RESULTS FROM A RANDOMIZED PHASE 2 STUDY OF GUADECITABINE, A NOVEL HYPOMETHYLATING AGENT (HMA), IN PATIENTS WITH RELAPSED OR REFRACTORY INTERMEDIATE OR HIGH RISK MYELODYSPLASTIC SYNDROMES (MDS) OR CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

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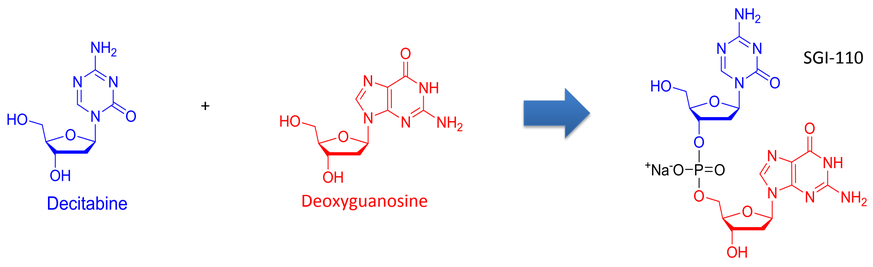
Background

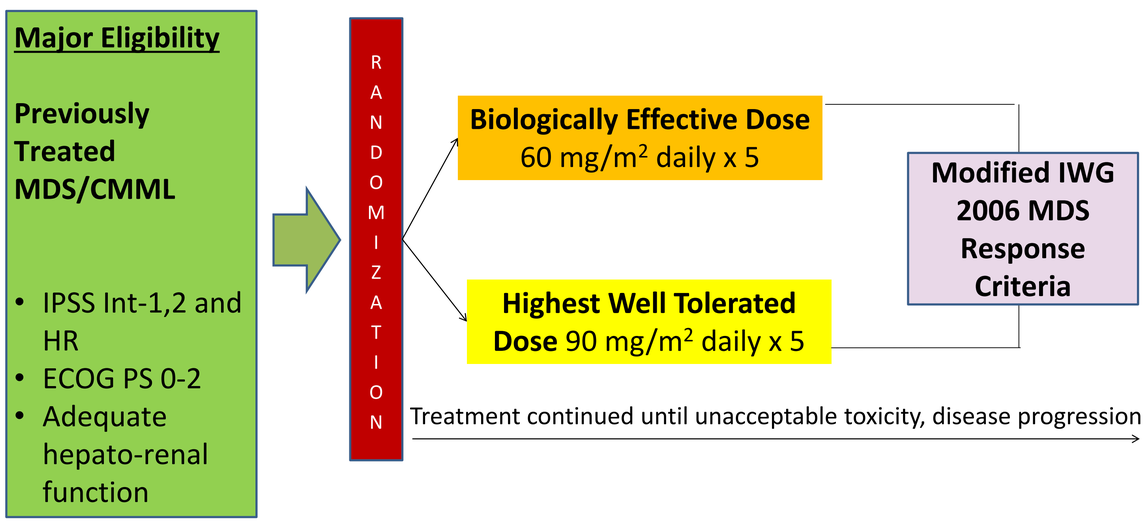
Guadecitabine (SGI-110) is a next generation hypomethylating agent (HMA) designed as a dinucleotide of decitabine and deoxyguanosine that is resistant to deamination by cytidine deaminase (CDA).
This results in a prolonged *in vivo* exposure to decitabine following small volume subcutaneous (SC) administration of guadecitabine.
Safety and clinical activity in resistant MDS and AML have been shown in a Phase 1 trial (Issa et al, Lancet Oncology, 2015).

