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RANDOMIZED PHASE 2 STUDY OF GUADECITABINE IN PATIENTS WITH HMA-NAÏVE HIGHER RISK MYELODYSPLASTIC SYNDROMES (MDS) OR CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

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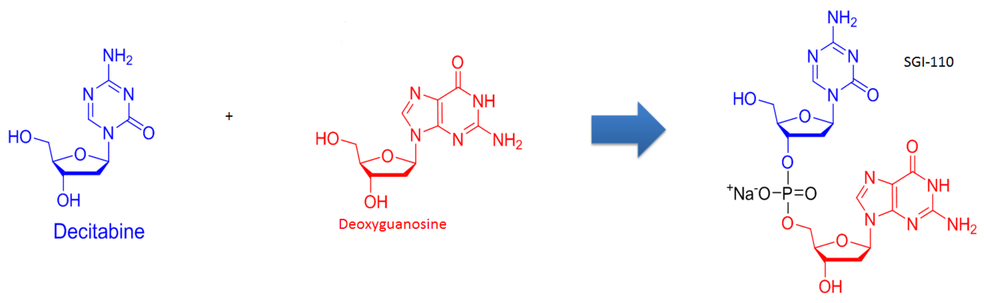
Background

- 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).
- As a result, sc guadecitabine administration (~1cc volume) results in prolonged in vivo exposure.
- Safety data in resistant MDS and AML have been published in a Phase 1 study (Issa et at, Lancet Oncology, 2015) and encouraging data have been presented in tn AML, r/r AML, and r/r MDS (Kantarjian, et al ASH 2015, Roboz, et al, ESMO 2014, Garcia-Manero, ESH 2016)
- Here data are presented for a cohort of HMA-naïve MDS or CMML patients randomized to receive two different doses of guadecitabine.

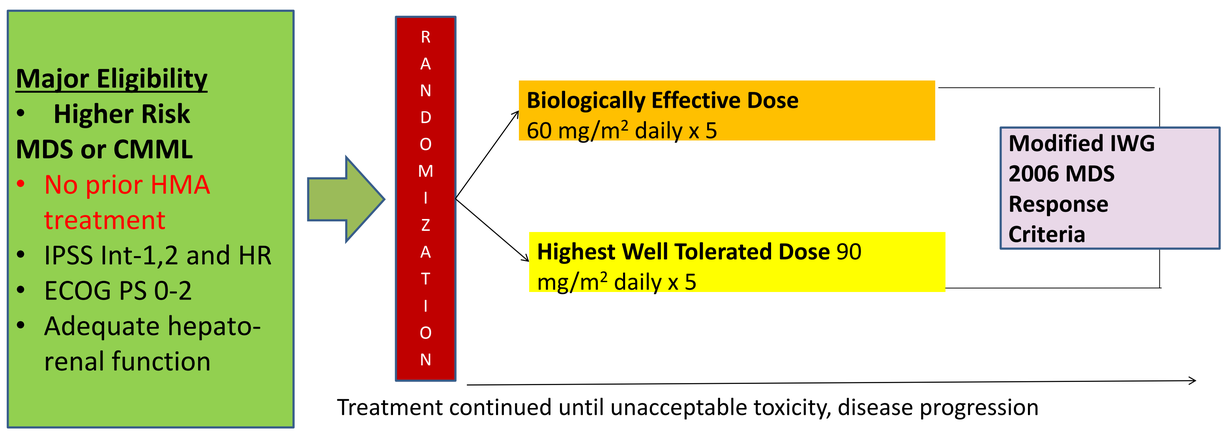
Figure 1: Guadecitabine (SGI-110): Next Generation HMA



METHODS & STUDY DESIGN

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

Figure 2: Phase 2 Study Design in Higher Risk MDS or CMML



RESULTS

Table 1: Patient Characteristics

Patient Characteristics		60 mg/m² QDX5 (n= 27)	90 mg/m² QDX5 (n= 22)	Total (n=49)
Median age (range)		71 (18-85)	70 (63-84)	71 (18-85)
Gender	M	78%	64%	71%
	F	22%	36%	29%
ECOG PS	0	22%	32%	27%
	1	70%	64%	67%
	2	7%	5%	6%
Median Prior regimens (range)		0 (0-1)	0 (0-1)	0 (0-1)
MDS by IPSS classification				
	INT-1	52%	41%	47%
	INT-2	4%	18%	10%
	HR	22%	14%	18%
	CMML	22%	27%	24%
Time Since Dx to C1D1 (days, median)		35	33	35
Median BM Blast%		2 (0-13)	7 (0-14)	3 (0-14)
Baseline BM blast	≤ 5%	74%	45%	61%
	> 5%	26%	55%	39%
RBC transfusion dep.		56%	41%	49%
Platelet transfusion dep		26%	23%	24%

Table 2: Treatment

Treatment Cycles	60 mg/m² QDX5 (n=27)	90 mg/m² QDX5 (n=22)	Total
Median # Tx cycles (range)	5 (1-49)	4.5 (1-41)	5 (1-49)
Dose Reduced Cycles	24%	54%	37%
Dose delayed Cycles	30%	41%	35%
Received 95-100% of intended dose	89%	77%	84%

