

A Phase 1 Trial of SNS-314, A Novel and Selective Pan-Aurora Kinase Inhibitor, in Advanced Solid Tumor Patients

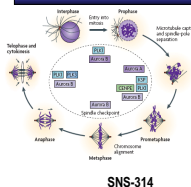
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ABSTRACT - UPDATED

Background: The Aurora Kinases are a family of serine/threonine kinases (Aurora Kinases (AK) A, B, and C) that play a key role in orderly progression through mitosis and have been implicated in a wide range of human tumors. Elevated expression levels of AKs have been detected in a high percentage of melanoma, colon, breast, ovarian, gastric, and pancreatic tumors, and in a subset of these tumors the AURKA locus (20q13) is amplified. SNS-314, a novel aminothiazole-derived urea, is a selective inhibitor of AKs A, B, and C with IC50 values in the low nanomolar range. **Methods:** The trial is a standard 3+3 phase 1 dose escalation study design. Patients (pts) with advanced solid tumors were treated with SNS-314 given as a three hour IV infusion once weekly X 3 (28 day cycle). Primary endpoints of the study are: safety, tolerability, and DLT assessment. Secondary endpoints of the study include: to determine the Maximum Tolerated Dose (MTD), SNS-314 pharmacokinetics (PK), potential pharmacodynamic (PD) correlates, and assessment of antitumor activity. PD evaluation comprised analysis of skin punch biopsies via immunohistochemistry (IHC) to assess histone H3 phosphorylation (pH3), using H+E stain as control for tissue integrity. **Results:** A total of 24 pts (13M/11F) have been enrolled into 7 cohorts: median age=58.5 (range 37-73). The initial dose was 30 mg/m² with subsequent dose escalation doubling until first observation of clinically significant ≥ Grade 2 related toxicity then according to a modified Fibonacci schema. Dose doubling occurred from 30 to 960 mg/m², and then a 50% increase was done to 1440 mg/m² per investigator discretion. SNS-314 has generally been well tolerated at the doses studied. There was one dose limiting toxicity (DLT) of grade 3 neutropenia preventing administration of all 3 doses of SNS-314. Pharmacokinetic estimates over the doses administered reveal dose linear increases in AUC of the plasma concentration versus time curves, a moderate to low clearance, and a terminal half-life of 10.4 hours. Pharmacokinetic parameters were similar after the first and third-weekly dose administrations, indicating no change in SNS-314 disposition following repeated administration. At all dose levels concentration vs. time profiles showed spikes in plasma concentrations or a flat terminal phase suggesting possible entero-hepatic recirculation of SNS-314. Inhibition of pHH3 induced by SNS-314 was observed in skin biopsies of patients treated at doses of 240 mg/m² and greater. There have been no objective responses to date. **Conclusions:** SNS-314 is a novel inhibitor of AKs A, B, and C. At the 240 mg/m² dose level we observe inhibition of Histone-H3 phosphorylation and serum SNS-314 levels exceeded preclinical target inhibitory levels. PD assessment of drug-mediated target modulation is ongoing. The compound has been well tolerated and no objective responses have been observed to date. Dose escalation continues.

BACKGROUND



Aurora A and B Are Required for Successful Mitosis

Aurora A controls centrosome maturation and mitotic spindle formation

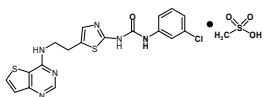
Aurora B ensures chromosome segregation and alignment as part of the chromosomal passenger protein complex

Aurora C is thought to function similarly to Aurora B

SNS-314

SNS-314 In Vitro Profile

- Aurora A IC50 9 nM
- Aurora B IC50 31 nM
- Aurora C IC50 3 nM
- EC50 cell proliferation 1.8-24.4 nM and EC50 induction of polyploidy (>4N DNA) 4.2-93 nM in a diverse panel of human cancer cell lines



STUDY OBJECTIVES AND TRIAL DESIGN

Study objectives:

Primary: to determine the safety and tolerability of SNS-314 administered as a 3 hour infusion once a week for 3 consecutive weeks followed by a rest week
Secondary: to determine the Maximum Tolerated Dose (MTD), SNS-314 PK, potential PD correlates, and assessment of antitumor activity

Trial Design:

Phase 1 dose escalation study
Standard 3 + 3 design with cohorts of 3-6 patients/cohort
Starting dose of 30 mg/m²
Dose doubling until CTC v 3 Grade≥2 clinically significant drug related toxicity; further escalation by modified Fibonacci schema
SNS-314 administered as a weekly 3 hour infusion x 3 weeks with one rest week (cycle length of 28 days); Patients can continue to receive SNS-314 treatment until progression or other protocol defined reasons
PK analysis obtained at day 1 and 15; PD analysis – skin punch biopsies for pHH3 (phosphohistone H3) at baseline and after infusion on day 1
At MTD, an additional 10 patients with accessible tumor will be biopsied for further PD analysis

