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LATE RESPONSES AND OVERALL SURVIVAL (OS) FROM LONG TERM FOLLOW UP OF A RANDOMIZED PHASE 2 STUDY OF SGI-110 (GUADECITABINE) 5-DAY REGIMEN IN ELDERLY AML WHO ARE NOT ELIGIBLE FOR INTENSIVE CHEMOTHERAPY

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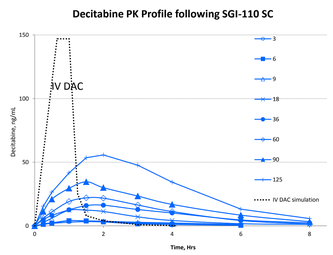
Background

- We previously reported results from a multicenter study of guadecitabine randomized to a 5-day regimen at either 60 or 90 mg/m^2 in 51 treatment naïve elderly AML patients not eligible for intensive chemotherapy[1]
- There were no significant differences in overall composite complete response (CRc: CR+CRp+CRi) or safety between the two doses; however 14 patients were still on treatment at the time of the prior analysis
- We present here current results on these patients with a median follow-up of 24 months (20.2-33) during which 38 death events occurred in the 51 patients treated (75%)

SGI-110 (guadecitabine), a Next Generation Hypomethylating Agent (HMA)

- Guadecitabine is a dinucleotide which incorporates and protects decitabine from deamination resulting in longer decitabine (DAC) half-life and longer exposure time (Figure 1). This allows decitabine incorporation into the 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/day subcutaneously (SC) on 5 consecutive days (lowest dose inducing maximum demethylation)

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

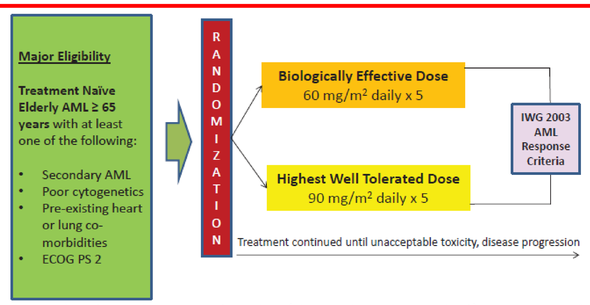


- Guadecitabine undergoes efficient conversion to yield decitabine over time. Slow/delayed conversion results in longer effective decitabine half-life of ~ 1.8 hr, ($T_{1/2}$ for IV DAC ~ 0.25-0.6 hr) and longer exposure window of ~11.8 hr (vs ~4 hr for IV DAC) compared to DAC IV
- PK data presented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

Study Design

Open-label randomized Phase 2 study of guadecitabine given as a 5-day regimen q28 days at either 60 or 90 mg/m^2 per dose SC in previously untreated elderly AML patients who are not candidates for intensive induction chemotherapy (TN IC-Ineligible AML)

Figure 2: Phase 2 Study Design in Treatment Naïve Elderly AML



- Primary Endpoint: Composite CR (CRc=CR+CRp+CRi) rates as defined by IWG criteria, 2003
- Secondary Endpoints: LINE-1 demethylation, duration of response, overall survival and safety

Results

Table 1: Treatment Naïve IC-Ineligible AML Patient Characteristics

Patient Characteristics	60 mg/m^2 (N=24)	90 mg/m^2 (N=27)	Total (N=51)
Median Age, (range)	78 (62-92)	77(66-92)	77(62-92)
Gender, M (%)	14 (58%)	16(59%)	30(59%)
ECOG PS (%)			
0	3 (13%)	8 (30%)	11 (22%)
1	10 (42%)	12(44%)	22 (43%)
2	11 (46%)	7 (26%)	18 (35%)
Secondary AML (%)	10 (42%)	13 (48%)	23 (45%)
Median BM Blast% (range)	40(21-90)	46(13-94)	40(13-94)
Median WBC [10^9/L] (range)	2.5(0.7-50)	2.9(0.9-51.4)	2.8(0.7-51.4)
Poor risk cytogenetics(%)	12(50%)	12(44%)	24(47%)

