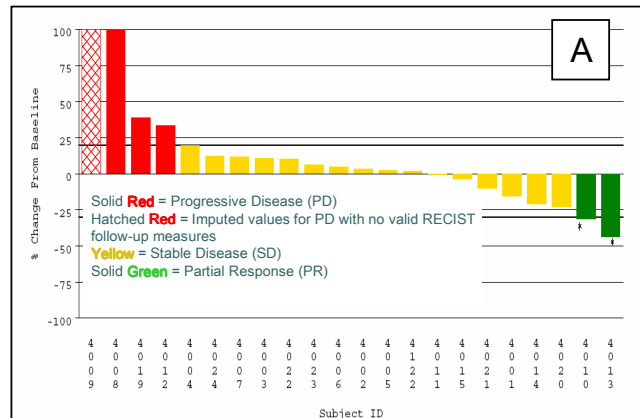


Figure 1. Waterfall plot of response (RECIST) of 22/26 SCLC Sensitive patients treated with SNS-595, for whom evaluation data was available

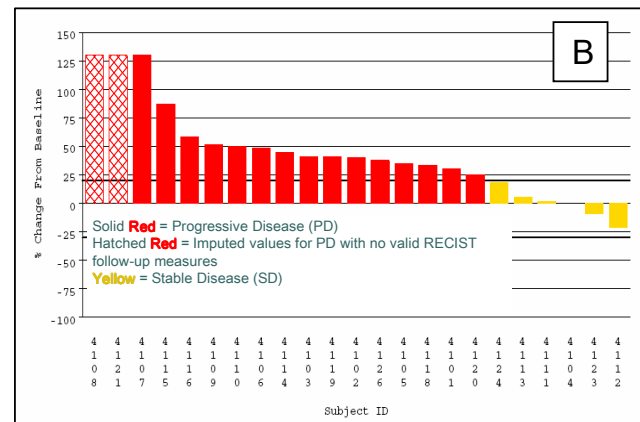


Figure 2. Waterfall plot of response (RECIST) of 23/25 SCLC Refractory patients treated with SNS-595, for whom evaluation data was available

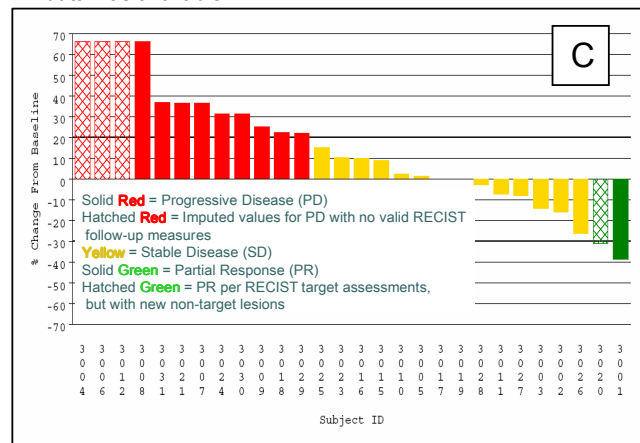


Figure 3. Waterfall plot of response (RECIST) of 28/31 NSCLC patients treated with SNS-595, for whom evaluation data was available

### CONCLUSIONS AND FUTURE DIRECTIONS

- ✓ SNS-595 demonstrates single agent activity in 2<sup>nd</sup> line lung cancer (NSCLC and SCLC) patient populations.
- ✓ SNS-595 was most active in SCLC sensitive population with 2/22 (9%) ORR and 16/22 (72%) stable disease.
- ✓ The incidence of Grade 3/4 neutropenia was lower in the lung cancer patients in this study (15% or less) than in a Phase 1 mixed tumor population of heavily pre-treated and minimally pretreated patients (34%) administered SNS-595.
- ✓ Further evaluation of SNS-595 in 2<sup>nd</sup> line SCLC sensitive patients should be at 60 mg/m<sup>2</sup>, the likely starting dose for minimally pre-treated patients.
- ✓ The nonclinical combination studies previously reported, which show additivity or synergy with commonly used agents, together with the evidence of clinical activity, suggest that further exploration of SNS-595 in combination with other chemotherapeutic agents is warranted.