Study of the correlation of baseline biomarkers and DNA demethylation to clinical responses in a phase 1/2, randomized study of SGI-110, a novel subcutaneous hypomethylating agent in the treatment of relapsed/refractory acute myeloid leukemia

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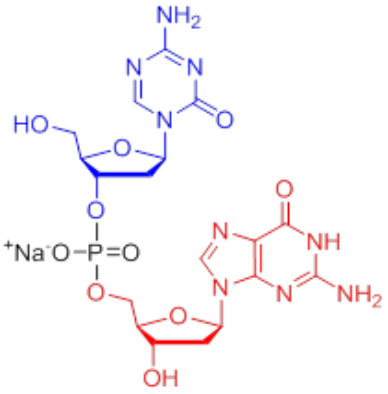
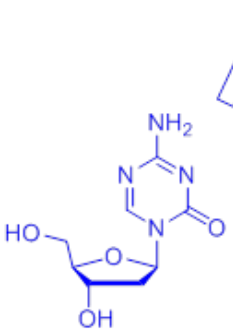
DNA Methylation in MDS/AML

- DNA methylation is an epigenetic process tightly linked to gene expression
- MDS and AML are characterized by frequent DNA methylation changes and mutations in epigenetic genes (e.g. TET2, DNMT3a, EZH2)
- DNA methylation inhibitors (azacitidine, decitabine) have demonstrated clinical activity in MDS and AML

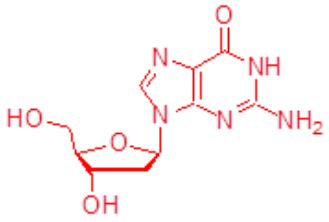
SGI-110, A Second Generation Hypomethylating Drug