Major Inclusion Criteria:

Written informed consent
Age ≥18 years
Advanced solid tumor for which no satisfactory treatment exists
Adequate hematologic, renal, and hepatic parameters

Major Exclusion Criteria:

Uncontrolled CNS metastases
History of arrhythmia or prolonged QTc interval; medications which prolong QT interval
Recent myocardial infarction, CVA
Allergies to Captisol®

Dose Limiting Toxicity (DLT) Definitions:

Grade 4 neutropenia >7 days
Grade 3 or 4 febrile neutropenia
Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding requiring platelet support
Uncontrolled nausea, vomiting, or diarrhea lasting >24 hours
Inability to receive all 3 doses of SNS-314 due to drug related AE
Any other clinically significant grade 3 or greater nonhematologic AE not considered related to underlying disease
Persistent QTc (Federica) >500 msec

DEMOGRAPHICS

Age (range)	58.5 (37 – 73)
Sex	54% Male 46% Female
Race	67% Caucasian 21% African-American 8% Asian 4% Native American

TUMOR TYPES N=23

Type	N
Nonsmall Cell Lung Cancer	8
Mesothelioma	3
Ductal Carcinoma	2
Sarcoma	2
Ovarian Cancer	2
Pancreas Cancer	2
Endocervical Cancer	1
Poorly Differentiated Cancer	1
Adenocystic Carcinoma	1
Small Cell Lung Cancer	1

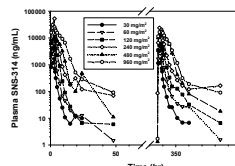
GRADE 1 AND 2 ADVERSE EVENTS (AEs) ≥ 15% (N=24) AND SERIOUS AEs

Event	%
Nausea	42
Constipation	21
Vomiting	21
Diarrhea	17
Fatigue	42
Urinary tract infection	17
Pain in Extremity	21
Headache	17
Anxiety	17
Cough	17

There were no grade 3 or higher AEs with an incidence of ≥ 15%.

There have been 2 SAEs to date: 1 of anemia, GI bleed, pneumonia 1 of left middle cerebral artery cerebral vascular accident. Both were judged to be unrelated to study drug per investigator assessment.

PHARMACOKINETICS



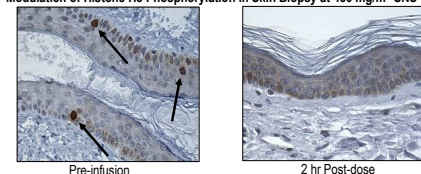
AUC increase was dose proportional while C_{max} was less than dose proportional from 30-960 mg/m².

- AUC increase was dose proportional while C_{max} was less than dose proportional from 30-960 mg/m².
- There was no drug accumulation.

PK Parameters		
T _{1/2} hr	CL L/hr/m ²	V _{ss} L/m ²
10.4	5.65	21.5

PHARMACODYNAMICS

Modulation of Histone H3 Phosphorylation in Skin Biopsy at 480 mg/m² SNS-314



SNS-314 Decreases pHH3 Phosphorylation in Skin Biopsies from Treated Patients

Dose (mg/m ²)	Decreased pHH3 After Tx	Pre-dose pHH3 (positive cells/field)	2 hr Post-dose pHH3 (positive cells/field)
240	Yes	1.4	0.7
	Yes	1	0
	Yes	4.7	0.7
480	Yes	0.6	0.1
	No	0.5	0.6
	Yes	3.0	0.7
960	Yes	3.0	0
	Yes	2.9	0.5
	Yes	1.7	0.3
1440	Yes	3	0.2
	Not Evaluable	0.2	0

- pH3 positivity defined as cells with intense staining in >50% of nuclear area
- Sample counts represent the number of positively staining cells per 100x field
Source of the pH3 (ser10) antibody – Cell Signaling Technology #9101

EFFICACY PER RECIST (N=17)

Complete/Partial Response	0
Stable Disease	5
Progressive Disease	12

The median number of cycles received was 2.

CONCLUSIONS AND FUTURE DIRECTIONS

- SNS-314 is generally well tolerated in this patient population.
- Pharmacokinetics is dose proportional for AUC.
- Pharmacodynamic modulation of pHH3 in skin biopsies was observed in most patients following treatment with SNS-314 at doses of 240 mg/m² or higher.
- Dose escalation continues – doses studied to date: 30-1440 mg/m².
- At the next dose level, approximately 1800 mg/m², predicted exposure would correspond to that at which activity was seen in animal models.