Results From the Dose Escalation Phase of a Randomized Phase 1–2 First-in-Human (FIH) Study of SGI-110, a Novel Low Volume Stable Subcutaneous (SQ) Second Generation Hypomethylating Agent (HMA) in Patients with Relapsed/Refractory MDS and AML

On behalf of the SGI-110-01 Study Team

Hagop Kantarjian[1], Gail Roboz[2], David Rizzieri[3], Wendy Stock[4], Casey O'Connell[5*], Elizabeth Griffiths[6], Karen Yee[7], Raoul Tibes[8], Guillermo Garcia-Manero[1], Farhad Ravandi[1], Katherine Walsh[9], Eric Feldman[2], Ellen Ritchie[2], Arati Rao[3], Carlos Decastro[3], Aaron Schimmer[7], Ruben Mesa[8], Ibrahim Syed[5*], Gavin Choy[10], Aram Oganesian[10], Pietro Taverna[10], Mohammad Azab[10], Woonbok Chung[11*], Jean Pierre Issa[11*]

MD Anderson Cancer Center, Houston TX[1], Weill Cornell Medical College, New York, NY[2], Duke University Medical Center, Raleigh, NC[3], University of Chicago Medical Center, Chicago, IL[4], USC Keck School of Medicine, University of Southern California, Los Angeles, CA[5], Roswell Park Cancer Institute, Buffalo, NY[6], Princess Margaret Hospital, Toronto, Canada[7], Mayo Clinic, Arizona, Scottsdale, AZ[8], Ohio State University, Columbus, OH[9], Astex Pharmaceuticals, Inc., Dublin CA[10], Fels Institute, Temple University, Philadelphia, PA[11], Stand Up To Cancer*

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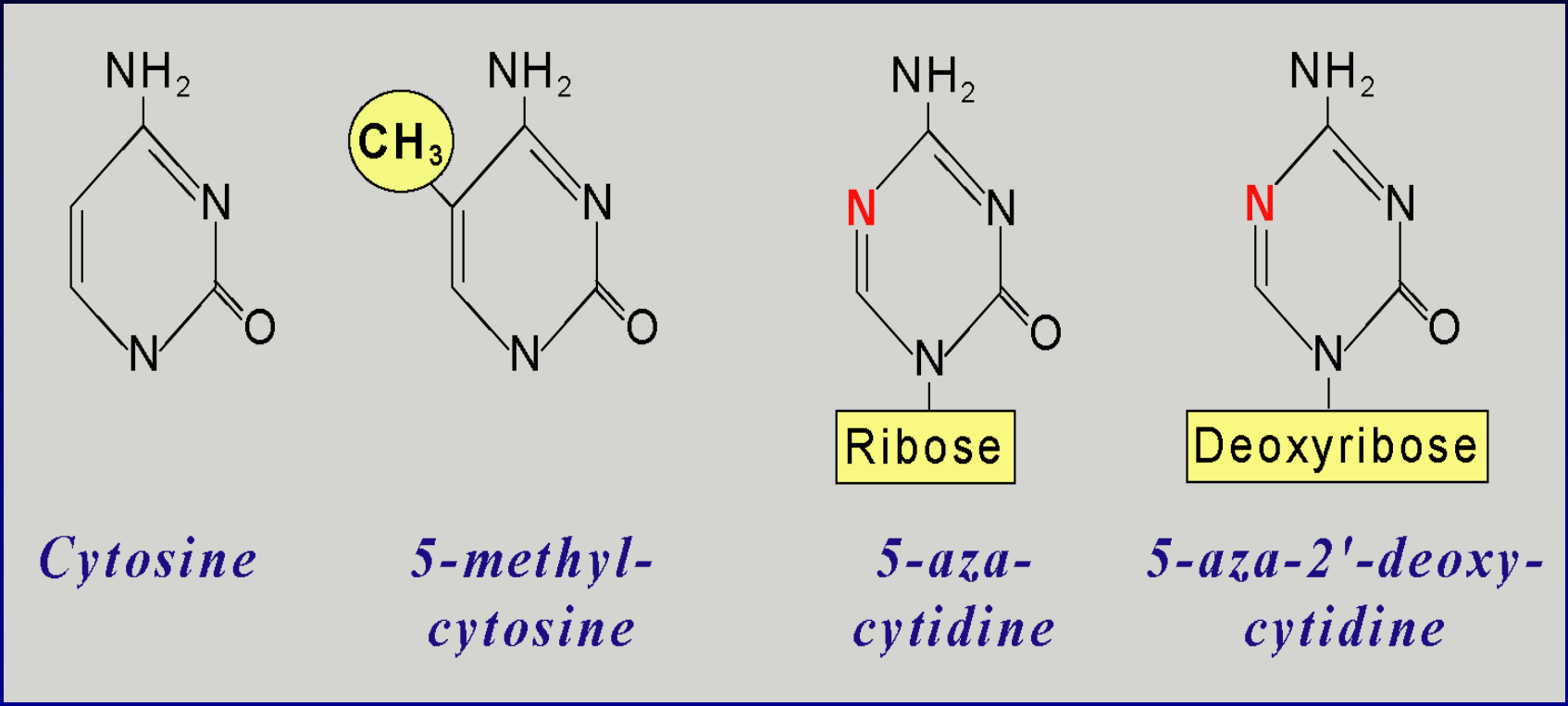
HMAs in Leukemia/MDS: Background

