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

Francisco Robert1, Claire Verschraegen2, Herbert Hurwitz3, Hope Uronis3, Ranjana Advani4, Andy Chen4, Pietro Taverna5, Nancy Havrilla5, Marc Evanchik5, Rachael Hawtin5,

1Duke University, Durham, NC; 2Stanford University, Palo Alto, CA; 3Sunesis Pharmaceuticals, Inc., South San Francisco, CA

BACKGROUND

The Aurora Kinases are a family of at least three kinase family members (Aurora 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 melanomas, 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 DLTs. Secondary endpoints of the study include: to determine the Maximum Tolerated Dose (MTD), SNS-314 PK; potential pharmacodynamic (PD) correlates, and assessment of antitumor activity. PD evaluation comprised analysis of skin punch biopsies via immunohistochemistry to assess histone H3 phosphorylation (pH3), using an H3 stain as control for tissue integrity.

RESULTS: A total of 24 pts (10 M/14 F) have been enrolled into 7 cohorts (range 37-73). The initial dose was 30 mg/m2 with subsequent dose escalation until first observation of clinically significant Grade 2 related toxicity. Dose doubling began at 30 mg/m2, and then at 50 mg/m2 was increased to 1440 mg/m2 per investigator discretion. SNS-314 has generally been well tolerated at the doses studied. There was one dose limiting toxicity of Grade 3 neutropenia prevention 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-time profiles showed spires in plasma concentrations or a flat terminal phase suggesting possible entero-hepatic recirculation.

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

TUMOR TYPES N=23

PHARMACODYNAMICS

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

**PK Parameters**

<table>
<thead>
<tr>
<th>T1/2 hr</th>
<th>CL/L/M²</th>
<th>V1/L/M²</th>
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<td>12.4</td>
<td>5.65</td>
<td>21.5</td>
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**AURORA 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
- IC50 induction of apoptosis 4.2-83 nM

**DEMOGRAPHICS**

| Age (range) | 56.5 (37-73) |
| Sex | Male 54%, Female 46% |
| Race | Caucasian 67%, African-American 21%, Asian 8%, Native American 4% |

**AURORA IN SKIN BIOPSIES**

- **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
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**Efficacy**

- **Complete/Partial Response:** 0
- **Stable Disease:** 5
- **Progressive Disease:** 12

**CONCLUSIONS AND FUTURE DIRECTIONS**

- SNS-314 is generally well tolerated in this patient population.
- Pharmacokinetics is dose proportional for AUC.
- Pharmacodynamic modulation of pH3 in skin biopsies was observed in most patients following treatment with SNS-314 at doses of 240 mg/m2 or higher.
- Dose escalation continues – dosing studies 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.

http://www.sunesis.com/insolvency/presentations_and_publications.php