Abst # 9010

LINE-1 and P15 Demethylation May Predict Response to Guadecitabine

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Background and Methods

Guadecitabine (formerly known as SGI-110) is a next-generation hypomethylating agent (HMA) composed of a dinucleotide of decitabine and deoxyguanosine (Figure 1). Guadecitabine is a dinucleotide resistant to degradation by cytidine deaminase (CDA) resulting in longer *in vivo* exposure to its active metabolite, decitabine, after a small volume (~ 1 mL) subcutaneous (SC) administration. A prospective phase 2 trial in 103 patients with relapsed or refractory AML (r/r AML) investigated 60 mg/m^2 and 90mg/m^2 doses in a 5-day regimen, and 60 mg/m^2 in a 10-day regimen given every 28 days. In that trial, LINE-1 was used to measure general DNA demethylation and P15 gene promotor methylation was used to measure a specific tumor suppressor gene demethylation during Cycle 1 as potential markers of biological activity that may predict clinical response (See Trial Design in Figure 2).

Figure 1: Guadecitabine (SGI-110)

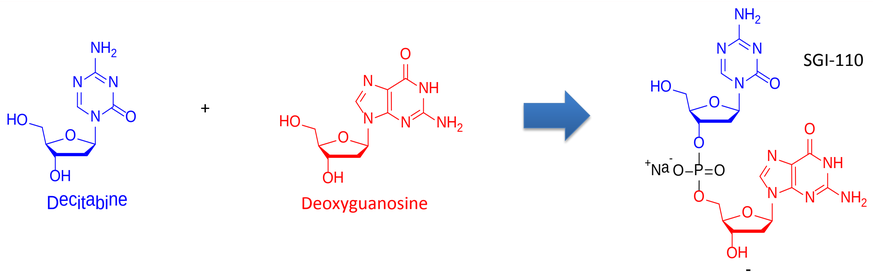
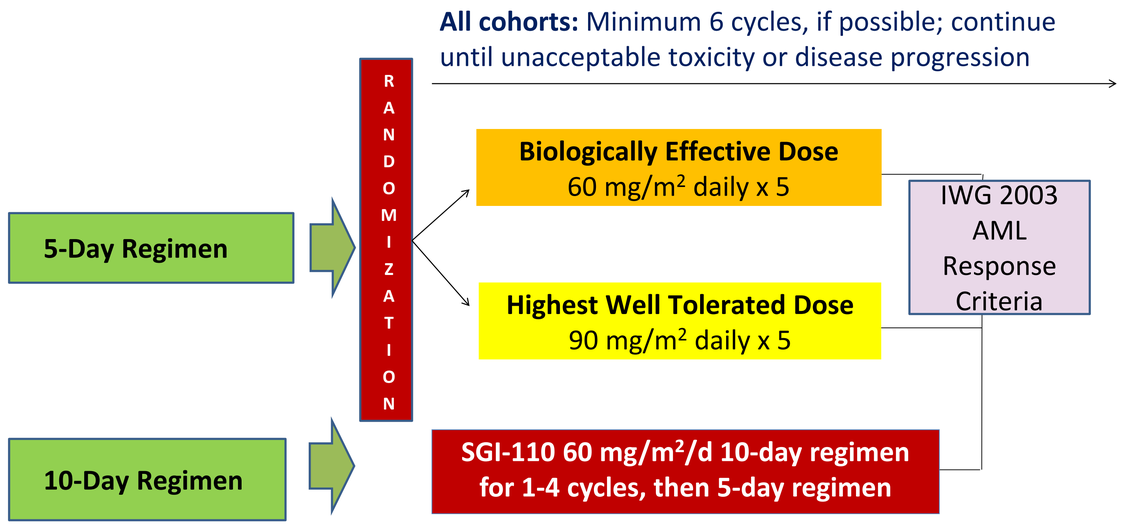


Figure 2: Phase 2 study design of guadecitabine in r/r AML patients



- **Primary Endpoint:** CRc rate (CR + CRp + CRi)
- **Biological Markers of Methylation:** LINE-1 and P15 gene promotor methylation measured at baseline and weekly post treatment in Cycle 1