SGI-110



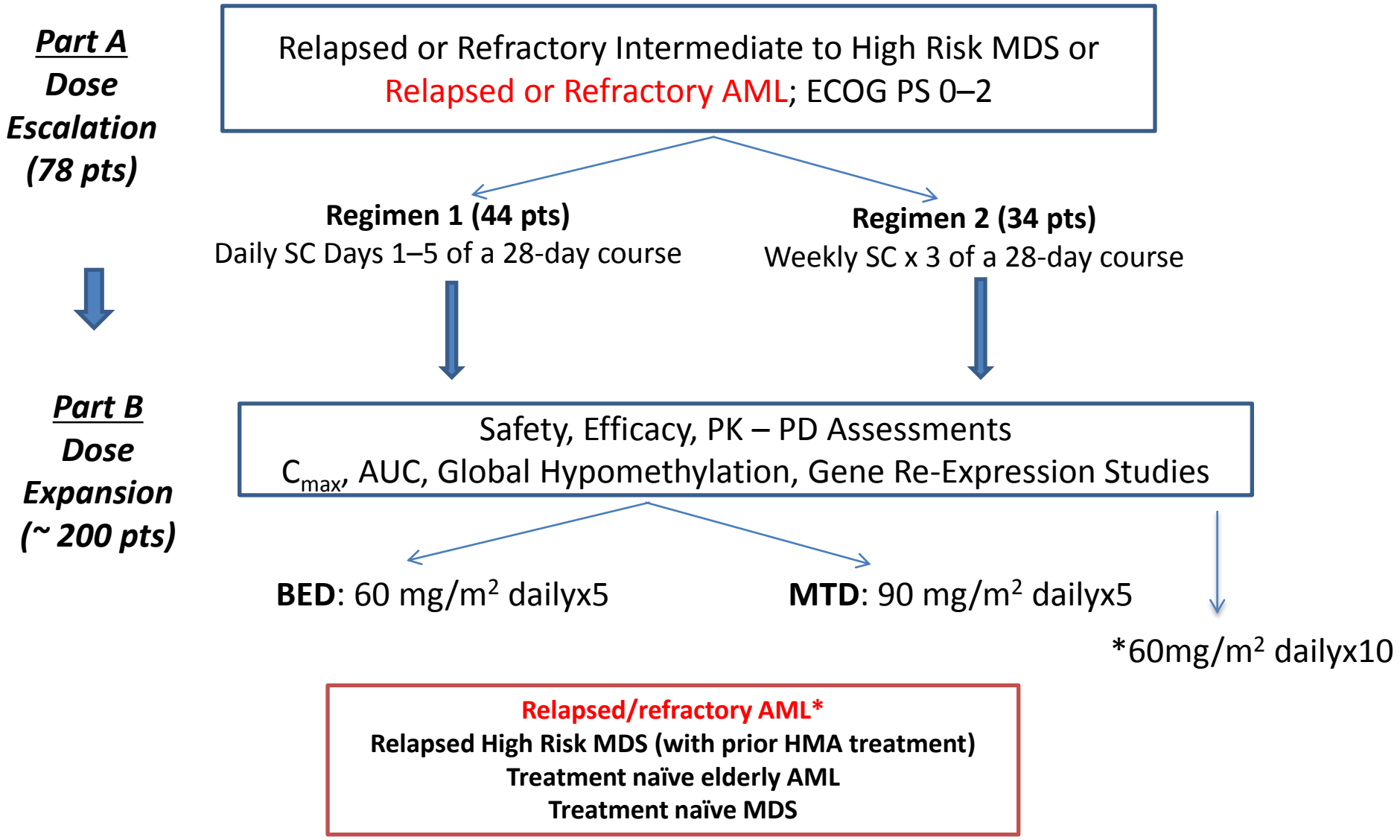
Decitabine



2'-Deoxyguanosine

- More resistant to cytidine deaminase
- Improved stability in-vitro

SGI-110 Phase 1/2 MDS & AML Clinical Trial

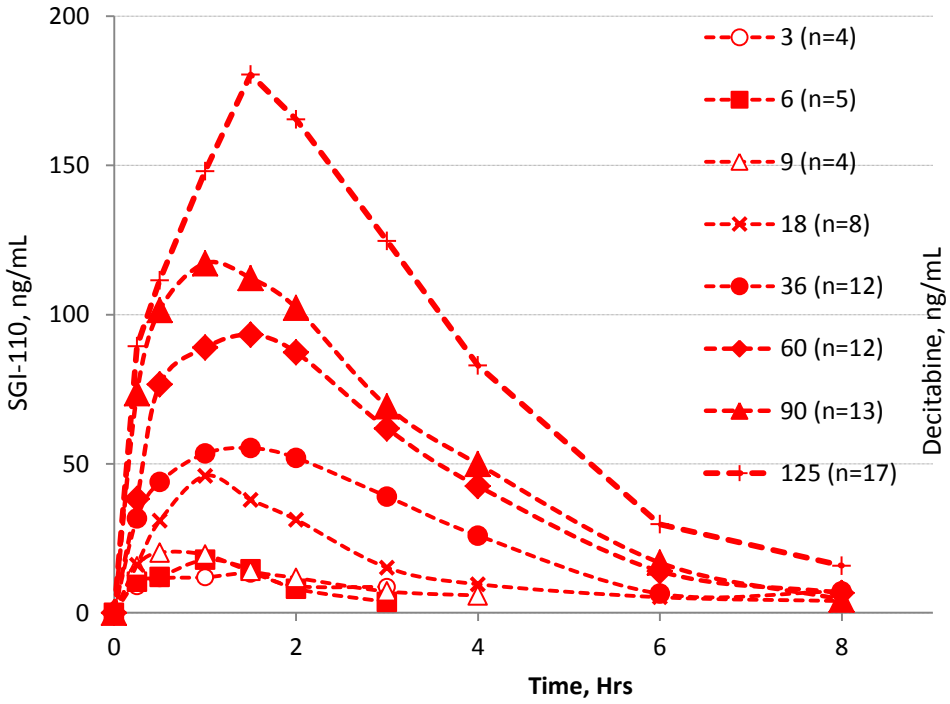


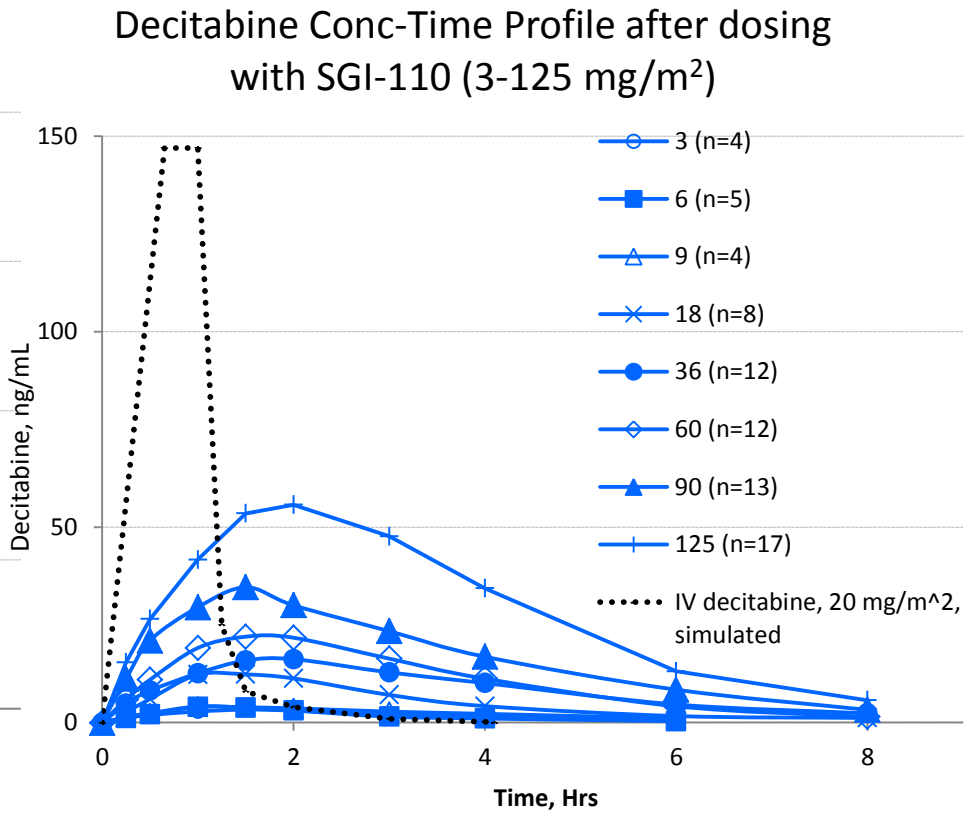
Patients Enrolled (AML and MDS)