Figure 1: Guadecitabine: Next Generation HMA



Methods

Figure 2: Phase 2 Study Design



- Primary Endpoint: Overall Response (CR, PR, mCR, HI)
- Secondary Endpoints: Transfusion independence, Overall Survival, Safety

Results

Table 1: Patient Characteristics

Patient Characteristics		60 mg/m² QD x5 (n=26)	90 mg/m² QD x5 (n=27)	Total (n=53)
Median Age (range)		73 (55-85)	72 (52-89)	72 (52-89)
Gender	M	62%	59%	60%
	F	38%	41%	40%
ECOG PS	0	23%	19%	21%
	1	54%	63%	58%
	2	23%	19%	21%
Prior decitabine (DAC) (%)		23%	41%	32%
Prior azacitidine (AZA) (%)		77%	78%	77%
Prior DAC **and** AZA		8%	19%	13%
Median Prior regimens		1 (1-4)	1 (1-4)	1 (1-4)
MDS by IPSS Classification	Int-1	8%	7%	8%
	Int-2	23%	26%	25%
	HR	35%	59%	47%
CMML		35%	4% *	19%
Time from last prior Tx	<3 m	67%	52%	59%
	3-6 m	12%	33%	23%
	> 6 m	21%	15%	18%
Duration of prior HMA	< 6 m	5 (19%)	8 (30%)	13 (25%)
	> 6 m	21 (81%)	19 (70%)	40 (75%)
Median BM Blasts %		5.5% (0-18%)	9% (1-19%)	8% (0-19%)
Baseline BM Blasts*	≤ 5%	13 (50%)	6 (22%)	19 (36%)
	> 5%	13 (50%)	21 (78%)	34 (64%)
Median Neutrophils/µL		1170	510	810
Median Platelets/µL		39,000	35,000	37,000
Median Hb g/dL		9.25 (7.1-12.9)	9.5 (7.4-13.5)	9.3 (7.1-13.5)
RBCs or Platelet transf. dep.		62%	70%	66%

*P = 0.047 *P = 0.005

Table 2: Treatment and Follow-up

Treatment Cycles	60 mg/m²/d x5 (N=26)	90 mg/m²/d x5 (N=27)	Total N=53
Median # Tx Cycles	4 (1-22)	5 (1-29)	5 (1-29)
Dose Reduced Cycles	36%	34%	35%
Dose Delayed Cycles	47%	43%	45%
Median Follow Up (range) in months	25.2 (20.4-29.5)	24.4 (19.4-30.1)	25.0 (19.4-30.1)

Results cont.

Table 3: Response to Treatment

Response	60 mg/m²/d x5 N=26 N (%)	90 mg/m²/d x5 N=27 N (%)	Total N=53 N (%)
CR	1 (3.8%)	1 (3.7%)	2 (3.8%)
mCR *	4/13 (31%)	11/21 (52%)	15/34 (44%)
PR	0	0	0
HI	5 (19.2%)	6 (22.2%)	11 (20.8%)

**** Evaluated only in patients who had BM blasts > 5% at baseline***

Table 4: Transfusion Independence (Combined Data)

Guadecitabine 8-week **RBCs** **Transfusion Independent** n (%)	**4/33 (12%)**
Guadecitabine 8-week **Platelets** **Transfusion Independent** n (%)	**6/16 (38%)**