Results

Baseline Characteristics

Table 1: r/r AML baseline patient characteristics

	Characteristic	5 Day[1] (60 or 90 mg/m^2) N=50	10 Day N=53
Subject	Median age, (range)	62 (22 – 81)	57 (29-82)
	Gender, M (%)	35 (70%)	27 (51%)
	ECOG PS 2 (%)	5 (10%)	9 (17%)
Prior Therapy	Prior HCT (%)	10 (20)	9 (17)
	Median # prior regimens (range)	2 (1 – 10)	2 (1-7)
	Prior HMA (decitabine or azacitidine)	3 (6)	8 (15)
Disease Risk	Poor risk cytogenetics (%)	20 (43)	22 (42)
	Secondary AML (%)	8 (16)	9 (17)

[1] There were no significant differences in patients characteristics, efficacy, or safety between 60 mg/m^2 (24 patients) and 90 mg/m^2 (26 patients) doses so data from the 5-day regimen were combined.

Clinical Efficacy

Table 2: Primary efficacy endpoint of CRc (CR+CRp+CRi)

Response Category[1]	5 Day (60 and 90 mg/m^2) (N=50) N (%)	10 Day (60 mg/m^2) (N=53) N (%)	P value
CR	4 (8%)	10 (19%)	**0.15**
CRp	0 (2%)	4 (7.5%)	
CRi	4 (8%)	2 (4%)	
CRc (CR + CRp + CRi)	8 (16%) (95 CI: 7, 29%)	16 (30%) (95 CI:18, 44%)	0.106

[1]International Working Group 2003 AML Response Criteria

Safety

Table 3: Grade ≥ 3 AEs in 10% or more patients regardless of relationship to treatment

Grade ≥ 3 AEs regardless of treatment relationship	5 Day (60 or 90 mg/m^2) (N=50)	10 Day (60 mg/m^2) (N=53)
Febrile neutropenia	56%	68%
Pneumonia	28%	47%
Thrombocytopenia	20%	51%
Anaemia	20%	43%
Neutropenia	10%	28%
Sepsis	10%	21%
Hypokalemia	16%	11%
Bacteremia	12%	11%

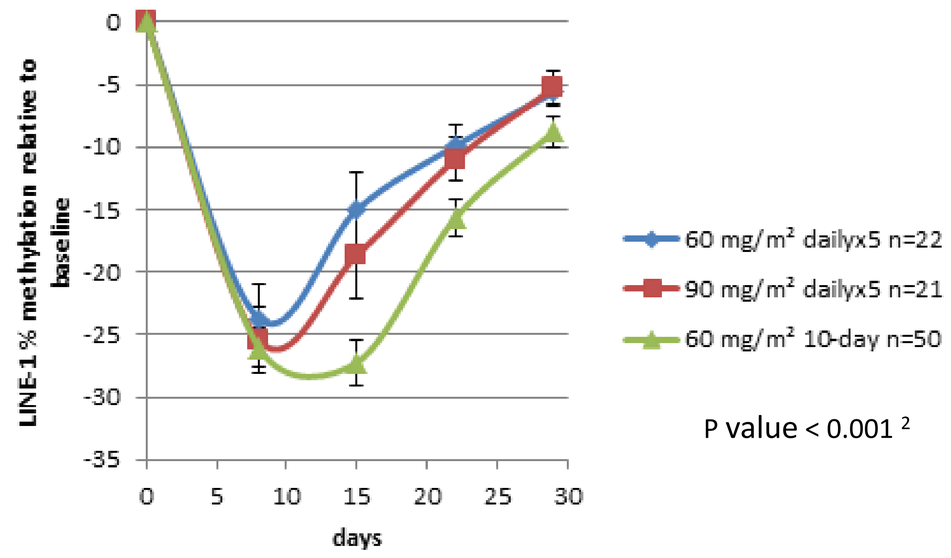
Safety

Table 4: 30 and 60-day all cause mortality

Regimen	Dose Level	N	30 day Mortality N (%)	60 day Mortality N (%)
5-Day	60 or 90 mg/m^2	50	3 (6%)	6 (12%)
10-Day	60 mg/m^2	53	1 (2%)	6 (11%)

