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First Results of a 10-Day Regimen of SGI-110 (Guadecitabine), a Second Generation Hypomethylating Agent (HMA) in Previously Untreated Elderly AML Who are Not Candidates for Intensive Chemotherapy

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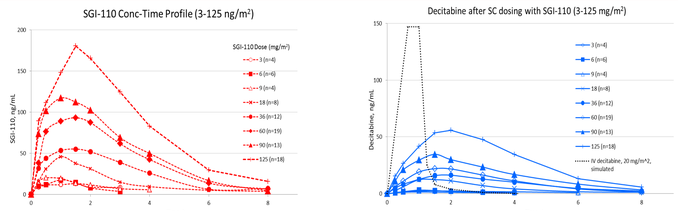
Background

- Elderly and unfit individuals with AML are often ineligible to receive intensive chemotherapy
- Hypomethylating agents (HMA) such as decitabine and azacitidine have shown efficacy and acceptable safety in these patients
- SGI-110 (guadecitabine) is a next generation HMA given as a small volume subcutaneous (SC) administration
- We previously presented Phase 2 data of SGI-110 using the standard 5-day regimen which showed good good clinical activity in these patients[1]
- We present here , the preliminary results (minimum follow up of 3 months) of a 10-day regimen of SGI-110 in treatment naïve (TN) AML patients who are ineligible for intensive chemotherapy (IC)

SGI-110 (guadecitabine), a Next Generation HMA

- Guadecitabine 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/m^2 SC on 5 consecutive days (lowest dose inducing maximum demethylation)

Figure 1: Guadecitabine SC Results in Prolonged Exposure Window to Active Metabolite Decitabine



- Guadecitabine undergoes efficient conversion to yield decitabine over time. Slow/delayed conversion results in longer effective decitabine half-life of ~ 1.8 hr, ($T_{1/2}$ for IV DAC ~ 0.25-0.6 hr) and longer exposure window of ~ 11.8 hr (vs ~4 hr for IV)
- PK data presented are from Phase 1 Dose Escalation

STUDY DESIGN

Open-label single arm phase 2 study of guadecitabine given as a 10-day regimen q 28 days for up to 4 cycles followed by 5-day regimen in previously untreated elderly AML patients who are not candidates for intensive chemotherapy (TN IC-Ineligible AML).

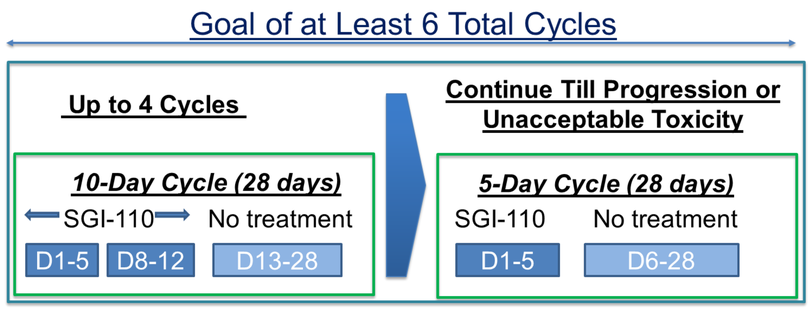
Overall Study Goals

- Primary: Evaluate the activity of SC guadecitabine given as a 10-day regimen in TN IC-ineligible AML as measured by the Overall Composite Complete Remission (CRc) rate (CR+CRp+CRi)[2].
- Secondary: Duration of response, overall survival (OS), and safety

Major Eligibility Criteria

- Adults > age 65 with treatment naïve AML ineligible for IC
- ECOG Performance Status 0-2
- No symptomatic CNS involvement
- No limits on WBC or blasts
- Adequate hepatorenal function
- Informed consent

