

First clinical results of a randomized phase 2 study of SGI-110, a novel subcutaneous hypomethylating agent, in 102 patients with Intermediate or High Risk MDS or CMML

On Behalf of the SGI-110 Investigative Team

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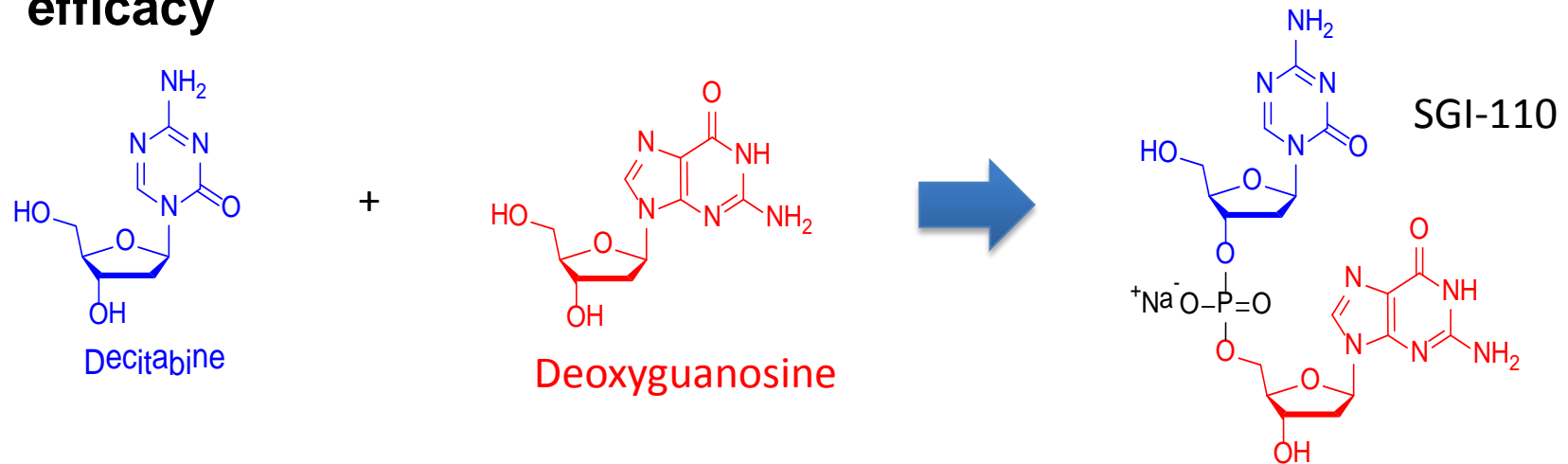
Background: DNA Methylation in MDS/AML

- **DNA methylation is an epigenetic process tightly linked to gene expression**
- **MDS and AML are characterized by frequent DNA methylation changes and mutations in epigenetic genes (e.g. TET2, DNMT3a, EZH2)**
- **First generation hypomethylating agents (azacitidine, decitabine) have demonstrated clinical activity in MDS and AML**