Cohorts	Dose or Dose/Schedule[1]		Number of Patients	
	QDx5	QWx3	QDx5	QWx3
Cohort 1	3 mg/m^2	6 mg/m^2	4	5
Cohort 2	9 mg/m^2	18 mg/m^2	4	3
Cohort 3	18 mg/m^2	36 mg/m^2	5	6
Cohort 4	36 mg/m^2	60 mg/m^2	6	6
Cohort 5	60 mg/m^2	90 mg/m^2	7	8
Cohort 6	90 mg/m^2	125 mg/m^2	6	6
Cohort 7	125 mg/m^2	NA	12	NA
Total			44	34

[1]PK guided dose escalation based on decitabine published pharmacokinetic parameters

SGI-110 and Decitabine PK Profiles in All Patients





- Decitabine effective half-life after SQ SGI-110 ~ 1.5-2.5 hrs, (IV DAC $T_{1/2}$ ~ 0.3 - 0.6 hrs): Up to 4-fold longer half-life of decitabine from SGI-110 compared to decitabine IV

Safety: Related AEs (≥ 5%) Daily and Weekly

Adverse Event	AML Patients (n=63) All Grades	Grade 3/4
Injection site pain	14 (22%)	0 (0%) / 0 (0%)
Thrombocytopenia	6 (10%)	1 (2%) / 4 (6%)
Diarrhea	5 (8%)	0 (0%) / 0 (0%)
Fatigue	5 (8%)	0 (0%) / 0 (0%)
Nausea	5 (8%)	0 (0%) / 0 (0%)
Decreased appetite	4 (6%)	0 (0%) / 0 (0%)
Neutropenia	4 (6%)	2 (3%) / 2 (3%)
Anemia	4 (6%)	3 (5%) / 0 (0%)
Leukopenia	4 (6%)	1 (2%) / 3 (5%)
Asthenia	3 (5%)	0 (0%) / 0 (0%)
Cough	3 (5%)	0 (0%) / 0 (0%)
Dry Mouth	3 (5%)	0 (0%) / 0 (0%)
Injection site hematoma	3 (5%)	0 (0%) / 0 (0%)
Vomiting	3 (5%)	0 (0%) / 0 (0%)

AML Patients Demographics

Patient Characteristics	AML (n=63)	QDx5 (n=35)	QWx3 (n=28)
Median Age, (range)	66 (29 – 86)	66 (36 – 86)	68 (29 – 83)
Gender, M:F (%)	41 (65) / 22 (35)	18 (51) / 17 (49)	23 (82) / 5 (18)
ECOG PS 0/1/2 (%)	13 (21)/ 41 (65)/9 (14)	8 (23) / 22 (63) / 5 (14)	5 (18) / 19 (68) / 4 (14)
Median % BM Blast at Baseline, (range)	46 (1 – 98)	57 (9 – 98)	22 (1 – 95)
Median # Prior Regimens, (range)	4 (1 – 9)	4 (1 – 9)	4 (1 – 7)
Prior decitabine (%)	23 (37)	12 (34)	11 (39)
Prior azacitidine (%)	19 (30)	10 (29)	9 (32)
Prior decitabine or azacitidine (%)	35 (56)	18 (51)	17 (61)

AML Complete Remissions - Patient Characteristics

Pt ID#	Dose (mg/m^2)	Regimen	Baseline Cytogenetic Category	# of prior regimen / prior BMT	HMA Exposure (yes/no)	BL WBC (k/uL) BL BM Blast (%)	Remission Status	Duration of remission (days)	Max LINE-1 % Demethylation
A	36	QDx5	Inter	1 / No	No	9 / 35	CRi	350	-13.3
B	60	QWx3	Poor	4 / Yes	Dac[1]	2.6 / 8	CR	558	-22.7
C	60	QDx5	Inter	5 / Yes	No	3.7 / 16.2	CR	114	-34.7
D	60	QDx5	Poor	4 / No	Dac[2] Aza[3]	2.3 / 35	CRi	47	-23.3
E	125	QWx3	NC	6 / No	No	5.7 / 22	CRp	42	-11.5

