There was no significant difference in median or mean LINE1 demethylation between overall responders and/or decitabine treatment failures with SGI-110, a Novel Second Generation Hypomethylating Agent (HMA).

Myelodysplastic syndromes (MDS) comprise a spectrum of bone marrow stem cell malignancies, characterized by dysplastic and ineffective hematopoiesis — leading to variable grades of peripheral cytopenias — and an increased risk of progression to acute myeloid leukemia (AML).

There are no proven effective treatments for intermediate or high risk MDS after failure of azacitidine and/or decitabine. SGI-110 is a novel potent hypomethylating agent (HMA) designed as a DNA-diluting agent with the following characteristics:

- Prolonging decitabine plasma half life as SGI-110 slowly releases decitabine from DNA up to 8+ hours.
- Improved small volume and stable formulation (estimated volume per daily SQ injection 1-2 mL; and stability up to one month after injection).
- Extending exposure time to decitabine after injection (incorporation into DNA).
- Lower Cmax than decitabine IV.
- Longer exposure window of decitabine up to 8+ hours.
- Overall exposure doubled with decitabine from SGI-110 versus DAC IV from 8 hours versus 3.4 hours.

There were conducting a phase 1/2 trial of SGI-110 in patients with relapsed or refractory MDS or AML. This presentation describes the clinical characteristics and outcomes of the MDS patients treated in the phase 1 part of the trial.

Cytosine Analogues as Hypomethylating Agents (HMAs)

- SGI-110 is a Decitabine-containing dinucleotide designed to have the following improvements over currently approved HMAs:
  - Protecting decitabine from deamination.
  - Prolonging decitabine plasma half life as SGI-110 slowly releases decitabine.
  - Extending exposure time to decitabine after injection (incorporation into DNA).
  - Improved small volume and stable formulation (estimated volume per daily SQ injection 1-2 mL; and stability up to one month after reconstitution).

SGI-110: Novel HMA with Improved Characteristics

SGI-110-01 Phase 1/2 Clinical Trial

Part A Dose Escalation (78 pts)

Relapsed or Refractory Intermediate to High Risk MDS or Relapsed or Refractory AML; ECOG PS 0-2

Part B Dose Expansion (~200 pts)

4 Groups: Relapsed/refractory AML; Relapsed High Risk MDS (with prior MDS treatment); Treatment naïve elderly AML; Treatment naïve MDS.

Primary:
- Define Biologically Effective Dose (BED) [lowest dose that achieves a maximum hypomethylating effect or gene expression in at least 3 successive dose levels] and Maximum Tolerated Dose (MTD) [DLT incidence in Course 1].

Secondary:
- Incidence and severity grades of DLT, AE, and labs; PK profile of SGI-110 and decitabine: Response rates, hematologic improvement and duration of response; Time to AML (only for MDS patients).

Baseline Characteristics of MDS Patients

Baseline Characteristics of MDS Patients

MDS Patient Enrollment by Dosing Regimen

- Daily x 5 (n=9): 1 (2 mg/m²), 2 (18 mg/m²), 1 (36 mg/m²), 1 (60 mg/m²), 1 (90 mg/m²), 3 (125 mg/m²).
- Weekly x 3 of (n=6): 1 (6 mg/m²), 3 (18 mg/m²), 2 (90 mg/m²).

PK and PD in All Patients (MDS and AML)

- Dose-dependent increase in demethylation up to 60 mg/m² daily x 5.
- Similar demethylation of 60, 90 and 125 mg/m² daily x 5, therefore BED established at 60 mg/m² daily x 5.
- SGI-110 daily x 5 regimen achieved superior demethylation than the weekly x 3 regimen.

MDS Response

- Total MDS Responders 62 (40%) [95% CI = 16%, 68%].
- Median response duration 92 days (range, 28–126 days).

LINE1 Demethylation and Correlation with Response in MDS Patients

- There was no significant difference in median or mean LINE1 demethylation between overall responders and non responders in MDS patients.
- Two patients who achieved mCR showed excellent LINE1 demethylation of > 10% (-19% and -38%).

SGI-110 Related Adverse Events in > 1 patient (n=15) [MDS]

- Most common AE: Injection Site Pain, Thrombocytopenia, Anemia, Neutropenia, Fatigue.
- Grade >/= 3: Thrombocytopenia, Neutropenia, Fatigue.
- Grade >/= 4: Neutropenia.

Conclusions

- SGI-110 delivers extended exposure of decitabine enabling:
  - Longer exposure window of decitabine up to 8+ hours.
  - T/C ratio of decitabine from SGI-110 is 4-fold longer than decitabine IV.
  - Lower Cmax than decitabine IV.
  - Pronounced demethylation with dailyx5; less demethylation with weeklyx3.
  - Responses observed in heavily pre-treated MDS patients for an overall response rate of 40% [95% CI = 16%, 68%]. Median response duration 92 days (range, 28–126 days); all patients enrolled were previously exposed to a hypomethylating agent.
  - BED 60 mg/m² dailyx5, MTD 90 mg/m² dailyx5 highest tolerable dose for MDS. Most common AEs: Injection site pain (only Grade 1) and myelosuppression.
  - Phase 2 Dose Expansion ongoing: randomization to 60 or 90 mg/m² dailyx5 for treatment naïve and relapsed/refractory MDS. As of 10 June 2013, more than 40 patients were enrolled in treatment naïve MDS group.

References