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

Response Category[i]	60 mg/m^2 (N=24) N (%) Response Rate	90 mg/m^2 (N=27) N(%) Response Rate	Total (N=51) N(%) Response Rate
CR	**9 (38%)**	**10(37%)**	**19(37%)**
CRi	3(13%)	4(15%)	7(14%)
CRp	1(4%)	2(7%)	3(6%)
CRc[ii]	**13(54%)**	**16(59%)**	**29(57%)**

i International Working Group 2003 AML Response Criteria[2]
ii CRc = CR+CRp+CRi

Table 3: Cycles of Guadecitabine to Best Response

	CR	CRp	CRi	Total
Cycles	N=19	N=3	N=7	N(%)
1	2	0	2	4(14)
2	3	0	0	3(10)
3	1	0	4	5(17)
4	5	1	1	7(24)
5	2	0	0	2(7)
6	2	0	0	2(7)
>6	4*	2$	0	6(21)

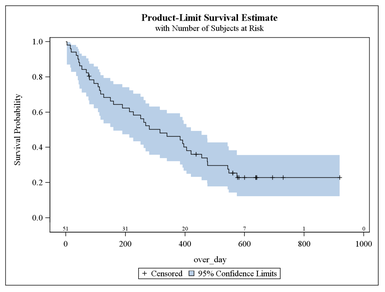
* 2 in cycle 7, 1 in cycle 9, 1 in cycle 10
$ 1 in cycle 8 and 1 in cycle 12

Table 4: Duration of Response

	60 mg/m^2 Mean Days (SD)	90 mg/m^2 Mean Days (SD)	Total Mean Days (SD)
CR	**317 (215)**	**302 (212)**	**309 (207)**
CRc	255 (234)	237 (199)	245 (212)

3 Responders underwent allogeneic stem cell transplant and were censored at that time from this analysis

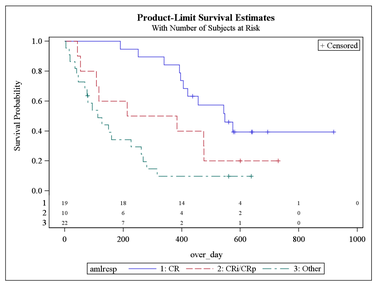
Figure 3: Kaplan-Meier Overall Survival



60 mg/m^2 vs. 90 mg/m^2
(No difference Log Rank test)

All patients plotted with 95% C. I.

Med Survival 10.5 mo
Med F/U 24 mo



Median Survival

CR	18.2 months
CRp + CRi	10.0 months
No Response	3.8 months

Table 5: Most Commonly Reported Grade ≥ 3 AEs Regardless of Relationship to Guadecitabine

	60 mg/m^2 (n=24) n (%)	90 mg/m^2 (n=27) n (%)	Total (n=51) n(%)
Febrile neutropenia	14(58%)	15(56%)	29(57%)
Thrombocytopenia	13 (54%)	11(41%)	24(47%)
Neutropenia	8(33%)	12(44%)	20 (39%)
Anaemia	8(33%)	7(26%)	15(29%)
Leucopenia	5(21%)	7(26%)	12(24%)
Pneumonia	5(21%)	7(26%)	12(24%)
Sepsis	2 (8%)	4 (15%)	6(12%)
Cellulitis	2 (8%)	3 (11%)	5 (10%)

Conclusions

- With longer follow up both response rates and median survival improved from previous report [1]
- No major differences were observed in clinical response, demethylation[1], overall survival, and safety between 60 and 90 mg/m^2 dailyx5
- In older patients "unfit" for intensive induction chemotherapy guadecitabine provides promising response rates (CR = 37%, CRc =57%) and median OS of 10.5 months in a poor prognosis patient population
- Responders had better survival (CR > CRi+CRp > No Response)
- Late responses were common for SGI-110, 28% of responses occurred after 6 cycles with 21% occurring after >6 cycles
- Patients should be treated with at least 6 cycles and continued in the absence of disease progression
- ASTRAL-1 is a Phase 3 trial evaluating guadecitabine in this patient group[3]

References

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

Poster presented at: European Hematology Association 20th Congress, Vienna, Austria June 11 - 14, 2015

Poster can be downloaded from www.astx.com

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