Biological Markers of Methylation (LINE-1)

Figure 3: LINE-1 demethylation[1] from baseline in Cycle 1



P value < 0.001 [2]

[1] A total of 93 patients had adequate samples for LINE-1 measurement at baseline
[2] Difference between the 10-day regimen and the combined 5-day regimen (no difference between 60 and 90 mg/m^2 doses in the 5-day regimen)

Table 5: Maximum LINE-1 demethylation in responders vs non-responders

	Number [1]	Max LINE-1 demethylation
Responders (CRc)	22	-34.9% [2]
Non-responders	69	-23.8%

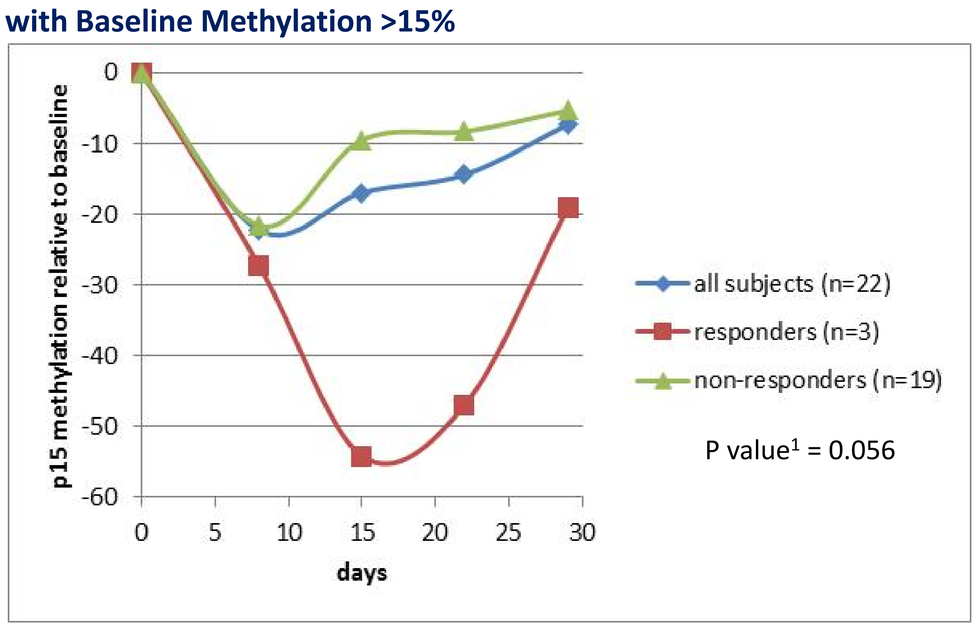
[1] A total of 91 patients had both baseline and post treatment LINE-1 measurement in Cycle 1
[2] P value=0.0002 for the difference in max LINE-1 demethylation between responders and non-responders

Biological Markers of Methylation (P15)

Figure 4: Baseline P15^{INK4B} Methylation in r/r AML Patients

Baseline methylation of P15 was not significantly different between responders and non-responders

Figure 5: P15^{INK4B} Demethylation post Treatment with Guadecitabine in r/r AML Patients with Baseline Methylation >15%



[1] P value of P15 demethylation in responders vs non-responders

Summary and Conclusions

- All doses and schedules of guadecitabine SC have shown clinical activity in r/r AML with a trend of higher CR and CRc using the 10-day regimen at 60mg/m^2/d SC
- All doses and schedules were tolerated despite higher % of Grade ≥ 3 AEs in the 10-day regimen with relatively low early all-cause mortality
- The more pronounced general DNA demethylation by LINE-1 and specific demethylation of tumor suppressor gene P15 in the first guadecitabine treatment cycle can predict better response to treatment
- This may be used to select patients who should continue treatment long term to achieve best response

 Poster presented at: ESH 4th Intl. Conference on AML "Molecular and Translational": Advances in Biology and Treatment, Estoril, Portugal Oct 5 – 7, 2017 Poster can be downloaded from www.astx.com 17SGI-110-PB17(706)

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