SGI-110 Background

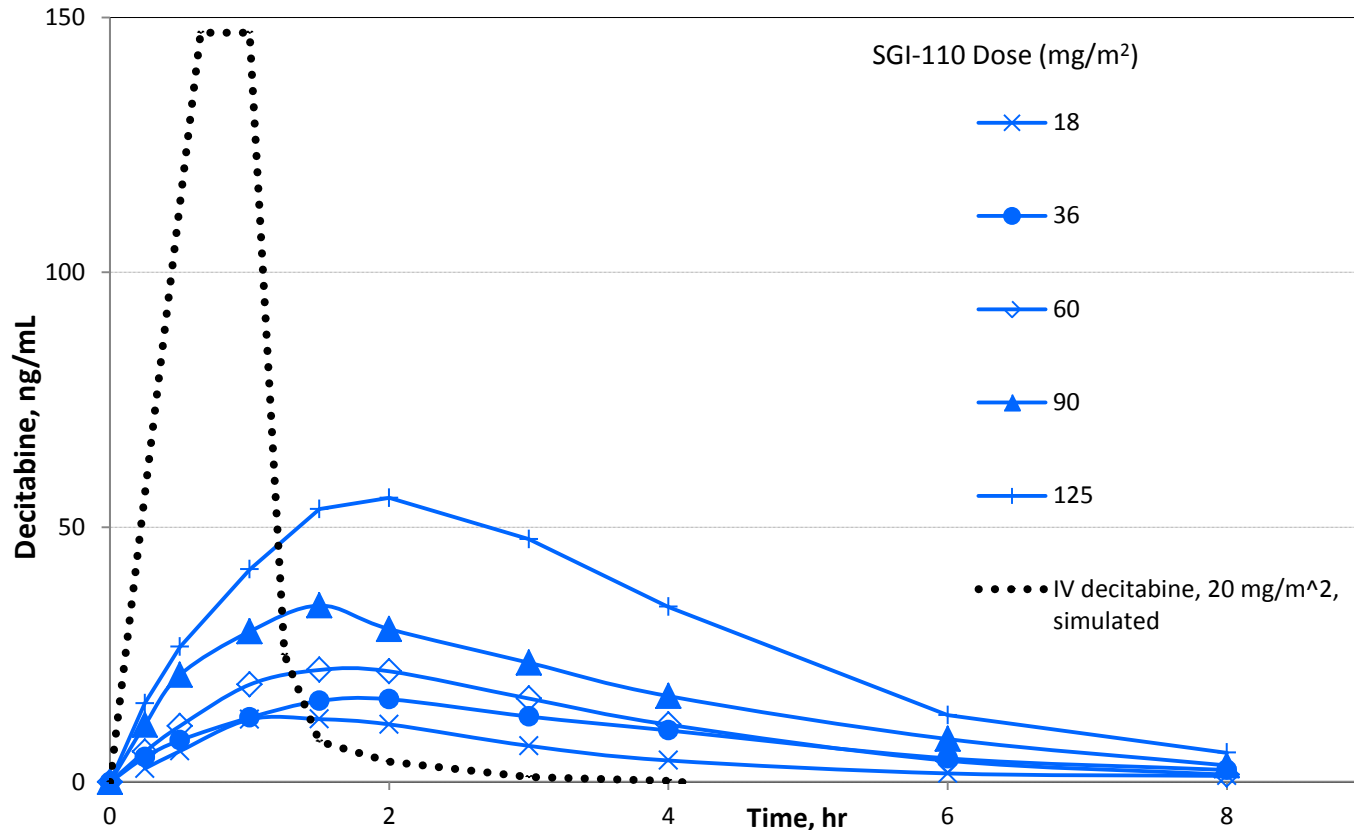
A Second Generation Hypomethylating Agent

- Decitabine is rapidly eliminated by Cytidine Deaminase, limiting drug exposure time to cancer cells *in vivo*
- SGI-110 is a Dinucleotide of Decitabine and Deoxyguanosine that prolongs the *in vivo exposure* of decitabine by protecting it from deamination
- Prolonged decitabine *in vivo* exposure may translate to better efficacy



