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)

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Financial Disclosures

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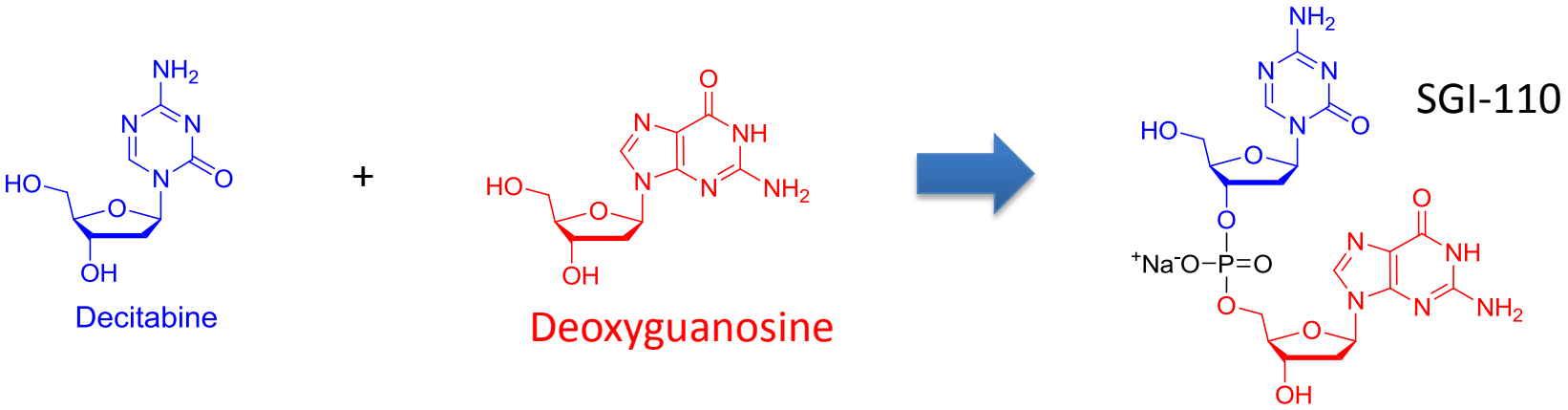
DNA Methylation in MDS/AML

- 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 Agent

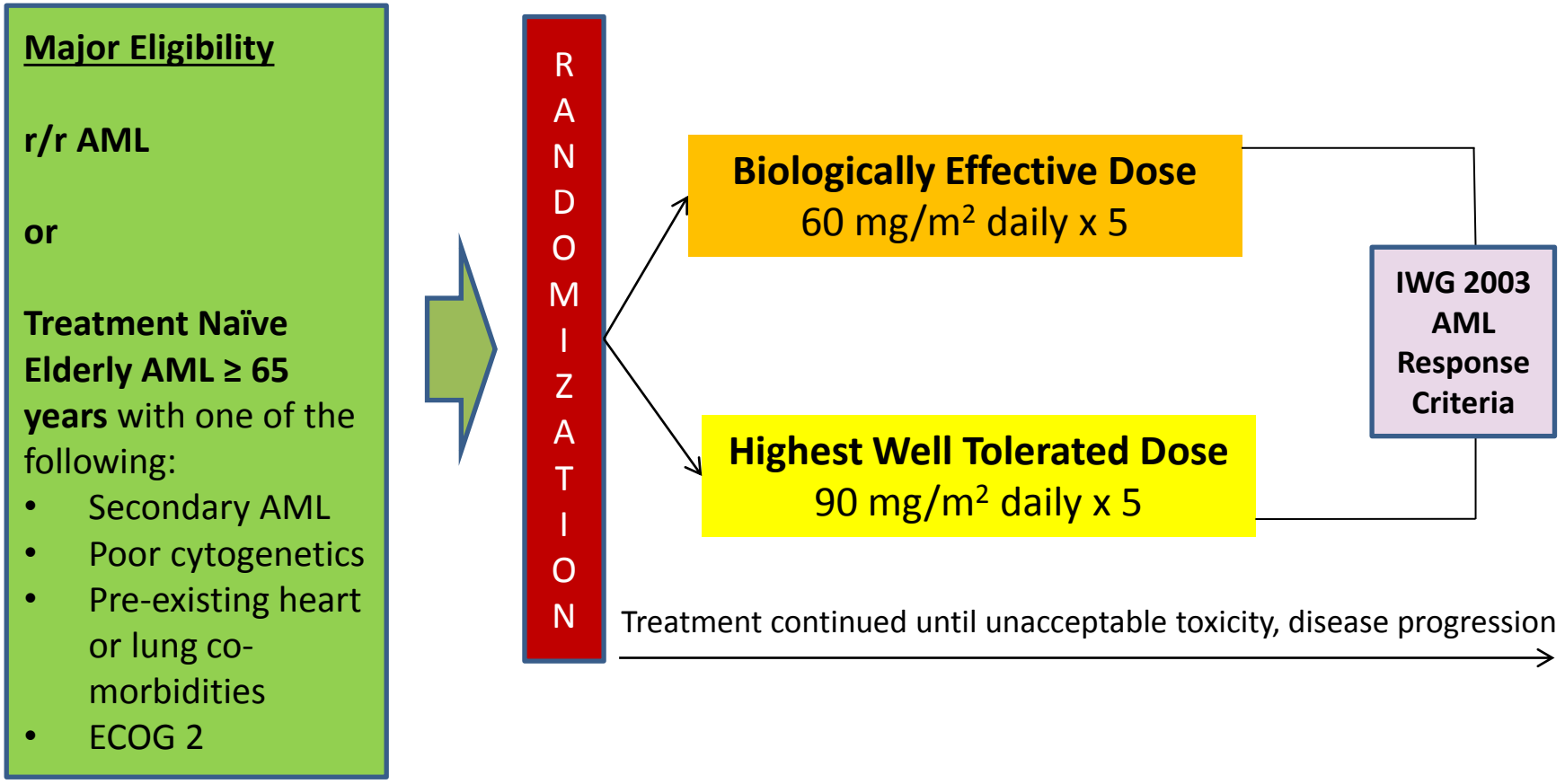
- Decitabine is rapidly eliminated by Cytidine Deaminase, limiting drug exposure time to cancer cells *in vivo*
- SGI-110 is a Dinucleotide of Decitabine and Deoxyguanosine that increases the *in vivo exposure* of decitabine by protecting it from deamination