Table 3: Response to Treatment

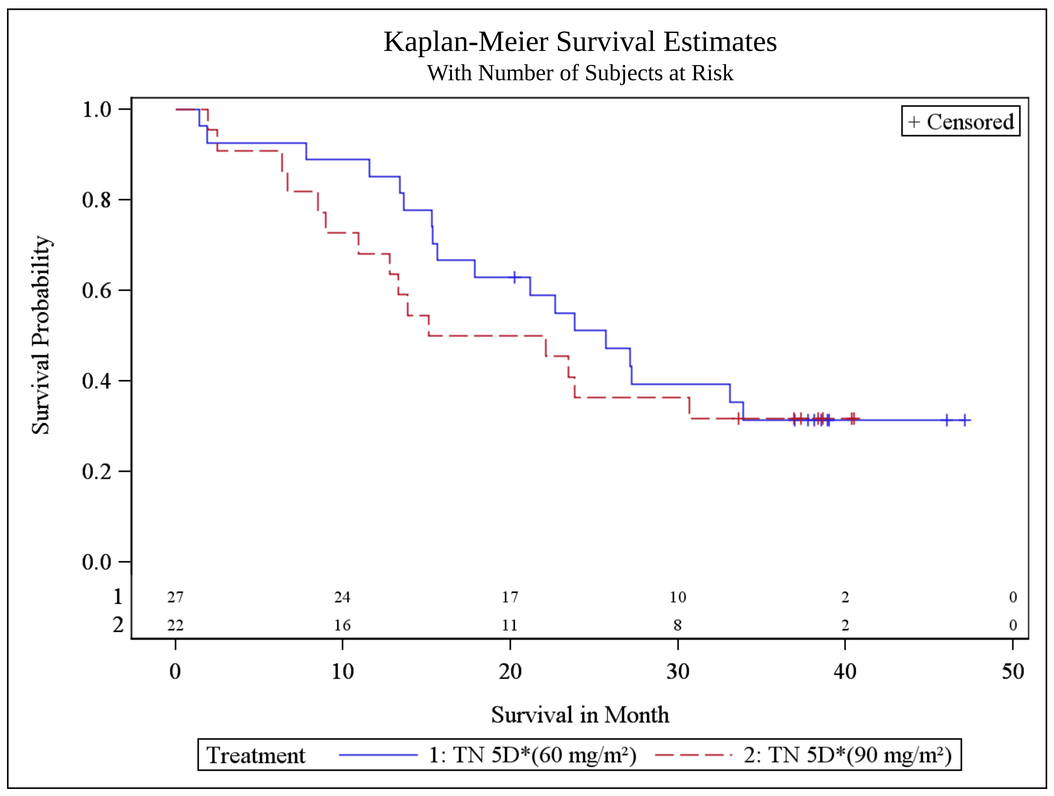
Response Category	60 mg/m² QDX5 (n=27)	90 mg/m² QDX5 (n=22)	Total (n=49)
CR	5 (19%)	6 (27%)	11(22%)
PR	0	0	0
mCR	2 (7%)	5 (23%)	7 (14%)
Hematologic Improvement			
Single Lineage	6 (50%)	5 (56%)	11 (52%)
Bi-lineage	4 (33%)	4 (44%)	8 (38%)
Tri-lineage	2 (17%)	0	2 (10%)
Overall response (CR+ PR+ mCR+HI)	13 (48%) 95% CI [28.7-68.1]	12 (55%) 95% CI [32.2-75.6]	25 (51%) 95% CI [36.3-65.6]
Median OS	25.7 mos. [15.3-33.9]	18.6 [9.0- NE]	23.4 [15.2-30.7]
24-month survival rate	51%	36%	44%

Table 4: Adverse Events Grade 3 or Higher Regardless of Tx Relationship (>10% of overall total)

Adverse Events	60 mg/m² QDX5 (n=27)	90 mg/m² QDX5 (n=22)	Total (n=49)
Thrombocytopenia	8 (30%)	13 (59%)	21 (43%)
Anemia	11 (41%)	10 (45%)	21 (43%)
Neutropenia	9 (33%)	14 (64%)	23 (47%)
Febrile Neutropenia	7 (26%)	10 (45%)	17 (35%)
Pneumonia	8 (30%)	5 (23%)	13 (27%)
Leukopenia	5 (19%)	4 (18%)	9 (18%)
Cellulitis	3 (11%)	4 (18%)	7 (14%)
Fatigue	1 (4%)	2 (9%)	3 (6%)
Sepsis	1 (4%)	3 (14%)	4 (8%)

Early Mortality (30- and 60-Day) by Dose			
Dose	N	30-Day	60-Day
60 mg/m2	27	0	2 (7.4%)
90 mg/m2	22	0	1 (4.5%)
Total	49	0	3 (6.1%)

Figure 3: Overall Survival in HMA-Naïve MDS Patients



CONCLUSIONS

- Patient characteristics were balanced between the 2 tested doses of guadecitabine
- **Efficacy**: Both doses were clinically active in HMA-Naïve MDS or CMML with 22% CR and 51% ORR (CR + PR + mCR + HI) for the combined groups. Median OS for the combined group was almost 2 years. The 60 mg/m² arm trended for longer survival (25.7 vs 18.6 mos.) compared to 90 mg/m²
- **Safety**: The safety profile was similar to what has been previously observed with guadecitabine with most events related to myelosuppression. There was a slightly higher incidence of thrombocytopenia, neutropenia, febrile neutropenia, and sepsis in the 90 mg/m² dose (not significant).
- The recommended dose of guadecitabine for the treatment of higher risk MDS and CMML is 60 mg/m² Dailyx5

REFERENCES

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Poster presented at: The 14th International Symposium on Myelodysplastic Syndromes, Valencia, Spain May 3 – 6, 2017

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