SGI-110 Phase 1 PK

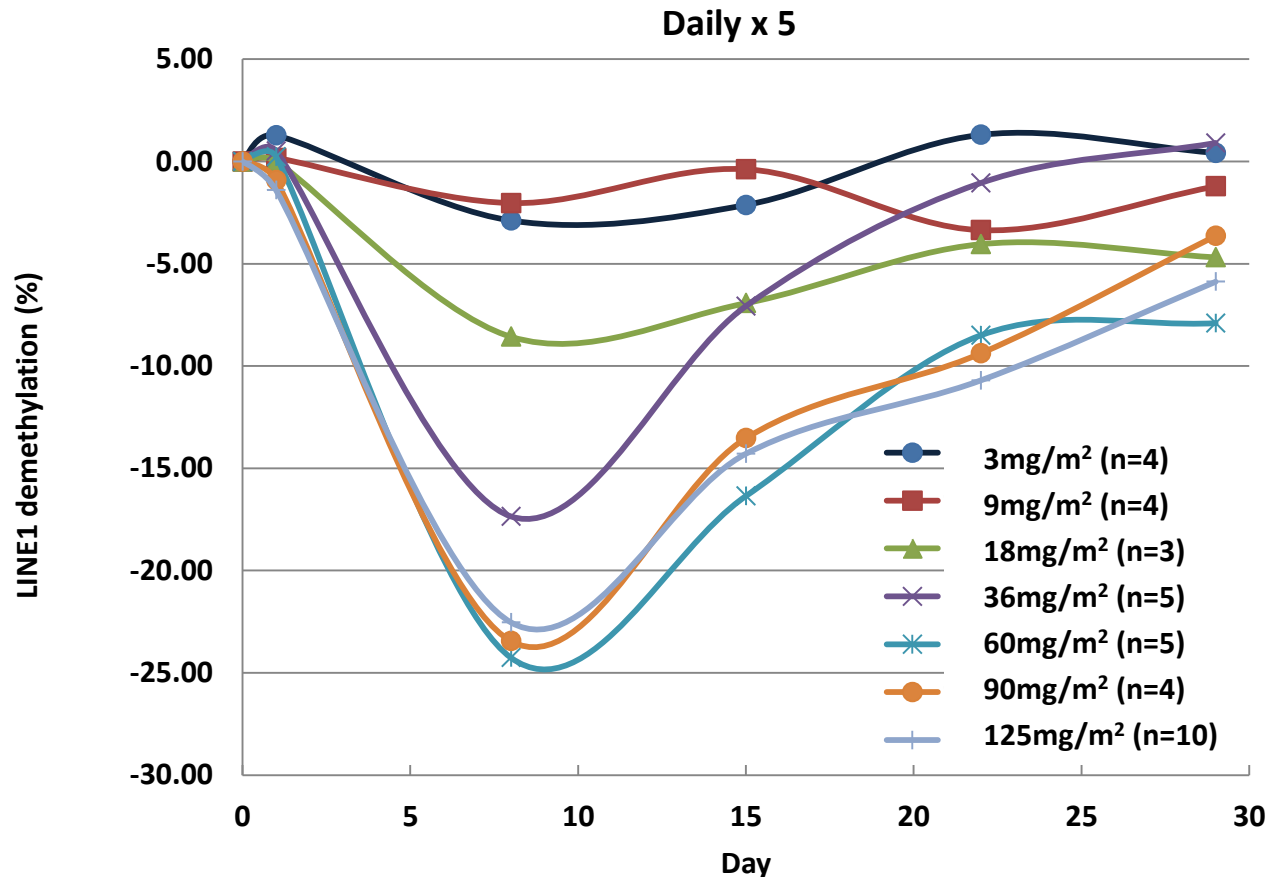
Prolonged Exposure time and $t_{1/2}$ of decitabine compared to decitabine IV



- Decitabine exposure window after SC SGI-110 is more than double (8hr+) compared to decitabine 20 mg/m² 1-hr IV infusion (3-4h, simulated)
- Prolonged decitabine $t_{1/2}$ (up to 2 hr vs 0.25-0.5 hr for decitabine IV) due to protracted release from SGI-110
- Lower decitabine C_{max} compared to decitabine IV

