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DNA demethylation activity over time and safety of 3 different dose-escalation regimens of SGI-110, a novel subcutaneous (SQ) hypomethylating agent (HMA), in the treatment of relapsed/refractory patients with MDS and AML

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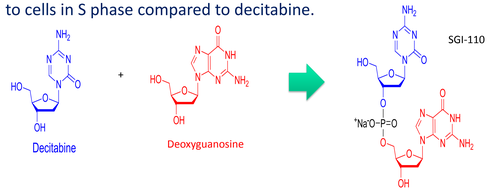
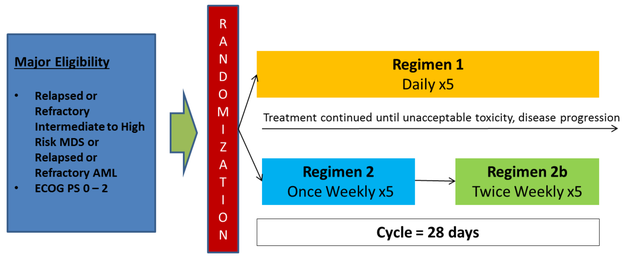
SGI-110 Background

- A second generation hypomethylating agent (HMA) characterized as a dinucleotide of decitabine and deoxyguanosine that increases the in vivo exposure of decitabine by protecting it from deamination.
- Administered as a small volume SQ injection, SGI-110 prolongs in vivo exposure time allowing more incorporation to cells in S phase compared to decitabine.



Phase 1 MDS and AML Study Design



- **Primary Endpoint:** Biologically effective dose or Maximum tolerated dose for each regimen
- **Secondary Endpoints:** Safety, PK-PD assessments, response rates, hematological improvement and duration of response

SGI-110 Phase 1 Results

Treatment Cohorts by Regimen and Dose

Dose or Dose Schedule[1]			Number of Patients		
Daily (mg/m²)	Weekly (mg/m²)	Twice Weekly (mg/m²)	Daily	Weekly	Twice Weekly
3	6	--	4	5	--
9	18	--	4	3	--
18	36	--	5	6	--
36	60	60	6	6	8
60	90	90	7	8	7
90	125	--	6	6	--
125	--	--	12	NA	--
Total			44	34	15

[1]Daily: Days 1 – 5; Weekly: Days 1, 8, 15; Twice Weekly: Days 1, 4, 8, 11, 15, 18; All regimens: 28-day cycle

Patient and Disease Characteristics

Characteristics by Regimen

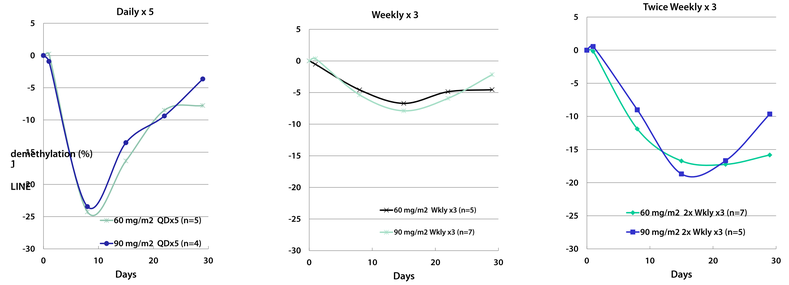
Characteristics	Daily (n=44)	Weekly (n=34)	Twice Weekly (n=15)
Age, median (range)	68 (36 – 86)	69 (29 – 83)	72 (51 – 84)
Male (%)	25 (57)	26 (76)	12 (80)
ECOG 0/1/2 (%)	10 (23)/ 28 (64) / 6 (14)	6 (18) / 24 (71) / 4 (12)	4 (27) / 9 (60) /2 (13)
Median % BM Blast at Baseline, range	38 (2 – 98)	19 (1 – 95)	20 (2 – 89)
Median WBC (10^9/L) at Baseline, range	3 (0.1 – 70)	2.6 (0.6 – 20.9)	3.2 (0.1 – 68.5)
Secondary AML (%), including antecedent MDS	12 (27)	8 (24)	5 (33)
Median Time in Days Since Diagnosis to C1D1, (range)	435 (7 – 10,364)	397 (6 – 2,170)	469 (12 – 2,008)
Median # of Prior Regimens (range)	4 (1 – 9)	2.5 (1 – 7)	1 (1 – 7)
decitabine (%) azacitidine (%) decitabine or azacitidine (%)	18 (41) 17 (39) 27 (61)	13 (38) 15 (44) 23 (68)	7 (47) 7 (47) 13 (87)

Characteristics by Disease

Characteristics	AML (n=74)	MDS (n=19)	Total (n=93)
Age, median (range)	67 (29 – 86)	73 (46 – 82)	70 (29 – 86)
Male (%)	49 (66)	14 (74)	63 (68)
ECOG 0/1/2 (%)	16 (22)/ 47 (64)/ 11 (15)	4 (21) /14 (74)/1 (5)	20 (22)/61 (66) /12 (13)
Median % BM Blast at Baseline, range	40 (1 – 98)	7.5 (2 -22.6)	23.5 (1 98)
Median WBC (10^9/L) at Baseline, range	2.8 (0.1 – 70)	3.0 (1.3 – 68.5)	2.9 (0.1 – 70)
Secondary AML (%), including antecedent MDS	25 (34)	--	--
Median Time in Days Since Diagnosis to C1D1, (range)	406 (6 – 10,364)	495 (9 – 4,081)	424 (6 –10,364)
Median # of Prior Regimens (range)	4 (1 – 9)	2 (1 – 6)	3 (1 – 9)
decitabine (%) azacitidine (%) decitabine or azacitidine (%)	30 (41) 22 (30) 44 (59)	8 (42) 17 (89) 19 (100)	38 (41) 39 (42) 63 (68)

Pharmacodynamics

- LINE-1 demethylation at the 2 highest dose levels and evaluated for all 3 regimens (60 and 90 mg/m²) are shown below.



