Identification of Novel Methylation Biomarkers to Predict Clinical Response to SGI-110, a Second Generation Hypomethylating Agent (HMA), in Patients with Acute Myeloid Leukaemia (AML)

Simone Juelliger1, John F Lyons1, Joern Lewin2, Mohammad Azab3 and Pietro Taverna2

1Astex Pharmaceuticals, Cambridge, UK; 2Epigenomics AG, Berlin, Germany; 3Astex Pharmaceuticals, Dublin, CA.

Abstract

No. 1050

Introduction

SGI-110 is a second generation hypomethylating agent (HMA) formulated as a dinucleotide of decitabine (DAC) and decoxyguanosine that prolongs the in vivo exposure of decitabine by protecting it from deamination. It gets injected subcutaneously as a small volume, allowing longer half-life and more extended decitabine exposure than DAC IV infusion. SGI-110’s differentiated pharmacokinetic profile resulted in potent hypomethylation and clinical responses in previously treated MDS and AML patients in a phase 1 trial (Kantarjian H et al. 2012).

Here, we have identified novel DNA-methylation biomarker candidates that may be predictive of response to SGI-110 using Differential Methylation Hybridisation (DMH) profiling of the NCI-60 cell line panel (Fassbender A et al. 2010). Cell lines were stratified based on SGI-110 EC50 values from Colony Forming Assays and the degree of LINE-1 (Long Interspersed Nucleotide Elements) demethylation post-SGI-110 treatment. Both stratification data sets were used to classify cell lines into either SGI-110 sensitive or resistant, and to generate 249 genomic methylation sites as candidate biomarkers of response to SGI-110. Fifty genomic fragments that characterized sensitivity and resistance to SGI-110 in cancer cell lines were selected for further validation. These candidate markers were tested in DNA samples from whole blood from 44 treatment naïve and relapsed/refractory AML patients that were classified into responders and non-responders following treatment with SGI-110 in our phase 2 clinical study.

We have identified DNA methylation patterns associated with sensitivity and resistance to SGI-110 in vitro. The validated methylation biomarker discovery process based on DMH and DBS approaches may help to identify and characterise specific subgroups of AML patients that could preferentially respond to SGI-110.

SGI-110 is a dinucleotide of decitabine and deoxyguanosine that protects decitabine from deamination.

Figure 1: Chemical structure of SGI-110

Differential Methylation Hybridization (DMH) Technology as a tool to identify novel biomarker candidates

Figure 2: DMH is a discovery technology for unbiased profiling of methylated loci throughout the genome. Epigenomics’ proprietary DMH 2 generation microarray was used to generate the Oncosign™ data set which covers about 50k genomic loci. This DNA methylation dataset includes the genome-wide profiles from untreated NCI-60 cell lines and was used to search for marker candidates based on cell line sensitivity to SGI-110.

DMH Profiles to Stratify SGI-110 sensitive and resistant cancer cell lines based on changes in colony formation

Figure 3A: Clonogenic approach of stratification

DMH Profiles to Stratify SGI-110 sensitive and resistant cancer cell lines based on LINE-1 EC50 values for demethylation

Figure 3B: LINE-1 Methylation approach of stratification

Global LINE-1 methylation analysis shows a clear correlation to genome-wide DNA-Methylation analysis using DMH

Figure 4: Comparison of the LINE-1 methylation analysis data with the genome-wide DMH data for diverse cancer cell lines using the average of 50k different sites (Oncosign).

Correlation of patient PB Blood Blast counts and Response in to relapsed/refractory AML patients

Figure 5: Box plots of blast content (%) in peripheral blood (PB) showing the variance of the blast content with partially very low or even no blast counts observed in the responders (n=15) versus the non-responders (n=29). The observation of less blasts in the patients that responded to SGI-110 treatment could be a very useful discriminator for response prediction. (Wilcoxon Test: p-value = 0.000391).

Conclusions

- Assessment of novel biomarker candidates to predict for SGI-110 treatment response were identified using colony formation and LINE-1 methylation analysis to stratify 23 cells lines from 7 different cancer types according to their sensitivity to SGI-110.

- There was a close correlation between high LINE-1 methylation level and high sensitivity to SGI-110.

- The global LINE-1 vs genome-wide Oncosign methylation comparison showed that LINE-1 methylation levels correlated well with the DNA-Methylation data measured with DMH from over 50k sites confirming the role of LINE-1 as useful indicator for SGI-110 sensitivity.

- 50 DNA fragment candidates were identified from 249 potential candidate markers from this analysis.

- These biomarker candidates might help to identify patient populations that preferentially respond to SGI-110.

References:


Kantarjian et al. Results from the dose escalation phase of a randomized phase 1-2 First in Human (FIH) study of SGI-110, a novel low volume subcutaneous (S) second generation hypomethylating agent (HMA) in patients with relapsed/refractory AML. 2012 Blood, vol 125, suppl 1, 1132a-214-4.

Disclosures:


© Astex Pharmaceuticals, Inc


Poster available to download from Astex’s website at www.astex.com