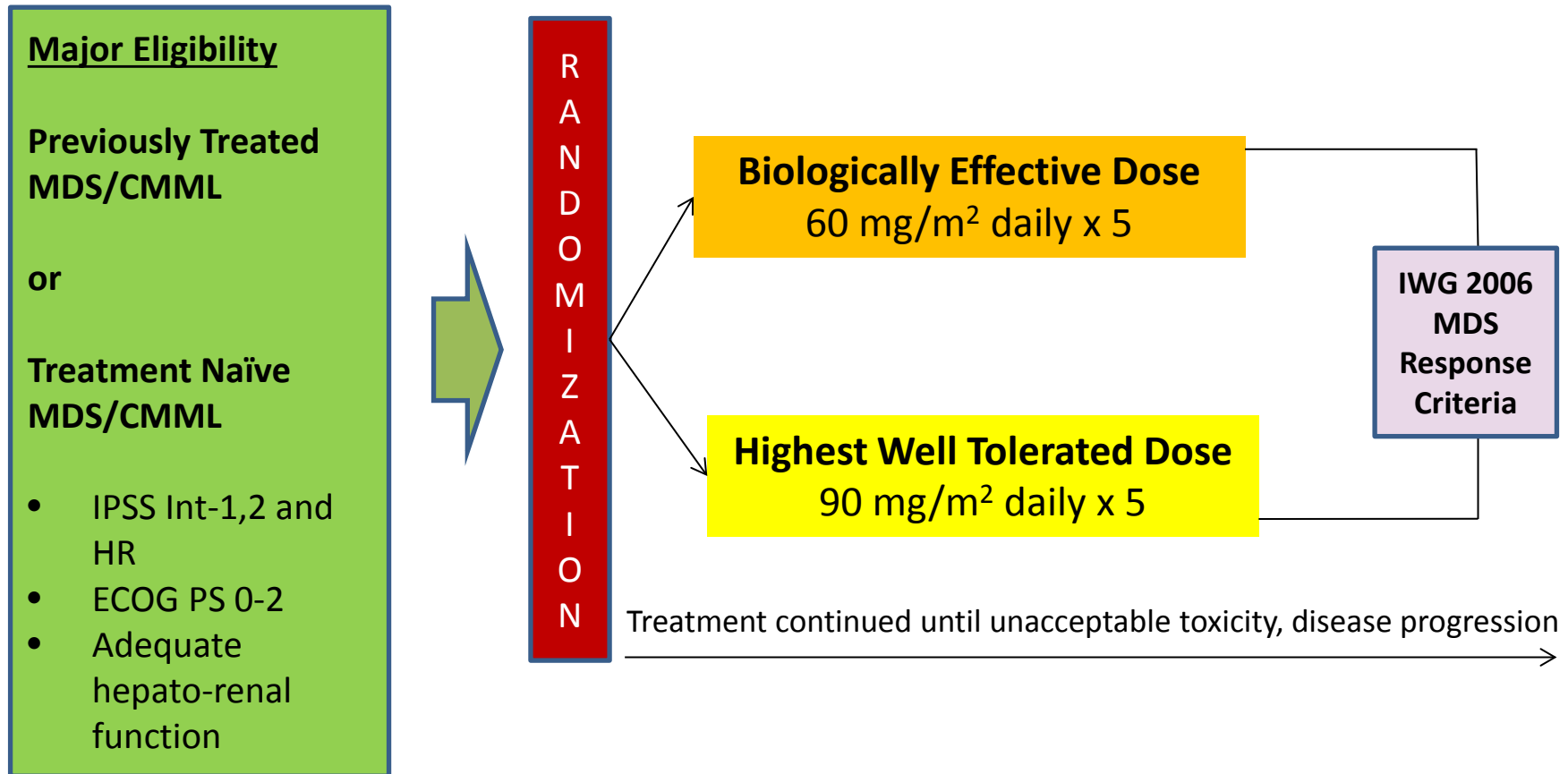
SGI-110 Phase 1 PD

Potent dose-dependent LINE1 DNA Demethylation



- LINE-1 demethylation increased with dose up to 60 mg/m² Dailyx5
- Maximum demethylation achieved at 60 mg/m² Dailyx5 (BED)
- MTD in MDS patients reached at 90 mg/m² Dailyx5

Randomized Phase 2 Study of SGI-110 in MDS/CMML¹



- **Primary Endpoint: Overall Response Rate (CR, PR, mCR, HI)**
- **Secondary Endpoints: Transfusion independence, LINE-1 demethylation, time to AML, overall survival**

¹ Data presented with data cutoff end of July 2014

SGI-110: Patients Characteristics By Dose

Patient Characteristics	60 mg/m ² (n=53)	90 mg/m ² (n=49)
Median Age, (range)	71.7 (18-86)	72.5 (52-89)
Gender, M n (%)	37 (70)	30 (61)
ECOG PS %: 0/1/2	23/62/15	24/63/12
Disease Category (IPSS) n (%)		
Int-1	16 (30)	11 (22)
Int-2	7 (13)	11 (22)
High Risk	15 (28)	18 (37)
CMML	15 (28)	7 (14)
Median BM Blast % (range)	4 (0-18)	8 (0-19)
Median Neutrophils (10 ⁹ /L)	1.19	1.16
Median Platelets (10 ⁹ /L)	42.5	45
Median Hb (g/dL)	9.25	9.30
Prior decitabine or azacitidine n(%)	25 (47)	27 (55)
Disease Status (n)		
Previously Treated MDS	26	27
Tx naïve MDS	27	22