- DNA methylation abnormal in most cancers and affects expression of key genes and pathways
- DNA methylation and epigenetic readers and writers often mutated in cancer
  - leukemias: DNMT3a, TET2, EZH2, ASXL1, MLL1-3, CBP, etc.
- Cancer phenotype can be reversed by DNA methylation reprogramming
- DNMT inhibitors or hypomethylating agents (HMAs) shown efficacy in clinical trials in MDS and AML

Cytosine Analogues as HMAs



Cytosine *5-methyl-cytosine* *5-aza-cytidine* *5-aza-2'-deoxy-cytidine*

Azacitidine (2004)[1] **Decitabine (2006)[1,2]**

[1]Year approved by FDA for MDS treatment
[2] Approved by EMA for elderly AML in 2012

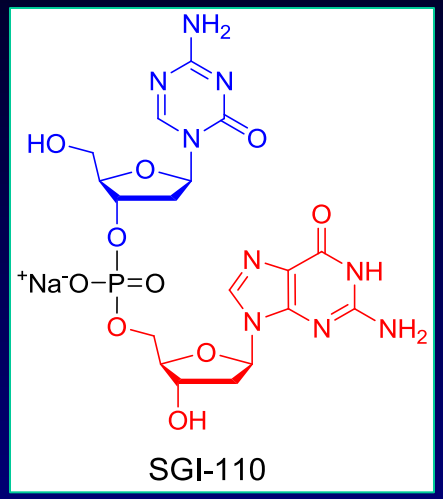
Santini *Ann Intern Med.* 2001;134:573-86

HMAs Clinical Results

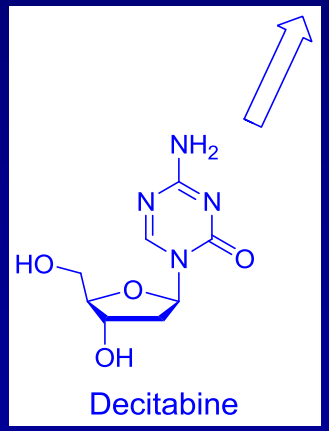
- Response rates 10–50% in MDS, AML and CMML; side-effects primarily myelosuppression
- Response duration up to 18 months but resistance eventually develops
- Prolonged survival in MDS compared to supportive care or chemotherapy
- Anecdotal responses in solid tumors

SGI-110: New DNMT Inhibitor

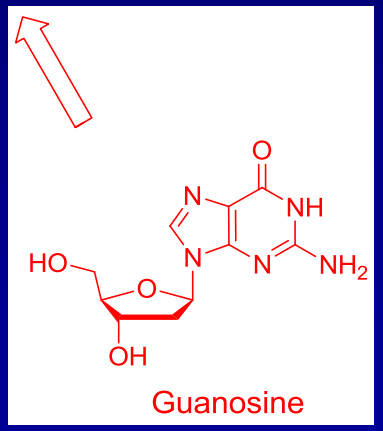
- Decitabine rapidly eliminated by Cytidine Deaminase limiting drug exposure time to cancer cells *in vivo*
- SGI-110 is dinucleotide of decitabine and deoxyguanosine; increases *in vivo* exposure of decitabine by protecting it from deamination
- Stable SQ formulation (up to 1 month after reconstitution)
- Small volume of injection: 100 mg/mL



