Guadecitabine (SGI-110) is a novel hypomethylating dinucleotide of decitabine (DAC) and deoxyguanosine that is resistant to degradation by cytidine deaminase 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. We reported previously results from the Phase 1 dose-escalation study in AML and MDS and the Phase 2 randomized dose-response study in r/r AML patients of SGI-110 given SC at 2 doses (60 and 90 mg/m^2) in a 5-day regimen or at 60 mg/m^2 in a 10-day regimen. Here we report an overall assessment of the association between clinical responses, global DNA demethylation assessed by LINE1 assay and baseline expression of a panel of 7 genes (CDA, P15, P21, DNMT3B, DNMT3A, DNMT1 and CTCF) assessed by qRT-PCR.

**METHODS**

Peripheral blood DNA and RNA samples from 122 patients with r/r AML were analyzed (27 patients from the dailyx5 and 95 from the dailyx10 regimen of the phase 2). Global DNA methylation at baseline and after treatment, was estimated using bisulphite-PCR. Baseline Expression of a panel of 7 genes was evaluated by quantitative RT-PCR:

- cytidine deaminase (CDA)
- cytidine deaminase 2B (P15)
- cytidine deaminase inhibitor 1 (P21)
- DNA (cytosine-S)-methyltransferase 1 (DNMT1)
- DNA (cytosine-S)-methyltransferase 3 alpha (DNMT3A)
- DNA (cytosine-S)-methyltransferase 3 beta (DNMT3B)
- CCCTC-binding factor/zinc finger protein (CTCF)

**CONCLUSIONS**

Guadecitabine (SGI-110) is a second generation HMA that delivers decitabine with a longer half-life and a longer exposure.

Clinical responses correlates with extent of LINE-1 demethylation in rAML.

Baseline gene expression signatures characterized clusters of patients with significantly different global DNA demethylation and response rates after guadecitabine.

**REFERENCE**