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Baseline biomarkers and DNA demethylation correlate with clinical responses in a phase 1/2, randomized study of guadecitabine (SGI-110), a novel subcutaneous (SC) hypomethylating agent (HMA), in the treatment of relapsed/refractory (r/r) acute myeloid leukemia (AML)

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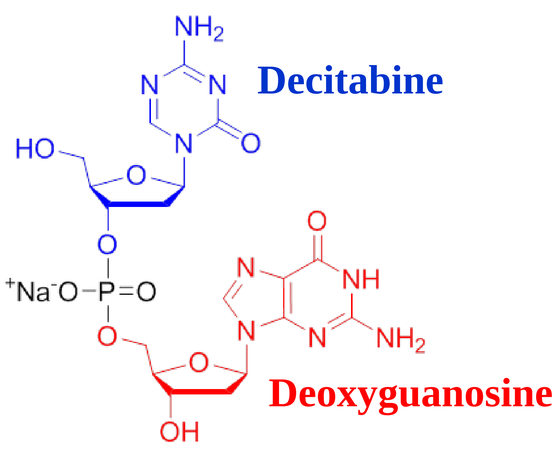
BACKGROUND

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[1] 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[2] or at 60 mg/m^2 in a 10-day regimen[3]. 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.

Guadecitabine : next generation HMA



- Rapid elimination by Cytidine Deaminase (CDA)shortens drug exposure time to cancer cells *in vivo* limiting efficacy because it is cell-cycle dependent (S-phase specific)
- Guadecitabine designed to increase the *in vivo* exposure/potential efficacy of decitabine by protecting it from de-amination through incorporation into a decitabine - deoxyguanosine dinucleotide

METHODS

Peripheral blood DNA and RNA samples from 122 patients with r/r AML were analyzed (27 from phase 1 study treated at 36 m/m^2/d or higher, 47 from the dailyx5 and 48 from the dailyx10 regimen of the phase 2).

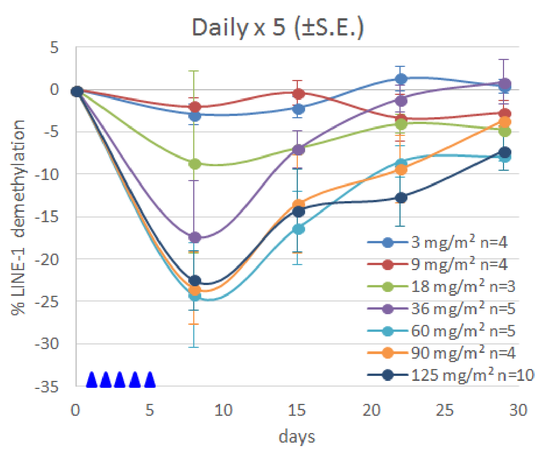
Global DNA methylation at baseline and after treatment, was estimated using bisulphite-pyrosequencing on the LINE-1 repetitive sequence for assessing guadecitabine pharmacodynamic (PD) effects.

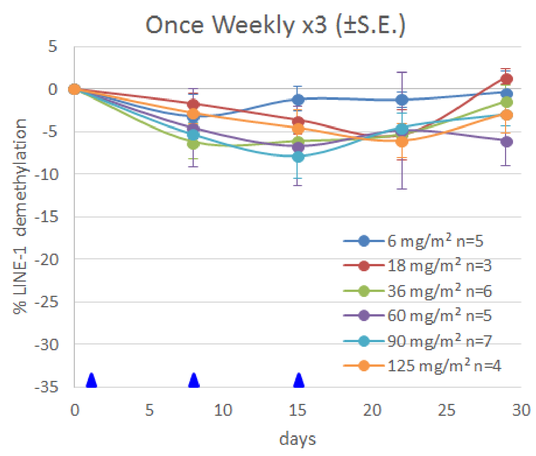
Baseline Expression of a panel of 7 genes was evaluated by quantitative RT-PCR :

- cytidine deaminase (**CDA**)
- cyclin-dependent kinase inhibitor 2B (**P15**)
- cyclin-dependent kinase inhibitor 1 (**P21**)
- DNA (cytosine-5)-methyltransferase 1 (**DNMT1**)
- DNA (cytosine-5)-methyltransferase 3 alpha (**DNMT3A**)
- DNA (cytosine-5)-methyltransferase 3 beta (**DNMT3B**)
- CCCTC-binding factor/zinc finger protein (**CTCF**)