- The daily regimen demonstrated the most potent average LINE-1 demethylation, while the Twice Weekly achieved the most prolonged LINE-1 demethylation. The least potent demethylation was observed with the Weekly regimen. Across the 3 regimens evaluated, SGI-110 dosing at 90 mg/m² did not produce significantly more demethylation compared to 60 mg/m².

MDS Responses - Patient Characteristics

Pt ID#	Dose (mg/m²)	Regimen	IPSS Risk Category	HMA Exposure (response)	BL WBC (k/uL) BL BM Blast (%)	Response Status[1]	Duration of Response (days)	Max LINE-1 % Demethylation
A	18	Daily	HR	Aza (PR), Dac (CR) Len/Dac (PR)	2.6 / 8	mCR	119	-19.3%
B	125	Daily	Int-2	Dac (NR) Aza (NR)	3.2 / 17	mCR	88	-37.8%
C	6	Weekly	HR	Aza (PR) Dac (NR)	2. 1 / 16	HI-E / HI-N	105	-4.5%
D	90	Weekly	HR	Aza/etinostat (PR) Aza (NR)	5.3 / 22.6	HI-E	84	-4.5%
E	90	Weekly	Int-1	Aza (PR)	1.3 / 2	HI-P / HI-E	181	-23.6%
F	60	Twice Weekly	CMML	Aza (NR)	21. 1 / 3	HI-P	106	-33.6%

AML Responses – Patient Characteristics

Pt ID#	Dose (mg/m²)	Regimen	Baseline Cytogenetic Category	# of Prior Regimen / Prior BMT	HMA Exposure (response)	Baseline WBC (k/uL) Baseline BM Blast (%)	Response Status[2]	Duration of Response (days)	Max LINE-1 % Demethylation
A	36	Daily	Inter	1 / No	No	9 / 35	CRi	350	-13.3
B	60	Weekly	Poor	4 / Yes	Dac (UKN)	2.6 / 8	CR	558	-22.7
C	60	Daily	Inter	5 / Yes	No	3.7 / 16.2	CR	114	-34.7
D	60	Daily	Poor	4 / No	Dac (NR); Aza (NR)	2.3 / 35	CRi	47	-23.3
E	125	Weekly	NC	6 / No	No	5.7 / 22	CRp	42	-11.5

Median duration of response = 106 days (range, 84 – 181) for MDS; 114 days (range, 42 – 558) for AML

Dac - decitabine; Aza – azacitdine; QD – daily; QW – weekly; Int – Intermediate, NC – not classifiable; NR – no response; UKN – unknown; PR – Partial Response; CR – Complete Response; CRi – CR with incomplete neutrophils; CRp – CR with incomplete platelet recovery; mCR – marrow CR; HI-E, HI-N, HI-P – hematological improvement erythrocytes, neutrophils, and platelets, respectively.

AML Responses and LINE-1 Demethylation

LINE-1 Demethylation	Number of AML Patients	Responders (CR/CRi/CRp)	Percent
< 10%	31	0	0%
≥ 10%	19	5	26%*
Total	50	5	10%

- AML complete remissions associated with ≥ 10% LINE-1 demethylation (*p < 0.01)

Safety and Tolerability by Regimen

Related Adverse Events ≥ 10% by Regimen and Grade 3/4

	Daily (n=44) (%)	Weekly (n=34) (%)	Twice Weekly (n=15) (%)
Adverse Event	All Grades / Grade 3 or 4	All Grades / Grade 3 or 4	All Grades / Grade 3 or 4
Anemia	14 / 11	9 / 9	20 / 13
Febrile neutropenia	7 / 7	6 / 6	13 / 13
Neutropenia	14 / 11	3 / 3	27 / 27
Thrombocytopenia	20 / 16	6 / 6	27 / 27
Diarrhea	7 / 0	12 / 0	0 / 0
Nausea	11 / 0	9 / 0	0 /0
Fatigue	11 / 0	9 / 0	27 / 0
Injection site hemorrhage	0 / 0	3 / 0	13 / 0
Injection site pain	25 / 2	32 / 0	53 / 0
Injection site reaction	5 / 0	3 / 0	13 / 0
Decreased appetite	9 / 0	6 / 0	13 / 0
Hematuria	0 / 0	0 / 0	13 / 0
Contusion	2 / 0	3 / 0	13 / 0
Epistaxis	5 / 0	3 / 0	20 /0

Conclusions

- SGI-110 is well tolerated across regimens evaluated with predicted and manageable adverse events.
- Clinical responses were observed in heavily pretreated MDS and AML patients, including those with prior HMA exposure. Responses in r/r AML patients was associated with LINE-1 demethylation ≥ 10%.
- The daily regimen produced the most potent hypomethylation while the twice weekly regimen resulted in the most prolonged hypomethylation.
- Phase 2 study in MDS and AML patients is ongoing where patients are randomized to either 60 or 90 mg/m² dailyx5.

References

1. Cheson BD, Bennett JM, Kopecky KJ et al. Journal of Clinical Oncology, 2003, 21:24; 4642 – 4649.
2. Cheson BD, Greenberg PL, Bennett JM et al. Blood, 2006, 18:2; 419 – 425.

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