SGI-110: Patients Characteristics By MDS Status

Patient Characteristics	Prev. Treated (n=53)	Tx Naïve (n=49)
Median Age, (range)	72.5 (52-89)	71.7 (18-85)
Gender, M n (%)	32 (60)	35 (71)
ECOG PS %: 0/1/2	21/58/21	27/67/6
Disease Category (IPSS) n (%)		
Int-1	4 (8)	23 (47)
Int-2	13(25)	5 (10)
High Risk	24 (45)	9 (18)
CMML	10 (19)	12 (24)
Median BM Blast % (range)	8 (0-19)	3 (0-14)
Median Neutrophils (10 ⁹ /L)	0.81	1.64
Median Platelets (10 ⁹ /L)	37	62.5
Median Hb (g/dL)	9.30	9.10
Prior decitabine or azacitidine n(%)	51 (96)	1 (2) ¹
Randomized Dose (n)		
60 mg/m ²	26	27
90 mg/m ²	27	22

¹Patient received only 1 prior cycle of HMA

SGI-110: Treatment Intensity and Number of Cycles ¹

By Dose	Median # (range)	% Cycles Dose Delayed	% of Cycles Dose Reduced
60 mg/m ²	4 (1-22)	33%	19%
90 mg/m ²	4 (1-15)	36%	22%
By MDS Status	Median # (range)	% Cycles Dose Delayed	% of Cycles Dose Reduced
Prev Treated	4 (1-11)	37%	23%
Tx naive	5 (1-22)	36%	21%

- **38 of 102 patients are still ongoing treatment (37%)¹**
- **Majority of Cycles completed on time and with intended dose**

¹ At time of data cutoff

SGI-110: Best Response¹ By Dose

Response Category ¹	60 mg/m ² (n=53)	90 mg/m ² (n=49)
	Response rate n (%)	Response rate n (%)
CR	4 (7.5)	5 (10.2)
mCR	6 (11.3)	6 (12.2)
HI	4 (7.5)	6 (12.2)
CR+mCR	10 (18.8)	11 (22.4)
Overall Response Rate	14 (26.4)	17 (34.7)

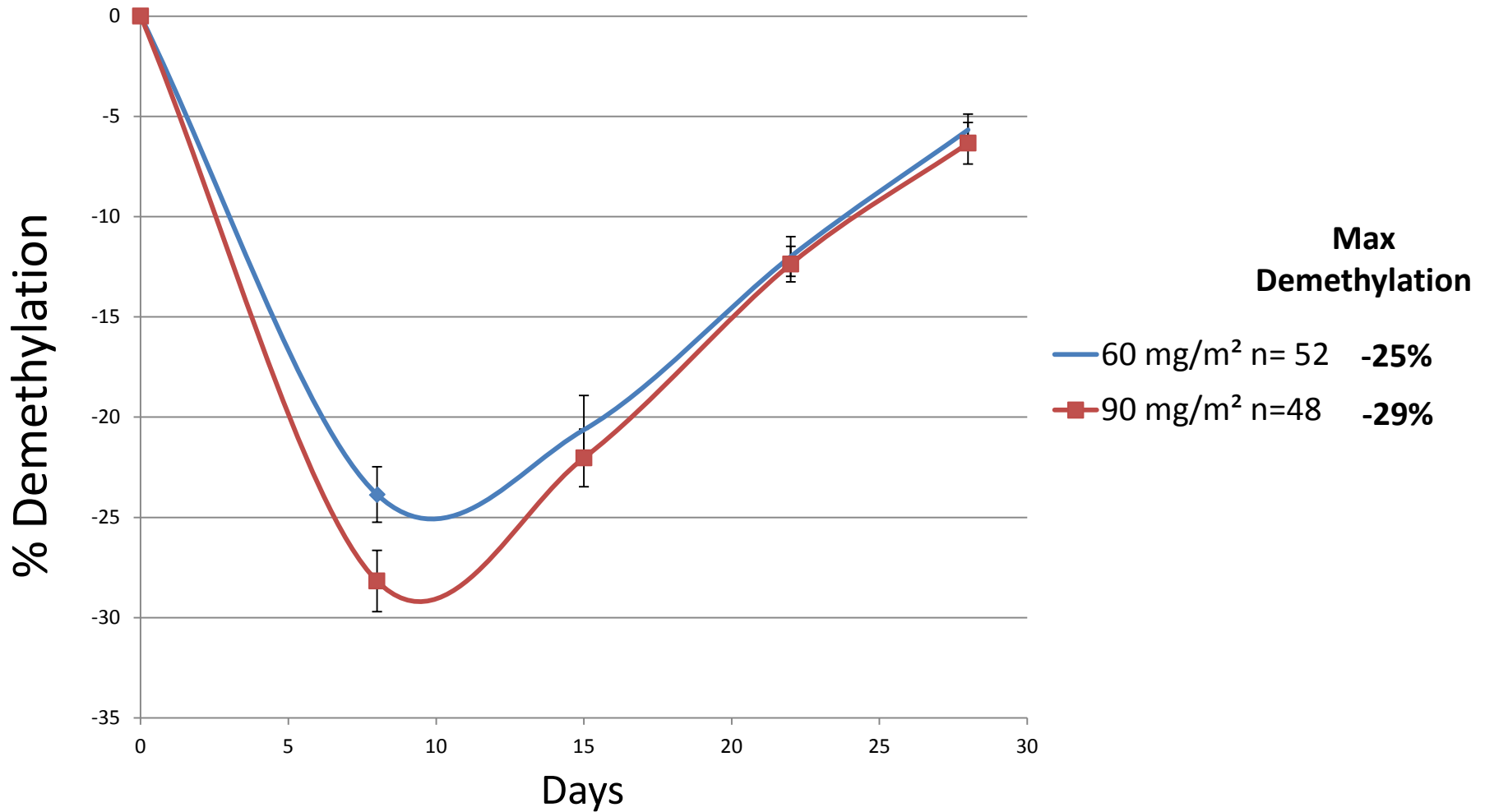
¹International Working Group 2006 MDS Response Criteria