Dac - decitabine; Aza – azacitdine; QD – daily; QW – weekly; Inter – Intermediate, NC – not classifiable; BMT – Bone Marrow Transplantation

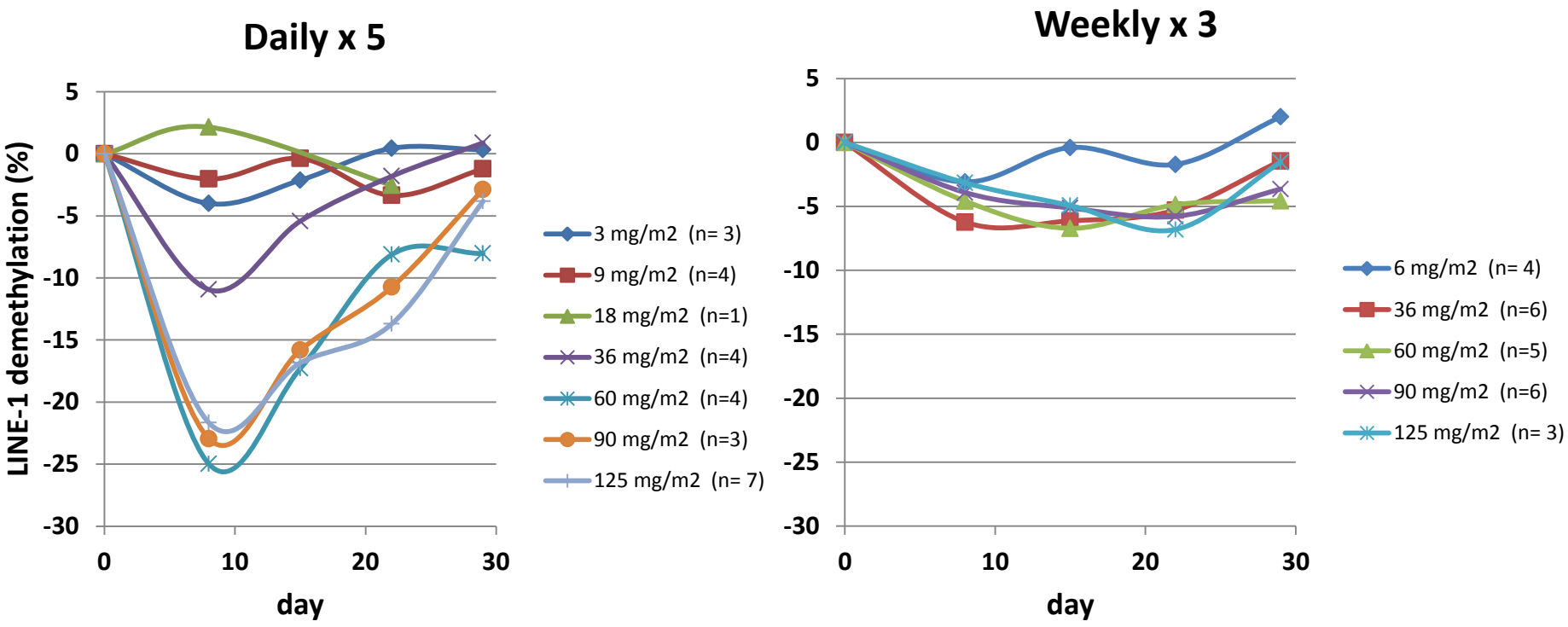
[1]received decitabine (response unknown) for 1 month; [2]received decitabine (no response) for 4 months; [3]received azacitidine (no response; duration unknown)

Median duration of remission = 114 days (range, 42–558)

Biomarkers Evaluated

Biomarker	Significance	Assay	Sample
LINE-1	Global DNA Methylation	Pyrosequencing of bisulfite treated DNA	Baseline and post-treatment DNA from peripheral blood
Cytidine Deaminase (CDA)	Decitabine deactivation	Residual serum enzymatic activity	Baseline Serum
Deoxycytidine Kinase (DCK)	Decitabine activation	Western Blot & Quantitative RT-PCR	Baseline protein lysate and RNA from peripheral blood
MicroRNA 29b (miR29b)	Degradation of DNMT3	Quantitative RT-PCR	Baseline RNA from peripheral blood
DNMT3b	De novo DNA Methylation	Quantitative RT-PCR	Baseline RNA from peripheral blood

Average LINE-1 Demethylation in AML Patients by Cohort



- Dose-dependent increase in demethylation up to 60 mg/m^2 daily x 5
- Similar demethylation of 60, 90 and 125 mg/m^2 daily x 5
- BED established at 60 mg/m^2 daily x 5
- Weeklyx3 regimen achieved less potent demethylation