SGI-110 Phase 1 Summary

- SGI-110 can be safety administered as a small volume SQ injection with myelosuppression, and injection site pain (mostly Grade 1) as most common adverse events
- Biologically effective dose (BED) is 60 mg/m^2 Days 1 – 5. MTD at 90 mg/m^2 SQ daily x 5 in MDS; not reached in AML
- Clinical activity observed in heavily pre-treated AML subjects with durable remissions: 2 CRs, 2 CRIs, 1 CRp in 55 AML patients treated at therapeutic doses (36 – 125 mg/m^2)
- CRs associated with ≥ 10% LINE-1 demethylation
- SGI-110 delivers decitabine with a 4-fold longer decitabine half-life and overall exposure of up to 8 hours (2-fold longer than IV decitabine)
- Maximum average LINE-1 demethylation for BED is 25%

Randomized Phase 2 Study of SGI-110 in AML



- Primary Endpoint: Overall remission rate (CR + CRp + CRi)
- Secondary Endpoints: Safety, duration of remission, overall survival

Patient and Disease Characteristics by Dose

Patient Characteristics	60 mg/m^2 (n=43)	90 mg/m^2 (n=47)
Median Age, (range)	69 (22 – 92)	70 (30 – 92)
Gender, M (%)	27 (63)	32 (68)
ECOG PS 0 1 2	 6 (14) 27 (63) 10 (23)	 11 (23) 28 (60) 8 (17)
Median BM Blast % (range)	36 (9 – 93)	36 (2 – 94)
Median WBC (10^9/L) (range)	2 (0.3 – 47)	2.5 (0.3 – 51.4)
Secondary AML (%)	9 (21)	15 (33)
Prior SCT (%)	5 (12)	5 (11)
Median # Prior Regimens, (range)	1 (0 – 5)	1 (0 – 10)
Patients Enrolled r/r AML Tx naïve AML	 24 19	 26 21

Patient and Disease Characteristics by AML Type

Patient Characteristics	r/r AML (n=50)	Tx Naïve AML (n=40)
Median Age, (range)	62 (22 – 81)	76 (62 – 92)
Gender, M (%)	35 (70)	24 (60)
ECOG PS 0 1 2	 7 (14) 38 (76) 5 (10)	 10 (25) 17 (43) 13 (33)
Median BM Blast % (range)	35 (2 – 94)	40 (13 – 94)
Median WBC (10^9/L) (range)	1.7 (0.3 – 18.7)	3.2 (0.7 – 51.4)
Secondary AML (%)	8 (16)	16 (42)
Prior SCT (%)	10 (20)	0 (0)
Median # Prior Regimens, (range)	2 (1 – 10)	0 (0 – 1)
# of Patients Randomized by Dose 60 mg/m^2 90 mg/m^2	 24 26	 19 21