SGI-110: Best Response¹ By MDS Status

Response Category ¹	Prev Treated (n=53)	Tx Naïve (n=49)
	Response rate n (%)	Response rate n (%)
CR	2 (3.8)	7 (14.3)
mCR	9 (17.0)	3 (6.1)
HI	1 (1.9)	9 (18.4)
CR+mCR	11 (20.8)	10 (20.4)
Overall Response Rate	12 (22.7)	19 (38.8)

¹International Working Group 2006 MDS Response Criteria

SGI-110: LINE-1 Demethylation in Cycle 1



SGI-110: Transfusion Independence

	60 mg/m ² (n=53)	90 mg/m ² (n=49)
Baseline RBCs Transfusion dependent	27/53 (51%)	24/49 (49%)
8-week RBCs Transfusion Independent n (%)	7/27 (26%)	5/24 (21%)
Baseline Platelets Transfusion dependent	13/53 (25%)	15/49 (31%)
8-week Platelets Transfusion Independent n (%)	4/13 (31%)	5/15 (33%)

SGI-110: Adverse Events Grade ≥ 3 in $\geq 10\%$ of Patients¹

Adverse Event	60 mg/m ² (n=53) Grade ≥ 3 AEs %	90 mg/m ² (n=49) Grade ≥ 3 AEs %
Anemia	38%	37%
Febrile Neutropenia	32%	33%
Neutropenia	42%	49%
Thrombocytopenia	38%	51%
Pneumonia	13%	20%
Leukopenia	11%	12%

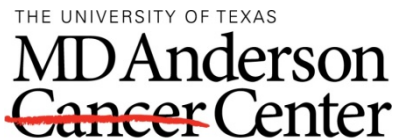
	60 mg/m ² (n=53)	90 mg/m ² (n=49)
8-week all-cause mortality n (%)	2 (3.8%)	1 (2.0%)

¹Regardless of relationship to SGI-110

Conclusions

- **SGI-110 is a new HMA with clinical activity in MDS/CMML**
 - **14% CR and 39% Overall response rate in Treatment Naïve MDS/CMML**
 - **21% CR+mCR and in Previously Treated MDS/CMML**
 - **No significant difference between 60 and 90 mg/m² Dailyx5 doses**
- **Potent demethylation and Transfusion independence with both doses**
- **Both doses well tolerated: slightly higher Grade \geq 3 Pneumonia and Thrombocytopenia with 90 mg/m² compared to 60 mg/m²**
- **Follow up for Survival is ongoing**
- **Future Development in MDS and AML:**
 - **MDS: Data warrant further Phase 3 development particularly in Previously Treated MDS**
 - **AML: Phase 3 in Treatment Naïve AML not candidate for intensive chemotherapy is being initiated**

Acknowledgements



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