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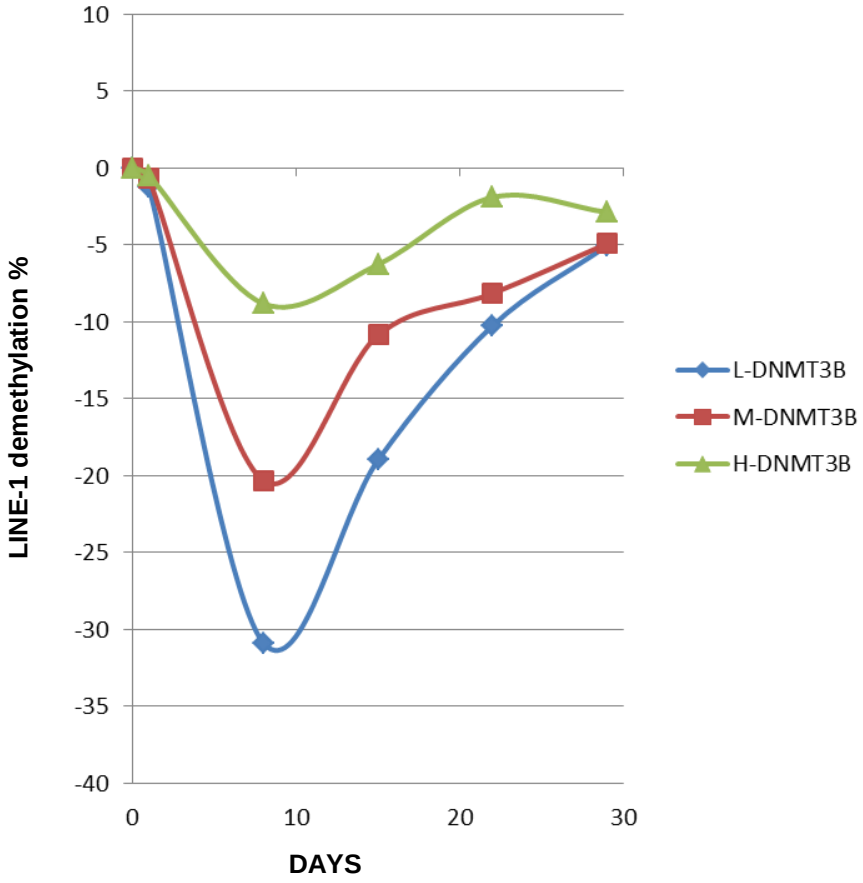
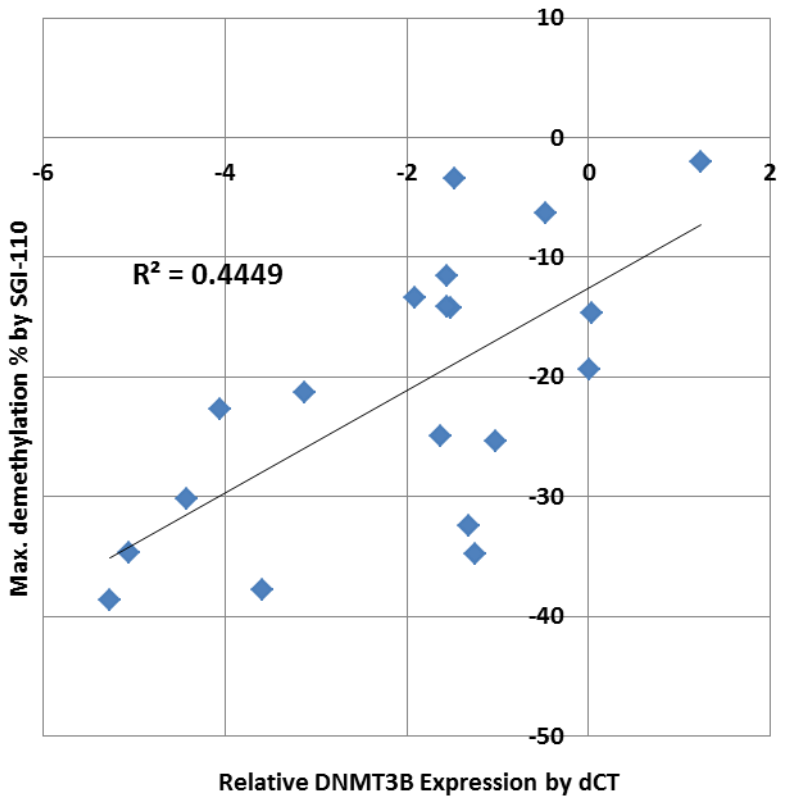
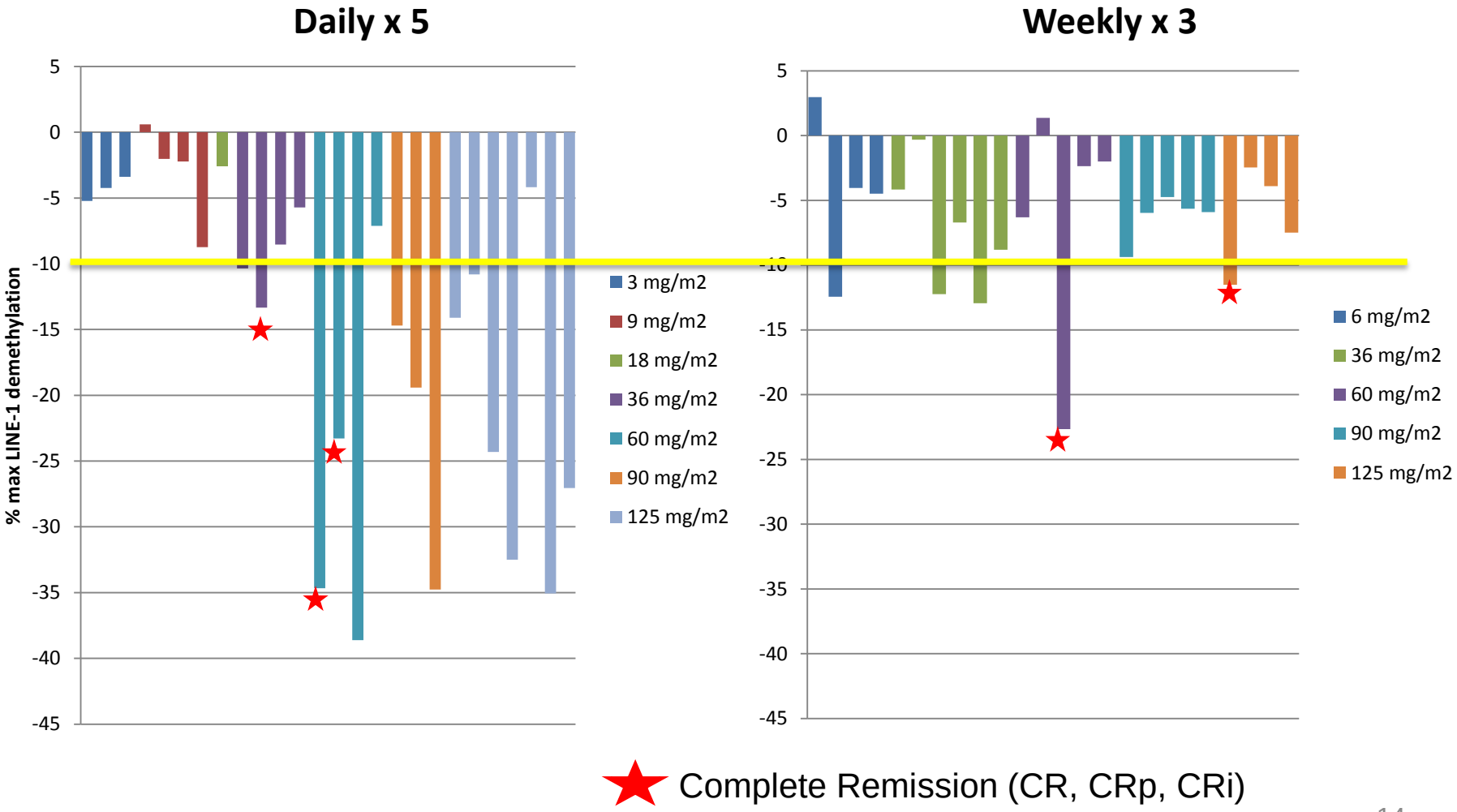
DNMT3b expression Correlates with LINE-1 Demethylation after SGI-110





