Hepatocellular Carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer death worldwide (1).

Sorafenib treatment improves survival in advanced disease, but no therapy has demonstrated significant activity after progression on sorafenib (12).

SGI-110, a nucleoside analog and deoxyguanosine (Fig 1), offers increased in vivo exposure of decitabine by protecting it from deamination due to slow release upon SQ injection. In Phase 1 AML/MDS studies, SGI-110 provides longer exposure and more potent pharmacodynamic compared to decitabine (23).

Preclinical studies demonstrated:
- In vitro, SGI-110 induced significant hypomethylation of tumor suppressor genes RASSF1A, SOC51 and DAB2IP in human cell lines HepG2 or Hep62 and resulted in a potent reduction in colony formation in low numbers of cells of SGI-110 (10).
- SGI-110 efficiently sensitizes HCC cells and xenografts to oxaliplatin by inhibiting distinct signaling pathways, allowing for high antitumor activity without systemic toxicity (Kuang et al., AARC 2015, Abst 253).

Numerous epigenetic alterations accumulate during hepatocarcinogenesis, leading to activation of oncogenes or loss of tumor suppressor genes in HCC. Specifically, increased methylation of genes implicated in HCC tumorigenesis has been associated with pathogenesis and poor outcome (13).

In this study, we evaluated therapeutic and biologic effects of SGI-110, a hypomethylating agent (HMA) with an open phase I/II design. PK and PD results of this open-label, phase 2 study in patients with HCC are presented here.

**Study Conduct**

- **Dosing in 28 day cycles**:
  - SGI-110 daily dose 1.5 of a 28-day cycle
  - Initial dose 60 mg/m²
  - Due to myelosuppression seen in first 4 subjects, the dose was reduced from 60 mg/m² to 45 mg/m² for subsequent patients
  - PK/ PD samples collected pre and post dosing
  - Disease assessment (radiological): every 8 weeks

- **Subjects are encouraged to remain on treatment for at least 6 cycles because delayed responses have been observed with HMAs**

**Pharmacodynamic (PD) and Pharmacokinetic (PK) Results of the Second-generation Hypomethylating Agent, SGI-110, in Patients with Hepatocellular Carcinoma (HCC) after Progression on Sorafenib**

**Study Background**

- **Hepatocellular Carcinoma (HCC)** is the sixth most common cancer and the third most common cause of cancer death worldwide (1).
- **Sorafenib treatment** improves survival in advanced disease, but no therapy has demonstrated significant activity after progression on sorafenib (12).

**Overall the mean 1-line demethylation relative to baseline was** - 34.5% ± 12.0%

**Demethylation was observed in blood from all subjects, including 7 subjects with Disease Control at 16 weeks**

**Overall average demethylation was** - 34%

**Six out of 7 subjects with disease control at 16 weeks showed potent MZB1-specific demethylation**

**Conclusions/Summary**

- **SGI-110 dosed at 45mg/m² D1 on a 28-day cycle** was generally well tolerated in an HCC population previously progressed on sorafenib.
- **Potential global DNA demethylation (LINE-1) was observed in blood and tumor DNA**
- **Extent of LINE-1 demethylation apparently was higher on cycle 2 than cycle 1 in tumor biopsies**
- **Demethylation was also observed in a majority of subjects on promoter of tumor suppressor gene MZB1 which is frequently hypermethylated and silenced in HCC**
- **Changes in blood and tumor LINE-1 and MZB1 methylation are promising and consistent with the desired biologic effect of SGI-110**
- **Correlation of data with previously performed studies (study 02 AMI/MDS) suggests that both SGI-110 and decitabine exposures in HCC subjects appear to be higher and more persistent**

**References**