A Phase 1 Dose-Escalation Study of the Novel Cell Cycle Active Agent SNS-595 in Advanced Leukemias

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SNS-595 is a novel, cell cycle-active cytotoxic naphthyridine analog that induces G2 arrest in a variety of preclinical and clinical models. SNS-595 has shown single-agent efficacy in preclinical models, including human multiple myeloma, acute myeloid leukemia, and metastatic breast cancer. In addition, SNS-595 is well tolerated in combination with other agents. Preclinically, SNS-595 shows predictable and highly reproducible pharmacokinetics. The phase 1 study was designed to establish the safety, tolerability, and maximum tolerated dose of SNS-595 in patients with advanced or refractory acute leukemia.

**Methods:**
- SNS-595 injection was administered as a slow IV push over 15 min on days 1, 8, and 15. A 3+1 design was used to determine the MTD.
- Intermittent 3+3 dosing schedule on days 1, 8, and 15 for patients with CR/PR.

**Results:**
- A total of 35 patients were enrolled. The most common adverse events were nausea, vomiting, diarrhea, and mucositis. One dose-limiting toxicity was observed at 6 mg/m².
- The recommended phase 2 dose was 9 mg/m².

**Conclusions:**
- SNS-595 appears to be well-tolerated in patients with advanced leukemias, with preliminary evidence of clinical activity as measured by decreases in leukemic blasts.

**Background:**
- SNS-595 is a novel naphthyridine analog, a class of compounds not previously used for cancer treatment, and is a cell cycle-active agent that acts through DNA-PK signaling in the S phase to induce apoptosis and a G2-phase arrest of the cell cycle. Neutropenia was the dose limiting toxicity in two phase 1 studies (Proc ASCO 2006). Preclinically, SNS-595 has been shown to reduce bone marrow cellularity and circulating neutrophils in mice in a dose-dependent fashion (Proc AACR 2006) and is synergistic with cytoreductive drugs in mouse xenograft models (Proc ASH 2008).

**Methods and Schema:**
- DLT Definition: Neutropenia or thrombocytopenia occurring thru Cycle 1 Day 1 dose
- NCIT CTAIE Grade 3 hematologic event(s) occurring thru Cycle 1 Day 29 that are assessed as clinically significant and related to study drug and that persist in the absence of viable leukemia beyond 8 weeks after the Cycle 1 Day 1 dose

**Patient Demographics:**
- Male: 17 (59%) Female: 7 (21%)
- Ethnic Background:
  - White: 13 (77%)
  - Black: 2 (12%)
- Status:
  - AML: 16 (94%)
  - ALL: 1 (6%)

**Safety Data:**
- SNS-595 is well-tolerated
- One dose-limiting toxicity has been observed to date: prolonged myelosuppression
- Grade 4 neutrophilic fever was observed in one patient and was attributed to study drug

**Pharmacokinetics:**
- Dose dependent increase in exposure and no change in CL or Vss with dose escalation
- No accumulation or change in pharmacokinetic parameters after repeat dosing

**Pharmacodynamics:**
- SNS-595 shows predictable and highly reproducible pharmacodynamics

**Evidence of Activity:**
- SNS-595 reduces bone marrow blasts in 3 of the 5 relapsed/refractory poor prognosis AML patients dosed at 50 mg/m², a level expected to be near the MTD based on preclinical models
- 75 year old African-American female with relapsed AML showed bone marrow blast decrease from 70-80% to <5% after initial therapy with SNS-595 (previous failure with idarubicin and etoposide)
- 78 year old African-American male with relapsed/refractory secondary AML (from MDS) and poor risk cytogenetics showed bone marrow blast decrease from 80% to 2% after initial therapy with SNS-595 (previous failure with treatment with 7+3; HDAC, gemcitabine, and azacitidine)
- 66 year old Caucasian male with primary refractory AML and normal cytogenetics showed bone marrow blast decrease from 31% to 5% after initial treatment with SNS-595 (previous failure treated with 7+3 (2 x), 2-CDA/Ara-C)

**Conclusions and future directions:**
- SNS-595 is a novel cell cycle inhibitor with a unique mechanism of action
- Demonstrates evidence of clinical activity in relapsed/refractory AML patients and was well tolerated
- Predictable and highly reproducible pharmacokinetics
- RTOG study continuing
- Phase 1b combination, SNS-595 and cytarabine, planned for 2007
- Phase 2 trials in ovarian cancer, NSCLC, and SCLC are in progress

**Table 1: Patient Demographics**

<table>
<thead>
<tr>
<th>Ethnic Background</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>White</td>
<td>13</td>
<td>11</td>
<td>24</td>
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**Table 2: Baseline Characteristics**

| Disease Status   | AML 16 (94%) | ALL 1 (6%) |

**Table 3: Study drug AE Summary**

| AEs (all CTCAE Grades) (n (# treated)) | 17 | 14 | 31 |

**Table 4: Pharmacokinetics (mean ± SD)**

**Table A: PK Profile of SNS-595 in patients with advanced hematologic malignancies**

- Define a recommended dose regimen for future phase 2 studies
- Obtain preliminary assessments of antileukemia activity

**Study Objectives:**
- Determine the safety and tolerability of escalating doses of SNS-595 Injection administered to patients assigned to one of two dosing schedules:
  - Schedule A: Once-weekly IV administration of SNS-595 Injection (Days 1, 8, and 15) for 3 doses per cycle
  - Schedule B: Twice-weekly IV administration of SNS-595 Injection (Days 1, 8, and 11) for 4 doses per cycle

**Table 1:**
- Patient Demographics
- Table 2: Baseline Characteristics
- Table 3: Study drug AE Summary

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- Baseline Characteristics
- Table 3: Study drug AE Summary

**Table 3:**
- Study drug AE Summary

**Table 4:**
- Pharmacokinetics (mean ± SD)

**Figure 1:**
- Pharmacokinetic profile of SNS-595 in patients with advanced hematologic malignancies