Response Summary By Dose

Response Category[1]	60 mg/m^2 (n=43)	90 mg/m^2 (n=47)
	Response rate (%)	**Response rate (%)**
CR	14.0	12.8
CRi	9.3	14.9
CRp	2.3	2.1
(CR + CRp + CRi)	**25.6 (95% CI: 13.5, 41.2)**	**29.8 (95% CI: 17.3, 44.9)**

[1]International Working Group 2006 AML Response Criteria

Response Summary By AML Type

Response Category[1]	r/r AML (n=50)	Tx Naïve AML (n=40)
	Response rate (%)	**Response rate (%)**
CR	4.0	25.0
CRi	8.0	17.5
CRp	4.0	0
(CR + CRp + CRi)	**16.0 (95% CI: 7.2, 29.1)**	**42.5 (95% CI: 27.0, 59.1)**

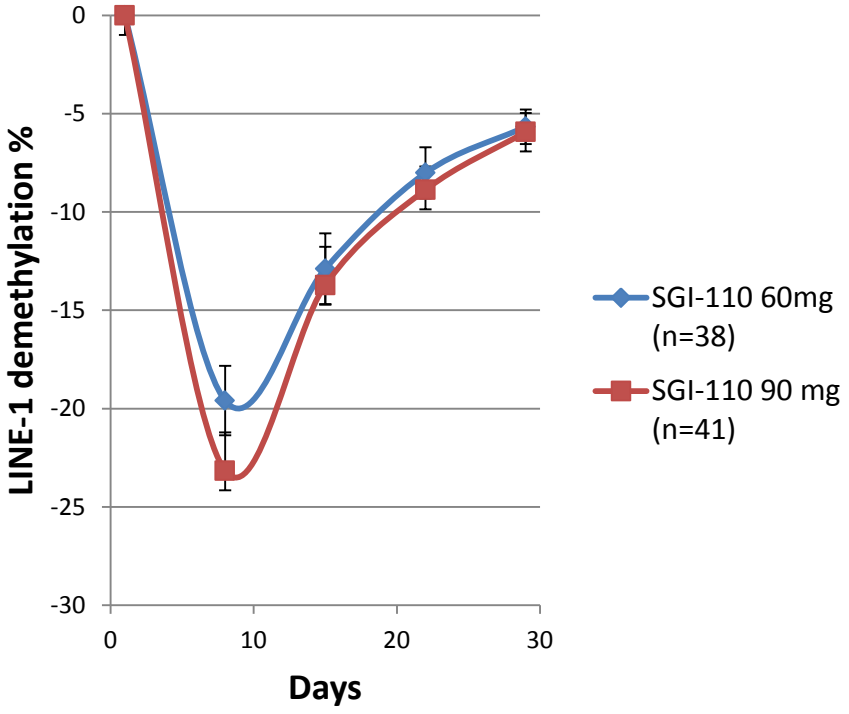
[1]International Working Group 2006 AML Response Criteria

