Guadecitabine (SGI-110) is a novel subcutaneous (SC) next generation hypomethylating agent (HMA) designed as a dinucleotide of decitabine (DAC) and deoxoguanosine that is resistant to degradation by cytidine deaminase (CDA) and results in prolonged in vivo exposure to its active moiety DAC. The differentiated pharmacokinetic profile offers the potential of improved biological and clinical activity and safety over currently available HMAs.

In the Phase 1 study, patients with r/r AML were treated at escalating doses of guadecitabine. In the Phase 2 study, r/r AML patients were randomized to receive guadecitabine at 60 mg/m² or 90 mg/m² SC daily for 5 days (daily x5). In a separate cohort, patients were treated with 60 mg/m² SC daily for 10 days (dailyx10: days 1-5 and 8-12) for up to 4 cycles followed by subsequent courses of the dailyx5 regimen. All regimens were dosed with a 28 day treatment cycle.

We have reported the clinical efficacy and safety results from the Phase 1 dose-escalation study in AML and MDS (Issa et al, Lancet Oncology 2015) and the Phase 2 randomized dose-response study in r/r AML at 2 dose (60 and 90 mg/m²) in a 5-day regimen (Kantarjian et al, ASH 2013) and 60 mg/m² in the 10-day regimen (Griffiths et al, ASCO 2014).

Baseline expression of genes associated with DNA methylation and HMA mechanism of action were consistently ranked as main predictor of clinical response irrespective of patient gender, dose and dosing schedule (Figure 2a).

Hematologic expression of CTCF and CDA were highest predictors of response (> 10% predictive power)

Age (11%) was also a significant predictor of response.

Methylation levels did not improve response classification accuracy when integrated with baseline gene expression (Figure 2b).

High LINE-1 methylation percent change from baseline on days (81.5%) and (22.5%) were good predictors response

Low DNM3B expression along with high CTCF and CDA expression are significant predictors when integrated with methylation predictors

Time from start of treatment cycle, dosing schedule and expression of CDA(highest) were good predictors of LINE-1 demethylation overall (Figure 2c).

FT3-ITD & NPM1 mutations and cytogenetic risk were not significant predictors of response.

In conclusion, in r/r AML patients, guadecitabine-induced global DNA demethylation was strongly associated with clinical response and our model based on baseline gene expression (high CTCF & CDA and low DNM3B) in patients’ peripheral blood and clinical/demographic characteristics (high age) can predict response to guadecitabine with 70% accuracy.

References