Individual LINE-1 Demethylation in AML Patients (n=50) by Cohort

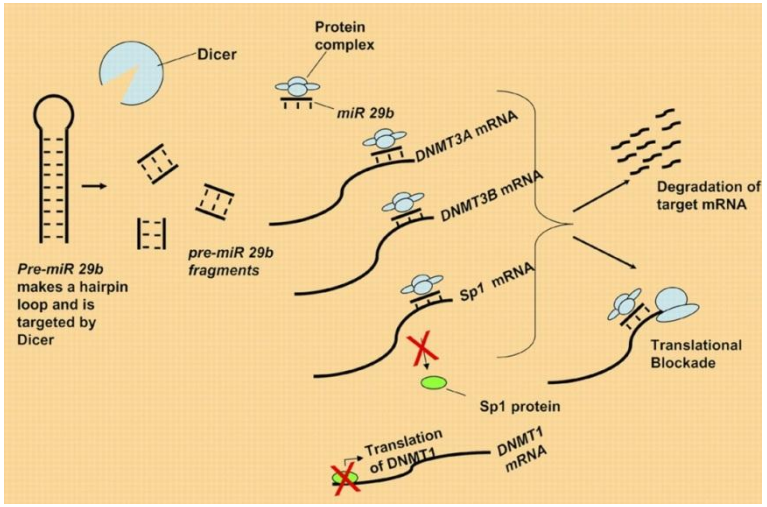


AML Complete Remissions vs. Demethylation (as measured by LINE-1)