Most Commonly Reported Related AEs 60 mg/m^2 vs. 90 mg/m^2

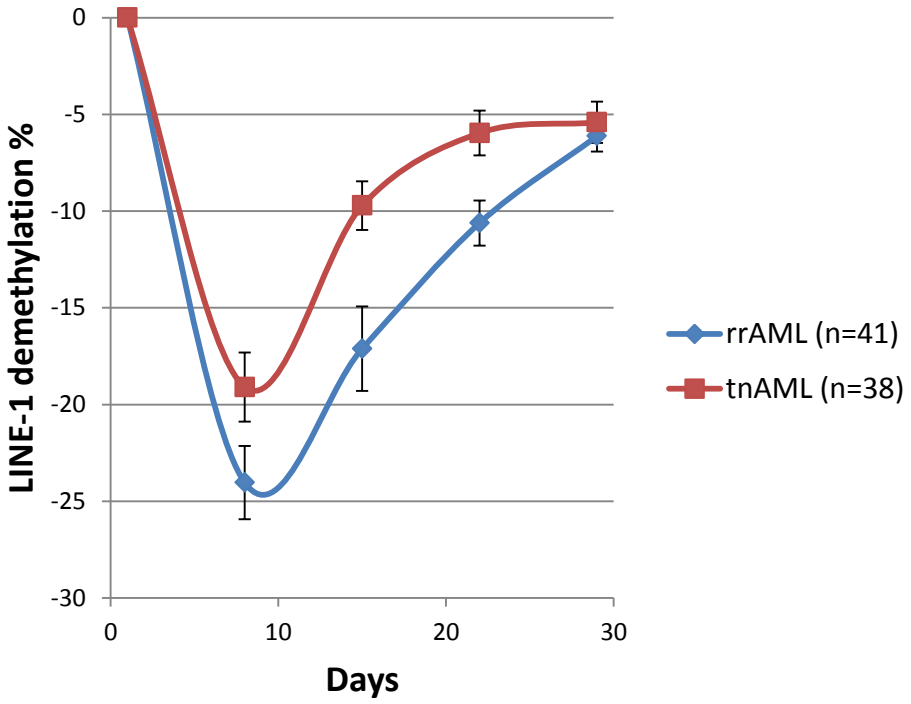
Adverse Event	60 mg/m^2 QD x 5 (n=43)		90 mg/m^2 QD x 5 (n=47)	
	All Grades	Grade 3 / 4	All Grades	Grade 3 / 4
	%	%	%	%
Injection site pain	35	0	43	0
Thrombocytopenia	30	26	19	17
Anemia	21	16	17	11
Leukopenia	16	14	21	19
Diarrhea	19	0	23	0
Febrile Neutropenia	14	12	23	23
Nausea	14	5	23	0
Injection site hemorrhage	12	0	6	0
Neutropenia	14	12	23	23
Fatigue	12	2	23	0
Constipation	9	0	21	0
Injection site hematoma	7	0	13	0
Decreased appetite	5	0	13	0
Dyspnea	0	0	11	2

Dose	N	30 day Mortality (%)	60 day Mortality (%)
60 mg/m^2	43	3 (7.0)	7 (16.3)
90 mg/m^2	47	1 (2.1)	5 (10.6)
All	90	4 (4.4)	12 (13.3)