SGI-110



Decitabine



Guanosine

SGI-110: Phase 1/2 Design

Part A
Dose Escalation (78 pts)

Relapsed or Refractory Intermediate to High Risk MDS or Relapsed or Refractory AML; ECOG PS 0–2

Regimen 1
Daily SQ Days 1–5 of a 28-day cycle

Regimen 2
Weekly SQ x 3 of a 28-day cycle

PK-PD guided dose escalation

Part B
Dose Expansion (~ 160 pts)

Safety, Efficacy, PK – PD Assessments
C_{max}, AUC, Global Hypomethylation, Gene Re-Expression Studies

BED: 60 mg/m^2 dailyx5

MTD: 90 mg/m^2 dailyx5

60 mg/m^2 dailyx10

3 Groups: Relapsed/refractory AML; Rx naïve elderly AML; Rx naïve MDS

Results from the Dose Escalation Phase 1 Part of Study SGI-110-01

SGI-110: Patients and Methods

- Main eligibility criteria:
  - Adults with relapsed or refractory intermediate or high risk MDS or AML
  - ECOG PS 0–2
  - Acceptable hepatorenal functions
  - Signed informed consent
- Methods:
  - Design: modified 3+3 design (6 patients/cohort)
  - Dose escalation guided by PK (decitabine AUC) and PD (LINE1 hypomethylation)
- Treatment:
  - SGI-110 administered SQ
  - Randomization dailyx5 or once weeklyx3 Q 28 days

SGI-110: Endpoints

- **Primary:**
  - Define Biological Effective Dose (BED) and MTD
  - BED determined by lowest dose that achieves maximum hypomethylation or gene expression in at least 3 successive dose levels
  - MTD determined by DLT incidence in Cycle 1
- **Secondary:**
  - Incidence and severity grades of DLT, AEs, and labs
  - PK profile of SGI-110 and decitabine
  - Response rates, hematologic improvement and duration of remission
  - Time to AML (MDS patients)
  - Survival
  - Incidence of blood and platelet transfusions
- **Exploratory:**
  - Identification of biomarkers of response to SGI-110

SGI-110: Dose Levels (mg/m^2)*

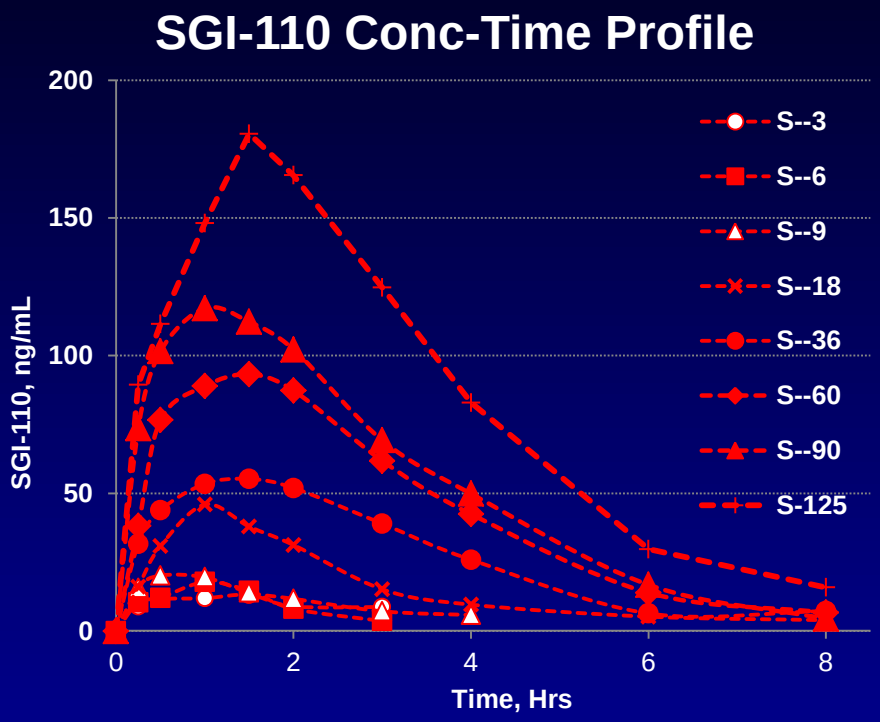
Cohorts	Dose/Schedule (mg/m^2)		Number of Patients	
	Dailyx5	Weeklyx3	Dailyx5	Weeklyx3
1	3	6	4	5
2	9	18	4	3
3	18	36	5	6
4	36	60	6	6
5	60	90	7	8
6	90	125	6	6
7	125	NA	12	NA
Total			44	34