* Evaluated only for patients who were transfusion dependent at baseline

Figure 3: Overall Survival By Dose

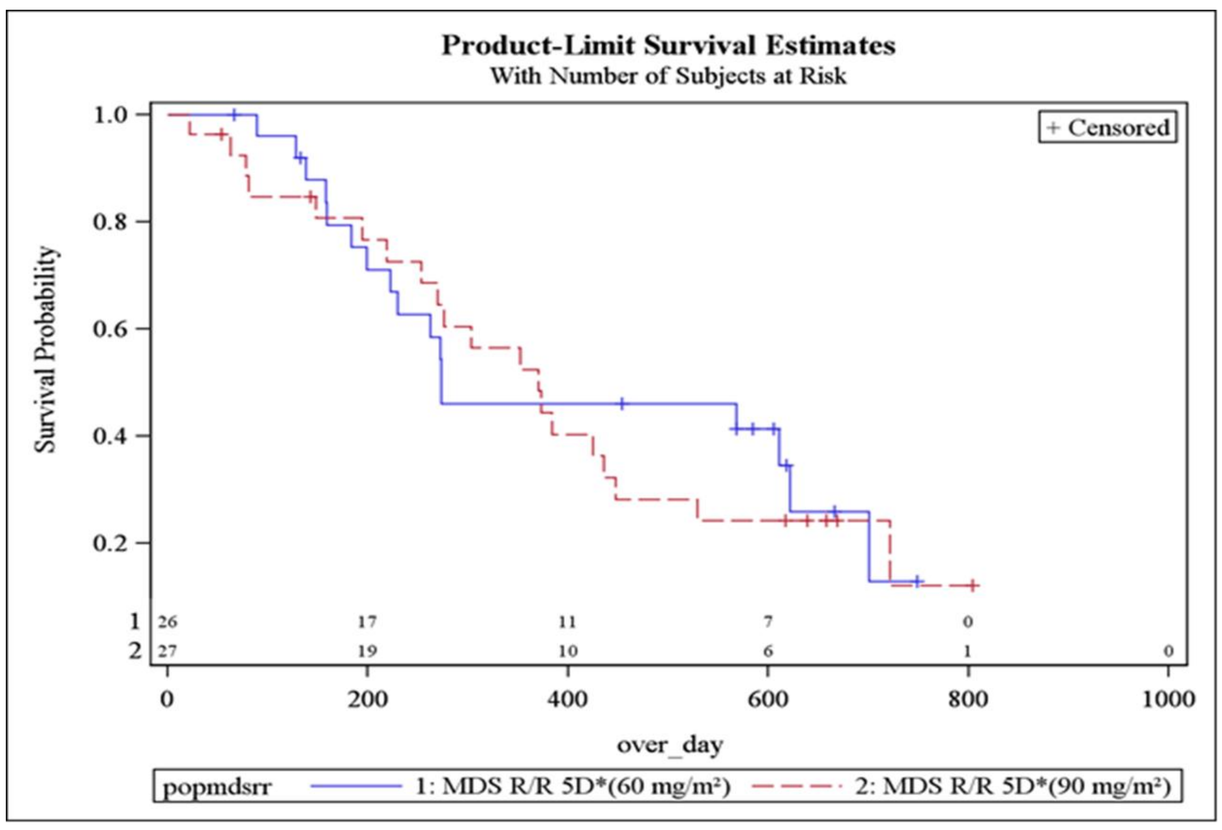


Table 5: Safety AEs Grade ≥ 3 Regardless of Tx Relationship

	60 mg/m² N=26	90 mg/m² N=27	Total N=53
Thrombocytopenia	54%	56%	55%
Anemia	54%	48%	51%
Neutropenia	50%	41%	45%
Febrile neutropenia	38%	37%	38%
Pneumonia	23%	41%	32%
Fatigue	12%	15%	13%
Leukopenia	8%	15%	11%
Sepsis	8%	15%	11%

All-Cause Early Mortality

Dose	N	30-day	60-day	90-day
60 mg/m²	26	0	0	1 (3.8%)
90 mg/m²	27	1 (3.7%)	1 (3.7%)	4 (14.8%)
Total	53	1 (1.8%)	1 (1.8%)	5 (9.4%)

Summary and Conclusions

- Patient characteristics generally balanced between the 2 doses of guadecitabine except for
  - Significantly higher % of CMML in the 60 mg/m² arm
- Efficacy: Both doses were clinically active in relapsed/refractory MDS or CMML previously treated with HMAs, with 4% CR and 44% mCR in patients with baseline BM blasts >5%.
- Safety: Both doses well tolerated with slightly higher incidence of pneumonia, leukopenia, and sepsis for the 90 mg/m² dose (not significant).
- No significant differences between the 2 doses in terms of efficacy and safety.
- The Phase 2 study supports Phase 3 development of guadecitabine 60 mg/m² dailyx5 in relapsed/refractory MDS and CMML.
- Phase 3 randomized study is being planned to start later this year (2:1 Randomization of Guadecitabine vs Treatment Choice).

Reference

Issa JP et al, Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukemia: a multicenter, randomized, dose-escalation phase 1 study, Lancet Oncol. 2015 Sep;16(9):1099-1110.

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Poster can be downloaded from www.astx.com
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