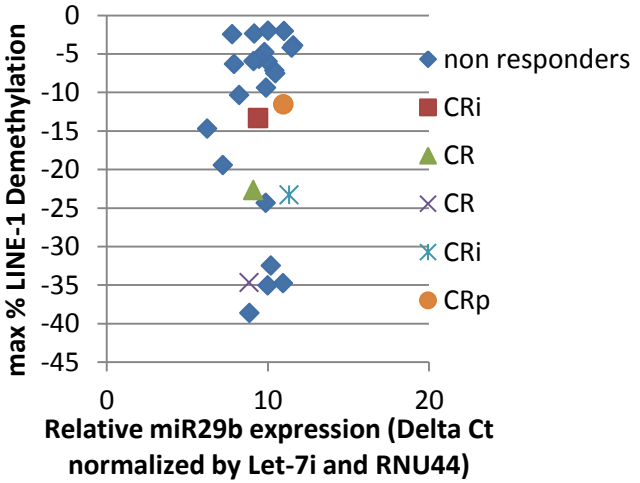
LINE-1 Demethylation	Number Treated	Complete Remission (CR/CRp/CRi)	Percent
< 10%	31	0	0%
≥ 10%	19	5	26%*
Total	50	5	10%

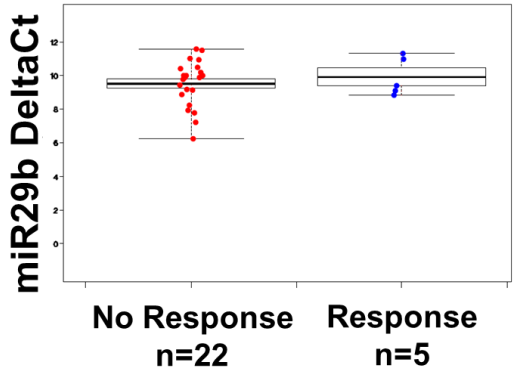
*(P< 0.01)

miRNA29b – No Correlation With LINE-1 Demethylation or Response



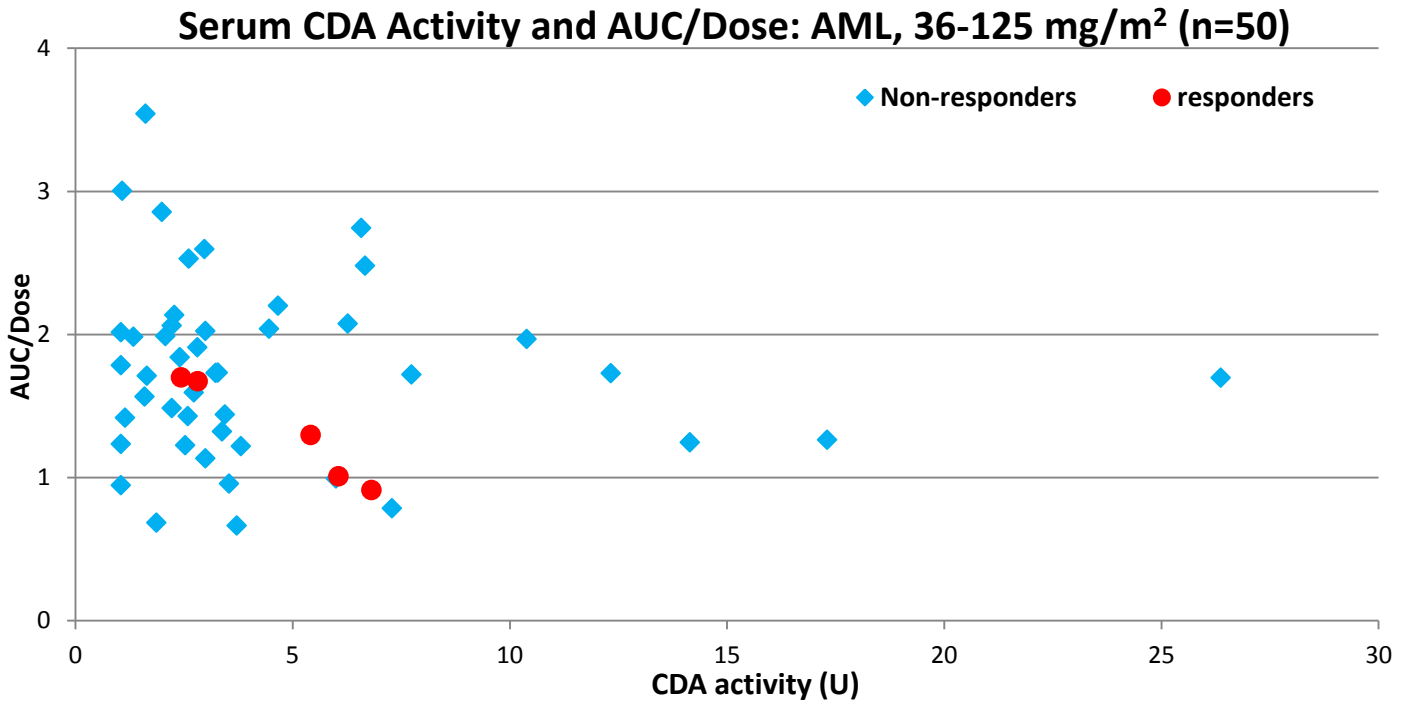
Garzon et al. Blood 2008; Blum et al. PNAS 2010