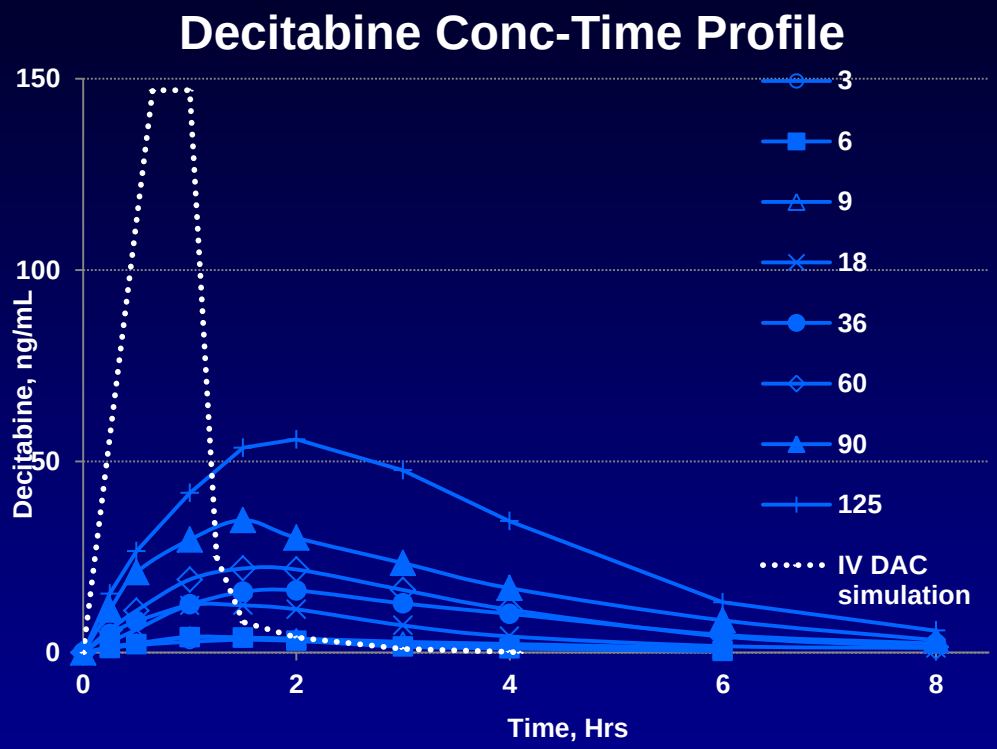
***PK guided dose escalation based on IV decitabine published PK parameters**

SGI-110: Baseline Characteristics

	All (n=78)	AML (n=64)	MDS (n=14)
Median age (range)	69 y (29–86)	67 y (29–86)	74 y (46–82)
Gender, M F	51 (65%) 27 (35%)	42 (66%) 22 (34%)	9 (64%) 5 (36%)
ECOG PS 0–1 2	 68 (87%) 10 (13%)	 55 (86%) 9 (14%)	 13 (93%) 1 (7%)
Secondary AML	-	26 (41%)	-
BM blasts % median (range)	31 (1–98)	46 (1–98)	5 (2–23)
Median prior regimens (range)	3 (1–9)	3 (1–9)	2 (2–6)
Prior DAC Prior AZA Prior DAC and/or AZA	31 (40%) 31 (40%) 49 (63%)	24 (38%) 18 (28%) 35 (55%)	7 (50%) 13 (93%) 14 (100%)