LINE-1 Demethylation by Dose and AML Type

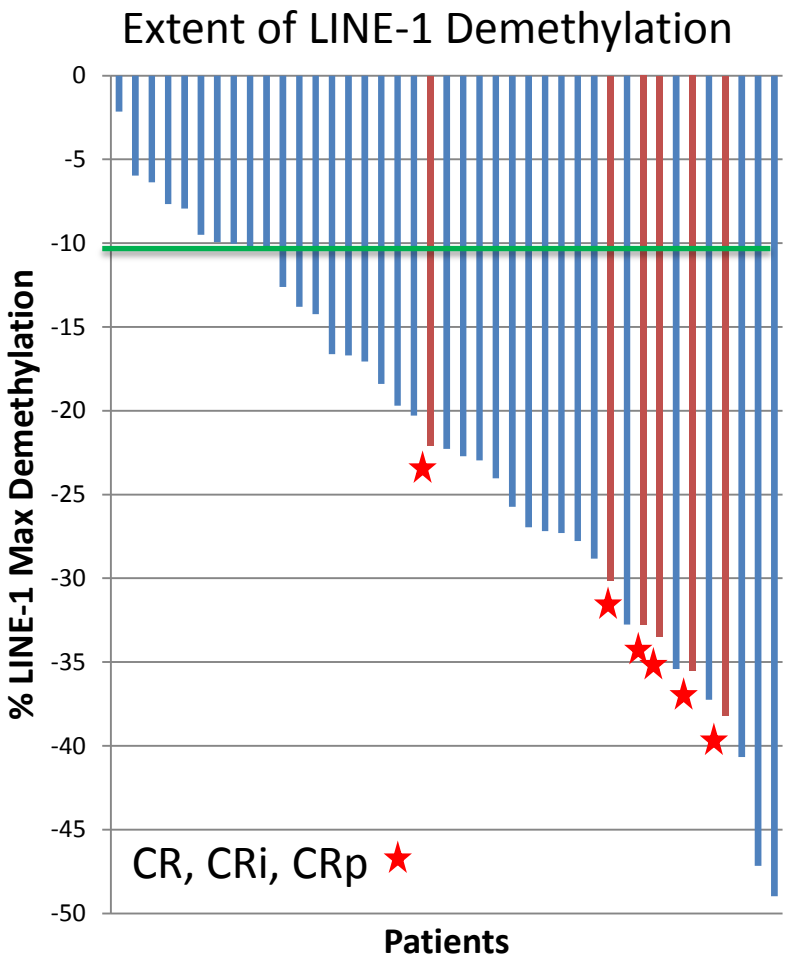


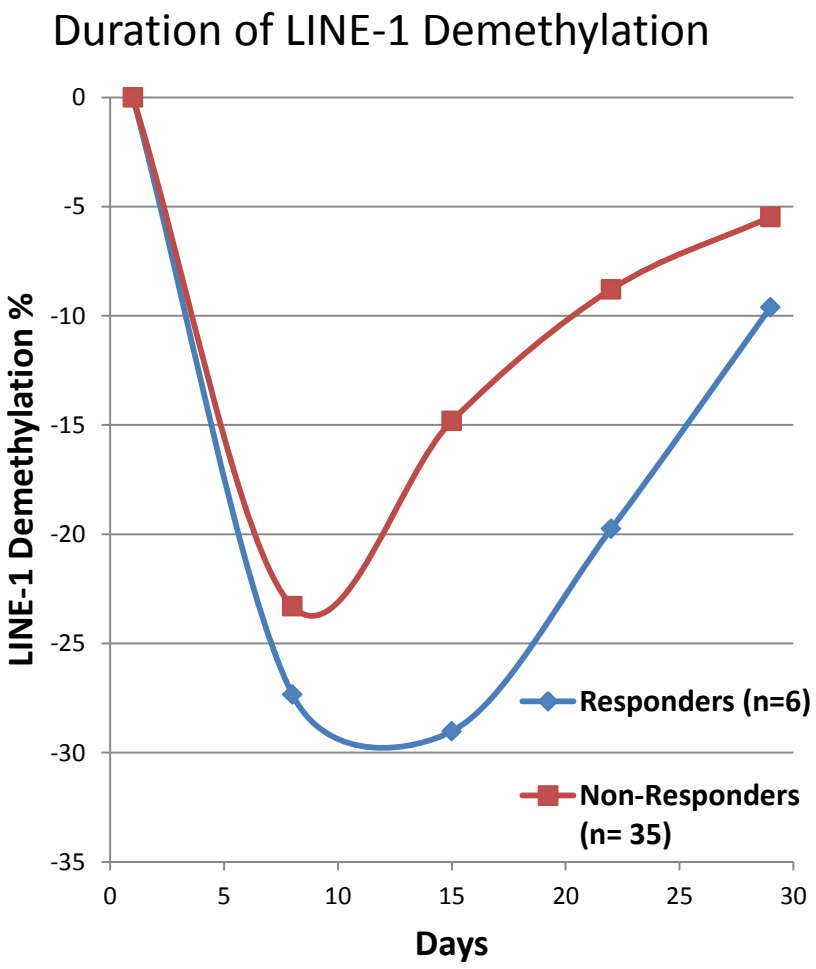
60 mg/m^2 vs. 90 mg/m^2



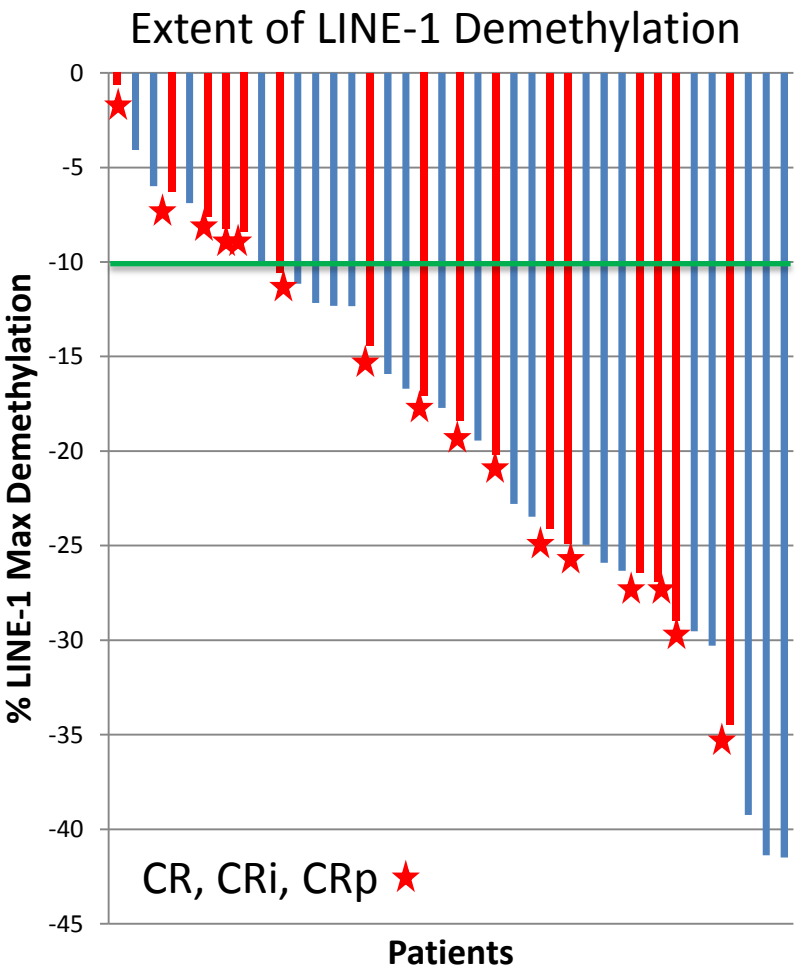
r/r AML vs. Tx Naïve AML

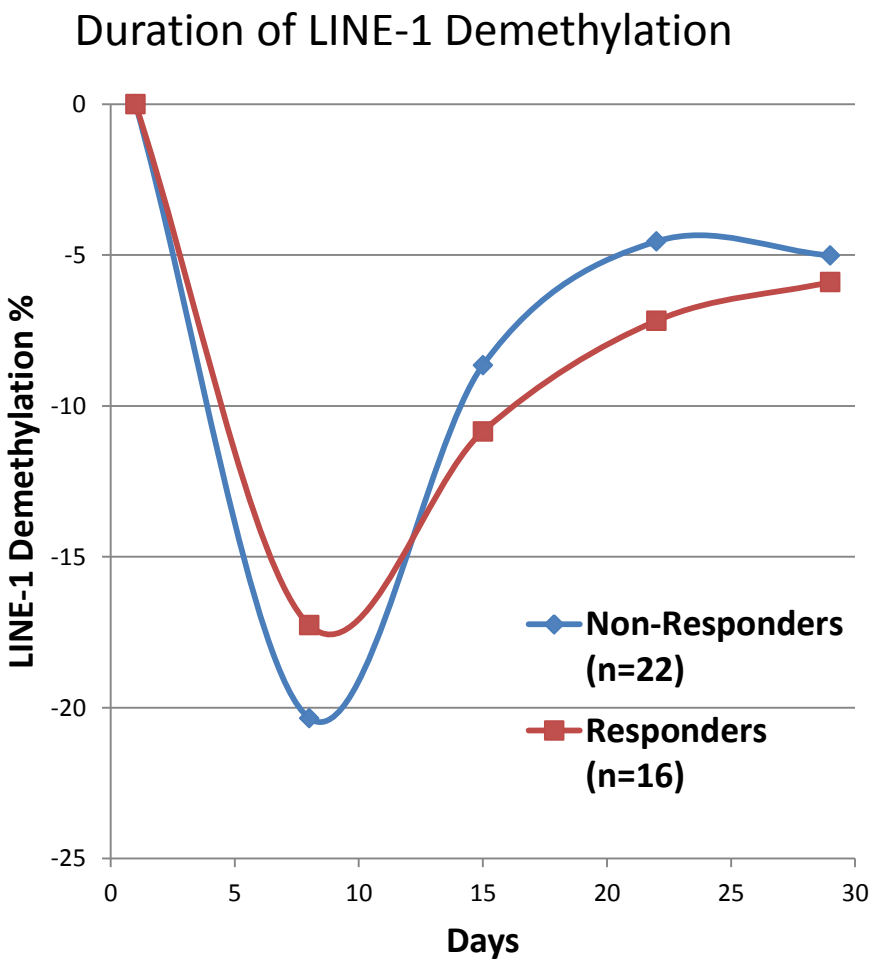
LINE-1 Demethylation and Response r/r AML (n=41)





LINE-1 Demethylation and Response Tx Naive AML (n=38)





Conclusions

- SGI-110 is a new HMA with clinical activity in AML
  - 43% remission rate in treatment naïve elderly AML ≥ 65 years
  - 16% remission rate in relapsed/refractory AML
  - Comparable remission rate at 60 mg/m^2 and 90 mg/m^2
  - Acceptable toxicity profile with myelosuppression and Grade 1/2 injection site events being most common

- PD analysis consistent with mechanism of action
  - Greater and more sustained demethylation in r/r AML responders
  - Responses occur at a lower demethylation threshold in front-line AML
  - No significant difference between 60 mg/m^2 and 90 mg/m^2

- Clinical activity and safety support Phase 3 development in AML

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