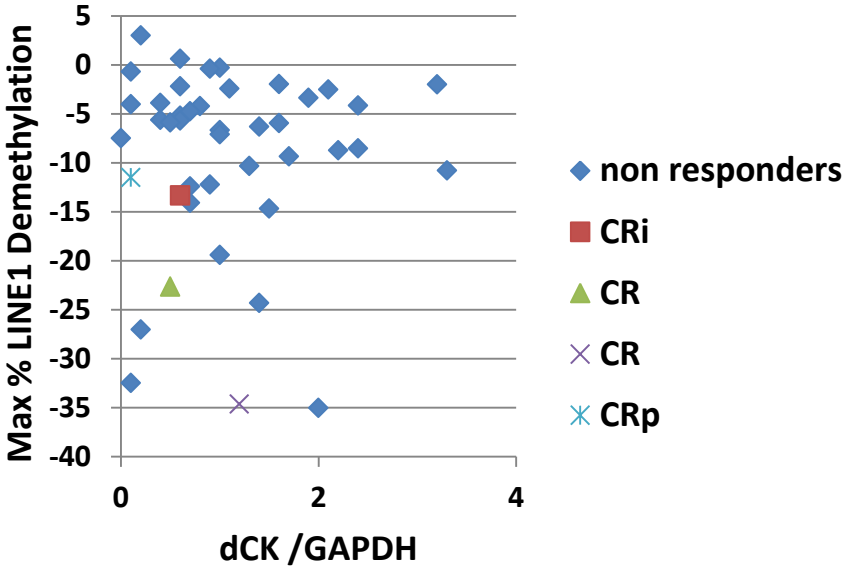
- 27 AML patients with miRNA29b and LINE-1 data
- No correlation between miRNA29b and LINE-1 demethylation
- No difference in miRNA29b expression between responders and non-responders

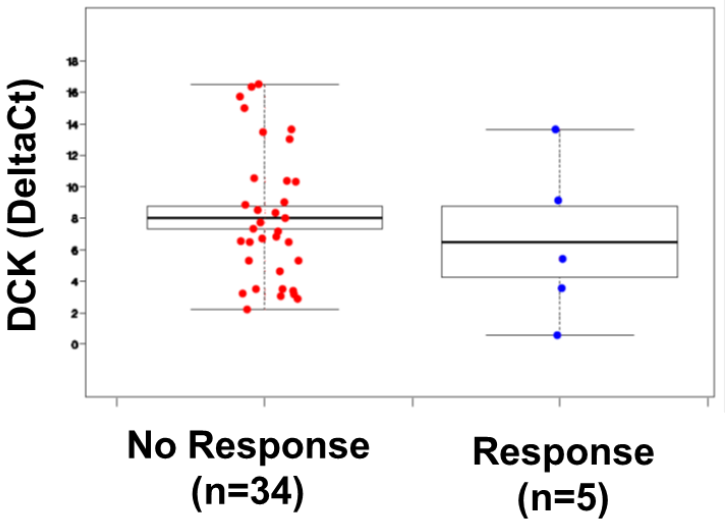
CDA Enzyme Activity and Decitabine Exposures



- High CDA enzyme activity correlated with lower decitabine exposures (p = 0.011) but not with demethylation
- Only 5 patients (10%) had high CDA enzyme activity (>10)

DCK Protein vs. LINE-1 Demethylation and Response





No correlation between DCK levels and either LINE-1 demethylation or response

Summary

- SGI-110 is a second generation HMA that delivers decitabine with a longer half-life and a longer exposure
- Remissions observed in heavily pretreated AML with acceptable toxicity (myelosuppression/local site reactions)
- LINE-1 demethylation is dose-dependent until 60 mg/m^2 SQ daily x 5 (BED); demethylation is necessary but not sufficient for a response, with a 10% minimal threshold
- Demethylation inversely correlates with levels of DNMT3b, providing a potential biomarker for patient and/or dose selection
- LINE-1 demethylation or clinical response are not associated with levels of miRNA29b, CDA enzyme activity or DCK protein (or mRNA) levels

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