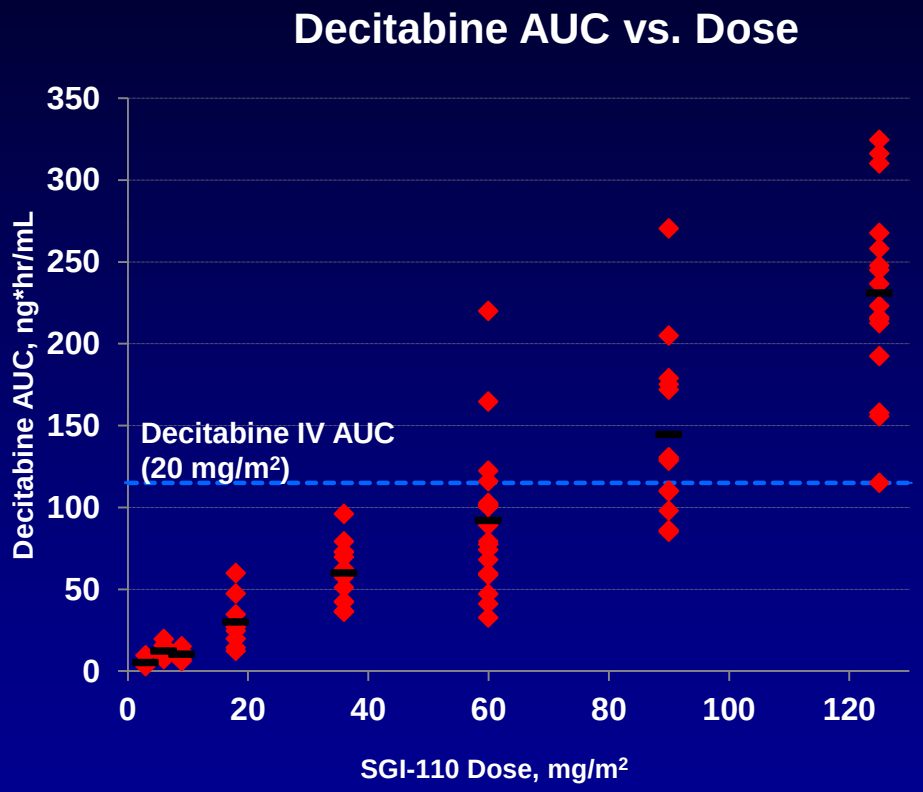
SGI-110 and Decitabine PK Profile after SGI-110 SQ