RESULTS

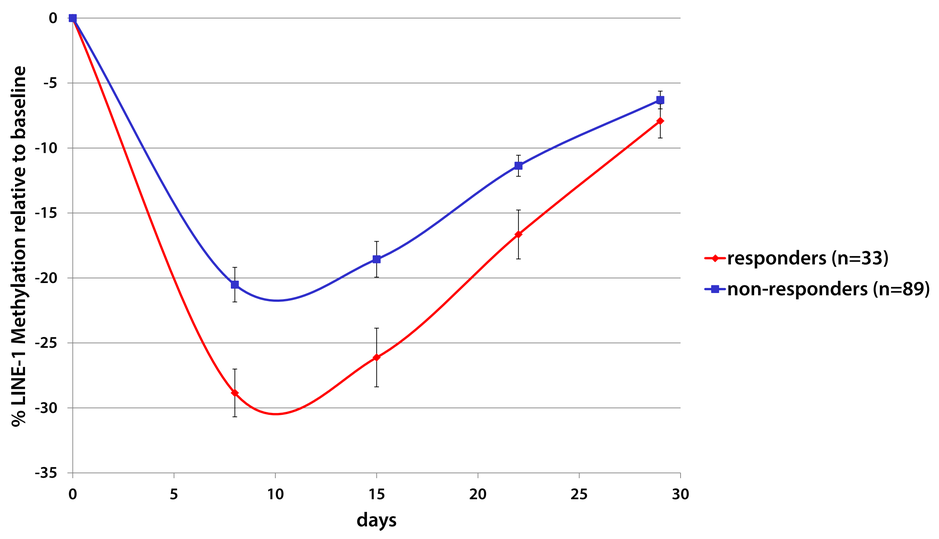
LINE1 demethylation after guadecitabine is dose and schedule-dependent





- Dailyx5 achieved better demethylation than weeklyx3
- Biologically Effective Dose (BED) of dailyx5 established at 60 mg/m2 dailyx5
- BED lower than MTD (90-125 mg/m2 dailyx5)