Figure 2: Guadecitabine 10-Day regimen for AML



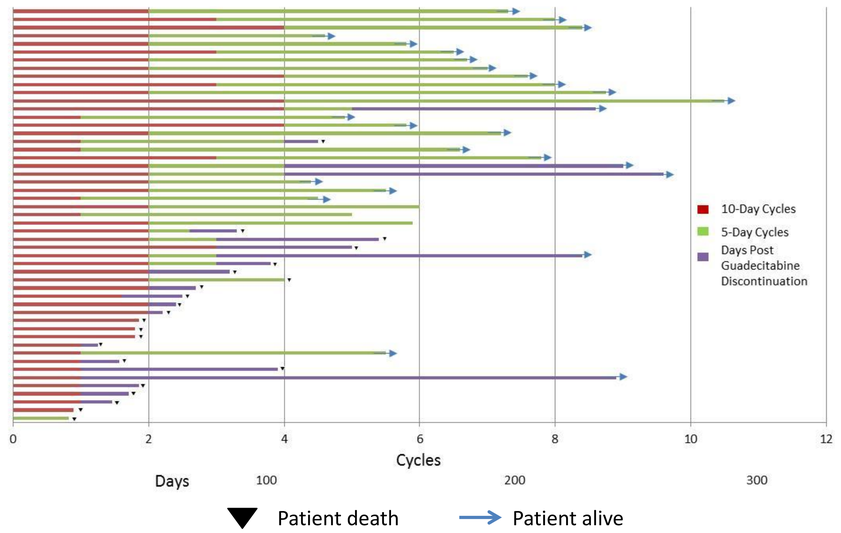
Guadecitabine was given as 60 mg/m^2/d SC days 1-5 and 8-12 Q28 days for up to 4 cycles based upon tolerance followed by treatment on days 1-5 Q28 days for a total of at least 6 cycles

Table 1: Treatment Naïve IC-Ineligible AML Patient Characteristics

Patient Characteristics	(n=52)
Median Age, (range)	77 (66-92)
Gender, M (%)	34 (65%)
ECOG PS (%)	
0	5 (10%)
1	26 (50%)
2	21 (40%)
Secondary AML (%)	13 (25)
Median BM Blast% (range)	50(16-98)
Median WBC [10^9/L] (range)	4.0(0.5-87.7)

RESULTS

Figure 3: TN IC-Ineligible AML Patients Treated with the 10 Day Regimen of Guadecitabine



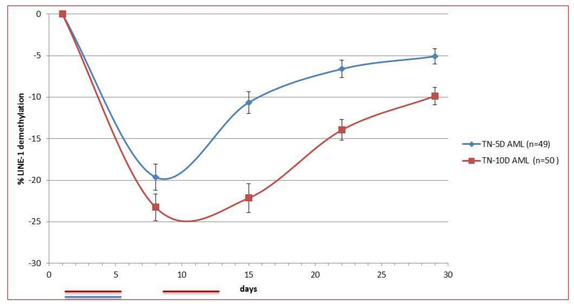
73% of patients (38/52) received 2 cycles of guadecitabine 10-day regimen
48% of patients (25/52) continue on treatment with 5-day regimen

Table 2: Clinical Responses in Treatment Naïve IC-Ineligible AML

Response Category[2]	Response rate (N=52)* N (%)
CR	**14 (27%)**
CRp	2 (4%)
CRi	8 (15%)
CRc (CR + CRp + CRi)	**24 (46%) [95% CI: 32, 61%]**

* 25 patients are still ongoing treatment with potential for more responders with longer follow up

Figure 4: Cycle 1 LINE-1 Demethylation 5-Day vs 10-Day Regimen



In treatment naïve AML patients, the 10-day schedule shows a longer duration of LINE-1 demethylation compared to the 5-day regimen

Table 3: Most Commonly Reported Grade > 3 AEs Regardless of Relationship (>10%)

	(n=52) (%)
Febrile neutropenia	48%
Thrombocytopenia	29%
Neutropenia	23%
Pneumonia	19%
Anaemia	17%
Sepsis	17%
Bacteremia	15%

Table 4: All-Cause Early Mortality

N	30 day Mortality N (%)	60 day Mortality N (%)
52	2 (4)	10 (19)

Conclusions

- 73% of patients were able to receive 2 cycles of the 10-day regimen of guadecitabine
- The guadecitabine 10-day regimen is clinically active with a good safety profile in treatment naïve IC-ineligible AML patients
- Preliminary results for the 10-day regimen do not seem to be superior to the 5-day regimen (CR=33%,CRi=22% OCR=55%)[1] in this population
- ASTRAL-1 Phase 3 trial of guadecitabine in TN AML unfit to receive IC is ongoing using 5-day regimen[3]

References

1. Yee K et al. (2014). European Hematology Association, abs S647.
2. Cheson BD et al, Journal of Clinical Oncolo gy, Vol 21, No 24 (December 15), 2003: pp 4642-4649
3. https://clinicaltrials.gov/ct2/show/NCT02348489?term=SGI-110+AML&rank=2

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