Abstract # 3074

First results of a Phase 2 study using a 10-day subcutaneous (SC) regimen of the novel hypomethylating agent (HMA) SGI-110 for the treatment of relapsed/refractory Acute Myeloid Leukemia (r/r AML)

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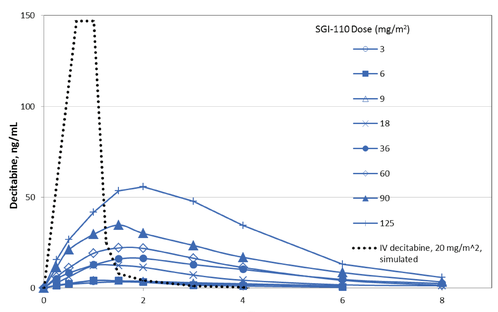
BACKGROUND

- Relapsed/refractory AML (r/r AML) is often drug-resistant with high mortality
- Hypomethylating agents (HMAs) such as decitabine and azacitidine have shown some clinical activity in r/r AML
- SGI-110 is next generation hypomethylating agent (HMA) given as a small volume subcutaneous (SC) administration
- We previously presented phase 2 data of SGI-110 in heavily pretreated r/r AML using a standard 5-day regimen Q 28 days showing an overall Complete Remission (CR+CRp+CRi) rate of 16% (Kantarjian et al, ASH, 2013)
- Here we present the first phase 2 results of SGI-110 given SC in a 10-day regimen Q 28 days

SGI-110, a next generation HMA

- SGI-110 is a dinucleotide which incorporates and protects decitabine from deamination resulting in longer decitabine half-life and longer exposure time (Figure 1). This allows decitabine incorporation into DNA of more cycling leukemic cells as a result of the longer exposure time
- Phase 1 data showed potent DNA demethylation as measured by LINE-1 with the biologically effective dose (BED) of 60 mg/m2 daily SCx5 (lowest dose inducing maximum demethylation)

Figure 1. Decitabine concentration time profile from SGI-110 escalating doses (3-125 mg/m^2)



METHODS

Study Design

The study was an open-label single arm phase 2 study of SGI-110 given as a 10-day regimen Q 28 days in r/r AML

Major Eligibility Criteria

1. Adult men or women 18 years or older with previously treated AML except Acute Promyelocytic Leukemia (M3 classification)
2. ECOG Performance Status 0-2
3. No symptomatic CNS involvement
4. No limit on number of prior regimens or prior therapy except for HMAs where only one prior cycle was allowed
5. No limits on WBCs count or blasts %
6. Adequate hepatorenal function
7. Signed Informed Consent

Main Study Objectives:

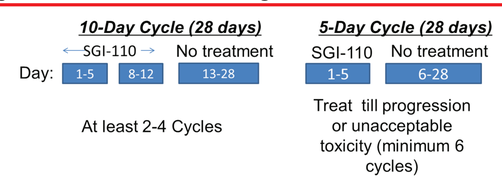
Primary:

- Evaluate the activity of SC SGI-110 given as a 10-day regimen in r/r AML as measured by the Overall Complete Remission (OCR) rate (CR+CRp+CRi).

Secondary:

- Duration of response, overall survival (OS), and safety

Figure 2: SGI-110 Treatment Regimen



SGI-110 was given SC 60 mg/m^2/d on days 1-5 and 8-12, Q 28 days for at least 2- 4 cycles, followed by SGI-110 60 mg/m^2/d on days 1-5 Q28 days for a total of at least 6 cycles

RESULTS

Table 1. Patient Characteristics

Patient Characteristics	N=53
Median Age, (range)	57 (29 – 82) Years
Gender, M (%)	27 (51%)
F (%)	26 (49%)
ECOG PS	
0	9 (17%)
1	35 (66%)
2	9 (17%)
Median BM Blast% (range)	32% (4% – 95%)
Median WBC (10^9/L) (range)	2.1 (0.2 – 75.5)
Secondary AML (%)	9 (17%)
Poor-risk Cytogenetics (%)	21 (40%)
Prior HCT (%)	9 (17%)
Median # Prior Regimens, (range)	2 (1 – 7)
Prior HMA treatment (azacitidine or decitabine)	7 (13%)

Table 2. Distribution of 10-day and 5-day cycles in treated patients (N=53)

Treatment Cycle	10-day dosing (Nb of pts)	5-day dosing (Nb of pts)
1	53	0
2	45	3
3	27	7
4	16	6
5	7	4
6	2	0
7	0	1
Total # of cycles (%)	150 (88%)	21 (12%)

- About half of patients received 3 cycles of SGI-110 daily x 10
- 88% of all cycles were given as the 10-day dose regimen

Table 3. Clinical Efficacy

Complete Response Category[1]	Complete Response rate N (%) (n=53)
CR	10 (19%)
CRp	4 (7%)
CRi	2 (4%)
Primary Endpoint Overall CR (OCR)=CR + CRp + CRi	**16 (30%) (95 CI:18, 44%)**

- Median duration of response (minimum, maximum): 163 (42, 274+) days
- Median overall survival (95% CI): 211 (169, 266) days

Figure 3: Mean LINE-1 DNA Methylation (Cycle 1)

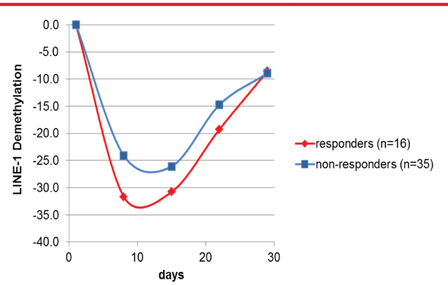


Table 4. LINE-1 Demethylation and Response

	Mean of Maximum LINE-1 demethylation % in Cycle 1 ± SE
Non- Responders	-28.53 ± 1.83
Responders	-36.11 ± 2.23
P value	0.0384

Table 5. Safety: Most Commonly Reported Related AEs

Adverse Event	(N=53) All Grades N (%)	(N=53) Grade ≥ 3 N (%)
Injection site events	26 (49)	0
Anaemia	19 (36)	16 (30)
Thrombocytopenia	18 (34)	18 (34)
Diarrhoea	18 (34)	0
Fatigue	16 (30)	2 (4)
Nausea	16 (30)	1 (2)
Constipation	10 (19)	0
Decreased appetite	10 (19)	0
Mucosal inflammation	10 (19)	2 (4)
Vomiting	9 (17)	0
Febrile neutropenia	8 (15)	7 (13)
Neutropenia	7 (13)	7 (13)

Table 6. Safety: 30- and 60-day All Cause Mortality

N	30-day All Cause Mortality (%)	60-day All Cause Mortality (%)
53	1 (1.9)	6 (11.3)

CONCLUSIONS

- Patients in the trial were heavily pretreated r/r AML with multiple prior regimens, including HCT
- SGI-110 SC daily x 10 was well tolerated, with low 30-day and 60-day all cause mortality (1.9% and 11.3%, respectively)
- Potent, sustained global DNA demethylation (LINE-1) was observed in most subjects and was higher in responders than non-responders
- The Overall CR rate was 30%, including CR at 19% and CR+CRp at 26% Results compare favorably with prior results of a 5-day regimen of SGI-110 in r/r AML (OCR 16%, Kantarjian et al, ASH 2013)
- SGI-110 is clinically active with an acceptable safety profile and should be investigated further in AML treatment

References

1. Cheson BD et al, Journal of Clinical Oncology, Vol 21, No 24 (December 15), 2003: pp 4642-4649
2. Kantarjian HM et al, Blood. 2013; 122(21): p. 497

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