r/r AML responders showed greater LINE-1 demethylation

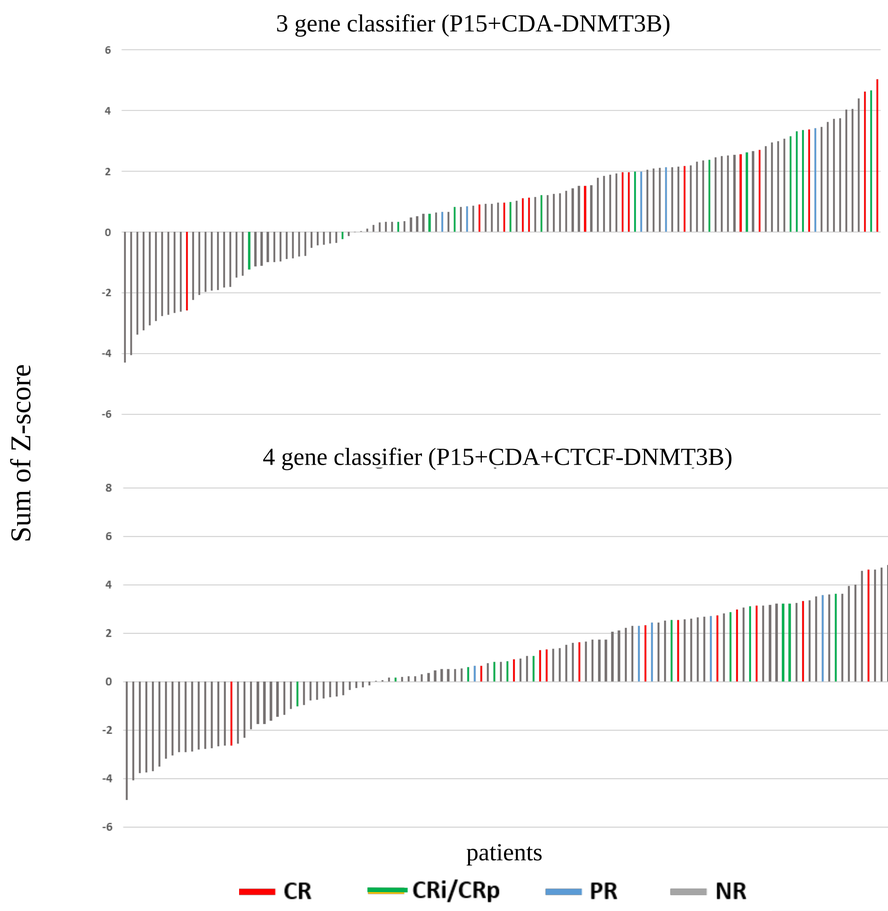


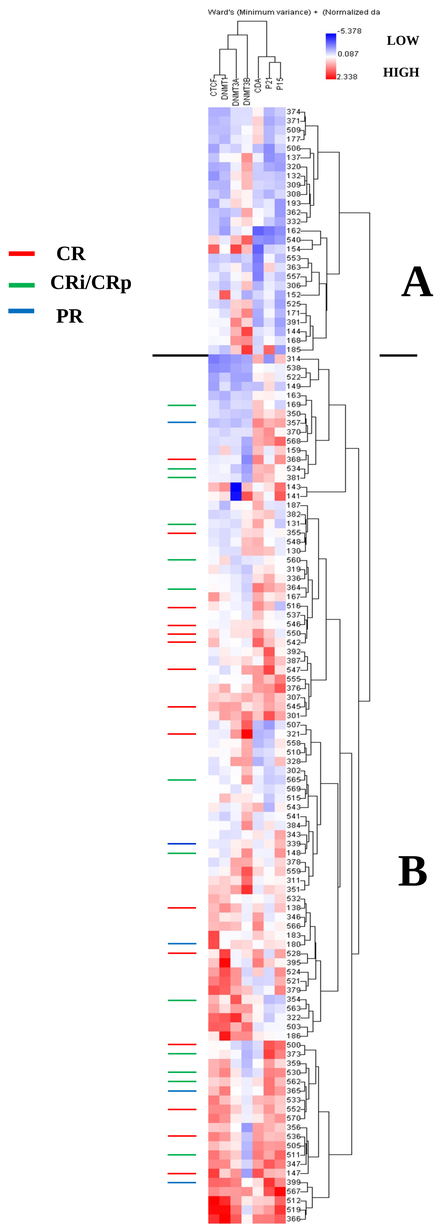
- Overall peak LINE-1 demethylation in Cycle 1 was significantly higher in responders (CR, CRi, CRp and PR) than non-responders (-31.06 ± 1.99 % in responders compared to -21.08 ± 1.45 % in non-responders, p=0.0003).

Clustering of r/r AML patients based on baseline gene expression profile

- Unsupervised clustering by baseline expression of the 7 gene panel grouped the patients into two clusters:
  - **A (N=27)**
    - ✓ high DNMT3B expression, low P15 expression, low CDA expression
    - ✓ reduced LINE-1 demethylation (-15%)
    - ✓ response rate 0 %
  - **B (N=95)**
    - ✓ low DNMT3B expression, high P15 expression, high CDA expression
    - ✓ Higher LINE-1 demethylation (-26%, p=0.0002)
    - ✓ response rate = 29.5 % (p= 0.0001)

- Three gene classifier z scores (CDA + P15 - DNMT3B) or four gene classifier z scores (CDA + P15 + CTCF - DNMT3B) were computed for each patient and each gene and were highly correlated with the 2 clusters
  - Cluster B was characterized by higher average Z-score (1.54 ± 0.16) then cluster A (-1.76 ± 0.27) p<0.0001.
  - Baseline z scores were also powerful at predicting response rates: only 1 CR ,1 CRp and 1 CRi showed a Z score < 0





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

REFERENCE

1. Issa JP et al, Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: a multicentre, randomised, dose-escalation phase 1 study, Lancet Oncology on line Aug 19th 2015
2. Kantarjian H et al , First clinical results of a randomized phase 2 study of SGI-110, a novel subcutaneous (SQ) hypomethylating agent (HMA), in adult patients with acute myeloid leukemia (AML), abst 497, ASH 2013
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Poster can be downloaded from www.astx.com