SGI-110, a Novel Second Generation Potent DNA Methyltransferase Inhibitor, In Development for the Treatment of MDS and AML.  
Preclinical Safety, Pharmacokinetics, and DNA Methylation Results of a Low Volume Subcutaneous (SC) Formulation

Abstract

- A novel second generation DNA methyltransferase inhibitor that is currently in Phase II clinical trial for treatment of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). SGI-110 is a unique combination of decitabine and guanosine developed to be more biologically stable than decitabine by making it less prone to deamination by cytidine deaminase, thus offering a promising alternative to current hypomethylating agents approved in MDS. SGI-110 demonstrated potent activity in vivo using different routes of administration (Chang JG, et al, MDM Cancer Ther, 2010; in press).

- We report here the results of a novel SGI-110 non-aphoresis formulation intended for clinical use. The clinical formulation can be administered in small volumes subcutaneously (SC) at a concentration of 100 mg/mL. We evaluated 2 regimens: daily SC x 5 days (in rats, and rabbits); and weekly SC (once weekly in rabbits, and cynomolgus monkeys; and twice weekly in rats). Both regimens are intended for 28-day cycles.

- The 5-day regimen was well tolerated up to a dose of 1.5 mg/kg x 5 in the most sensitive species (rabbits) which is equivalent to 16 mg/kg x 3 in humans. The weekly regimen was also well tolerated up to 1.5 mg/kg x weekly in rabbits, and up to 3 mg/kg x weekly in monkeys (equal to 36 mg/kg x 3 in humans). Rats tolerated much higher doses (30 mg/kg/day x 5; and 20 mg/kg twice weekly x 4 weeks). The main toxicity was myelosuppression in all species. The relative biavailability of SGI-110 dosed SC is close to 100%. In vivo, SGI-110 slowly converts to decitabine in rats, and much slower conversion in monkeys compared to other species, possibly sustaining efficacy for longer duration. Dose proportion pharmacokinetics and no significant accumulation of both SGI-110 and decitabine levels were evident after SC treatment in both the 5-day and the weekly regimens. We studied changes in LINE-1 DNA methylation in rats and monkeys following SGI-110 SC administration. Changes in LINE-1 DNA methylation after SGI-110 SC weekly x 4 in rats at tolerated doses of 12.5, 25 and 50 mg/kg were evident during the first recovery week (Day 31) and were dose-dependent. Maximum methylation reduction was observed with 30 mg/kg x weekly in SGI-110. These data in rats suggest a delayed pharmacodynamic effect. 

- In monkeys, SGI-110 was administered at 3 mg/kg x SC for 3 weeks (Days 1, 8 and 15). Reduction in LINE-1 DNA methylation became evident by Day 8, reached a maximum decrease in red cell mass; all erythroid, neutrophil and lymphocyte counts were not a significant difference at Day 29.

- Global hypomethylation was also observed in rats (data not shown).

- Significant LINE-1 methylation reduction was sustained in monkeys for up to 4 weeks using the 3 mg/kg SC dose (Fig. 1). Importantly, changes in LINE-1 DNA methylation were observed in most species in chronic studies (data not shown).

- PK results show SGI-110 has therapeutic exposure in both rat and monkey, with the potential for once weekly SC dosing every 28 days.

- SGI-110 weekly SC administration results in 30% decrease in global LINE-1 DNA methylation in monkeys.

- PK results of SGI-110 and decitabine were not a significant difference at Day 29.

In conclusion, based on the non-human primate monkey data, this uniquely developed low volume subcutaneous SC formulation of SGI-110 may allow sustained efficacy with less toxicity at a lower volume compared with other formulations.

Conclusions

- Safety data from SGI-110 is not rat, rabbit, and monkey showed the expected myelosuppression which was reversible upon drug discontinuation.

- PK levels of SGI-110 and the derived decitabine increased with higher doses. SGI-110 converts rapidly to decitabine in vivo. However, the PK levels of decitabine in rat and monkey were lower than expected.

- Global LINE-1 hypomethylation was achieved in both rats and monkeys at well tolerated doses.

- Significant LINE-1 methylation reduction was sustained in monkeys for up to 4 weeks using the 3 weekly SC injections (Day 1, 8, and 15) offering a frequent and more convenient dosing schedule compared to once weekly SC dosing.

- Clinical phase I is ongoing in refractory MDS or AML patients with both SGI daily, qd weekly and twice weekly 28 days).

- Weekend human dose is 3 mg/kg/day, daily x 5 days and 8 mg/kg/day, weekly x 3 days.

PK of SGI-110 and Decitabine; Monkey

- *p < 0.05

- No significant accumulation was observed for SGI-110 or decitabine.

- Significant accumulation was observed for SGI-110 at each dose.

- No significant accumulation was observed for SGI-110 or decitabine.

- Changes in LINE-1 methylation levels observed from once weekly dosing (data not shown).

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