IN VIVO IMMUNOMODULATORY ACTIVITY OF SGI-110, A SECOND GENERATION HYPMETHYLATING AGENT, IN HEMATOLOGIC MALIGNANCIES

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Abstract

Second generation DNA hypomethylating agents use pharmacokinetics properties supporting their clinical application in cancer therapy. Among these, SGI-110 is a decitabine synthesized as a deoxyguanosine with combination of SGI-110 to decitabine, longer apparent half-life and lower Cmax than predicted equivalently on its immuno-modulatory activity.

Conclusions:

This work has identified a novel property of SGI-110 to re-express immune-biologically relevant antigens in AML and MDS patients; SGI-110 induces global genomic DNA demethylation in PBMC from AML and MDS patients, in a dose-dependent manner; SGI-110 induces the constitutive methylation levels of NY-ESO-1 and MAGE-A1 promoter in AML and MDS patients, in a dose-dependent manner; SGI-110 induces NY-ESO-1, MAGE-A1 and MAGE-A3 expression in PBMC from AML and MDS patients; the daily x3 treatment schedule was more effective as compared to the weekly x3 treatment schedule.

Altogether these findings identify novel immunomodulatory properties of SGI-110, providing the scientific rationale for its clinical development to implement new combined chemo-immunotherapeutic approaches for the treatment of cancer patients.

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Fig A: SGI-110 Phase 1/2 Clinical Trial Design

SGI-110 was administered 5 days/week (A) or weekly (B) regimens. (C) Percentage of NY-ESO-1 promoter methylation, relative to baseline, for each cohort of patients enrolled in the daily (A) or weekly (B) regimens. (C) Percentage of MAGE-A1 promoter methylation, relative to baseline, for each cohort of patients enrolled in the daily (A) or weekly (B) regimens.

Fig B: Quantitative RT-PCR analysis of NY-ESO-1 and MAGE-A1 expression in PBMC from AML and MDS patients treated with SGI-110

Quantitative RT-PCR analysis of NY-ESO-1 expression in PBMC from AML and MDS patients treated with SGI-110. (A) NY-ESO-1 expression in PBMC from AML and MDS patients treated with SGI-110. (B) MAGE-A1 expression in PBMC from AML and MDS patients treated with SGI-110.

Fig C: Comparison of quantitative RT-PCR and qMSP analyses of NY-ESO-1 in AML and MDS patients

Comparison of quantitative RT-PCR and qMSP analyses of NY-ESO-1 in AML and MDS patients treated with SGI-110. (A) NY-ESO-1 expression in PBMC from AML and MDS patients treated with SGI-110. (B) NY-ESO-1 promoter methylation, relative to baseline, for each cohort of patients enrolled in the daily (A) or weekly (B) regimens. (C) MAGE-A1 expression in PBMC from AML and MDS patients treated with SGI-110. (D) MAGE-A1 promoter methylation, relative to baseline, for each cohort of patients enrolled in the daily (A) or weekly (B) regimens.