PHARMACOKINETIC/PHARMACODYNAMIC CORRELATION WITH CLINICAL RESPONSES IN A PHASE 1 STUDY OF PATIENTS WITH RELAPSED/REFRACTORY ACUTE LEUKEMIA AS TREATED WITH SNS-595

Michelle R. Arkin1, Rebecca Ricklis2, Jeffrey Lance3, Frank Giles4, Ute Hoch1, Tarra Fuchs-Knotts1, David Stockett1, Nguyen Tan1, Matt Suster1, Don Young1, Glenn Michelson1, Judith A. Fox1, Judith E. Karp2

**Introduction and Background**
- SNS-595 is a novel naphthyridine derivative that causes highly selective, replication-dependent DNA-damage, irreversible G2 arrest, and rapid onset of apoptosis.
- The complex mechanism of action of SNS-595 includes non-classical inhibition of topoisomerase II that is clearly differentiable from classic inhibitors such as etoposide and doxorubicin.
- SNS-595 is in Phase 1 and 2 clinical trials in hematologic and solid malignancies.
- Preliminary clinical, pharmacokinetic (PK) and correlating results from an on-going escalating-dose phase 1 trial of SNS-595 in refractory acute leukemias are presented.

**Mechanism of Action of SNS-595**
- SNS-595 inhibits DNA-damage and apoptosis are observed at 60 mg/m² Qwk (Table 2).
- SNS-595 demonstrates:
  - Clinically important activity, including CR and CRp, when administered on either a weekly or biweekly schedule.
  - Potential for flexibility when dosed in combination with other anti-leukemia agents.
  - Allowing multiple cycles of SNS-595 without reduction in dose.
  - No dose-limiting gastrointestinal toxicities, including mucositis, yet observed at clinically active doses.
  - DNA damage responses, consistent with its mechanism of action.
  - A relationship between sustained threshold levels and clinical responses.

**PK Parameter is Associated With Clinical Activity**
- SNS-595 is a novel naphthyridine derivative that causes highly selective, replication-dependent DNA-damage, irreversible G2 arrest, and rapid onset of apoptosis.
- Clinical Responses Appear To Correlate With Time above threshold concentration of 1 µM per week.
- Table 1: Grade 3 or 4 Adverse Events with > 5% Incidence
- Table 2: Grade 3 or 4 AE and LAS with >5% incidence

**Evidence For Mechanism-Based Activity in Peripheral Blasts**
- DNA Damage And Apoptosis Are Observed At 60 mg/m² Qwk Pt 2024 Shows Greater Apoptotic And Bone Marrow Responses Than Pt 2025
- CONCLUSIONS AND FUTURE DIRECTIONS:
  - Next Steps: Initiate a Phase 1b study of SNS-595 in combination with cytarabine in patients with advanced acute leukemias later this year.
  - SNS-595 demonstrates:
    - Clinically important activity, including CR and CRp, when administered on either a weekly or biweekly schedule.
    - Potential for flexibility when dosed in combination with other anti-leukemia agents.

**FACS analysis of hH2AX**
- Western analysis of PARP

<table>
<thead>
<tr>
<th>Patients Tested</th>
<th>Cycle 1</th>
<th>CRp</th>
<th>CR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 µg x 3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60 µg x 3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2: Bone Marrow Responses in AML**
- Patients in RED are still on study.
- CR+Ref: complete remission and complete remission with partial hematologic recovery.
- CRp: partial remission.
- Data excluded from analysis if not a complete hematologic recovery and complete cytogenetic remission.
- DNA damage seen with PARP cleavage.

**Clinical Responses**
- Clinical Responses Appear To Correlate With Weekly Time Above 1 µM Threshold Concentration
- Time above 1 µM per week (% per week) (µM per week: mean ± SD)
- Table 3: PK Summary
- SNS-595 Plasma Concentration-Time Profiles

**SAFETY DATA**
- **Table 1: Grade 3 or 4 Adverse Events with > 5% Incidence**
- **Table 2: Grade 3 or 4 AE and LAS with >5% incidence**

**Correlation Between PK and PD**
- Patients with > 95% reduction in BM blasts
- Dose, mg/m²
- Time above 1 µM in plasma (hrs)
- Schedule A
- Schedule B

**Clinical Results**
- DNA damage → hH2AX → Apoptosis → hH2AX + cleaved PARP
- PK Parameter is Associated With Clinical Activity
- Clinical Responses Appear To Correlate With Weekly Time Above 1 µM Threshold Concentration
- Table 3: PK Summary