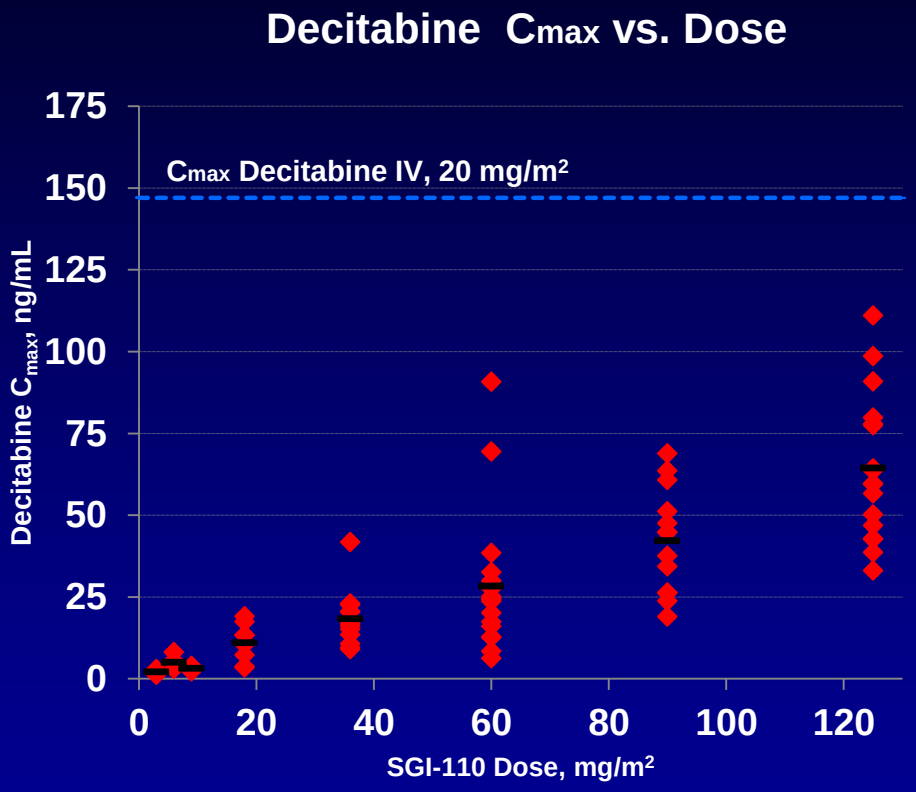




- Decitabine effective $T_{1/2}$ after SQ SGI-110 ~ 1.5-2.5 hours, (decitabine IV $T_{1/2}$ ~ 0.6 hours): 4-fold longer $T_{1/2}$ of decitabine from SGI-110 compared to decitabine IV

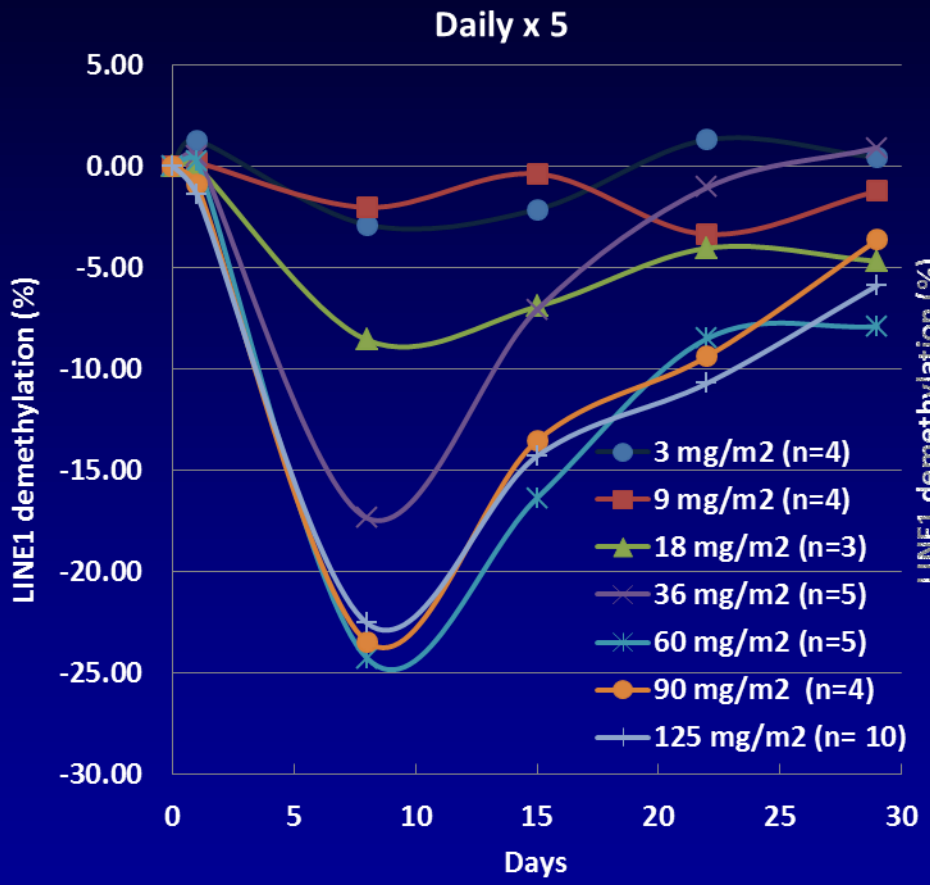
SGI-110: Decitabine Exposures (Individual Patients) after SGI-110 SQ

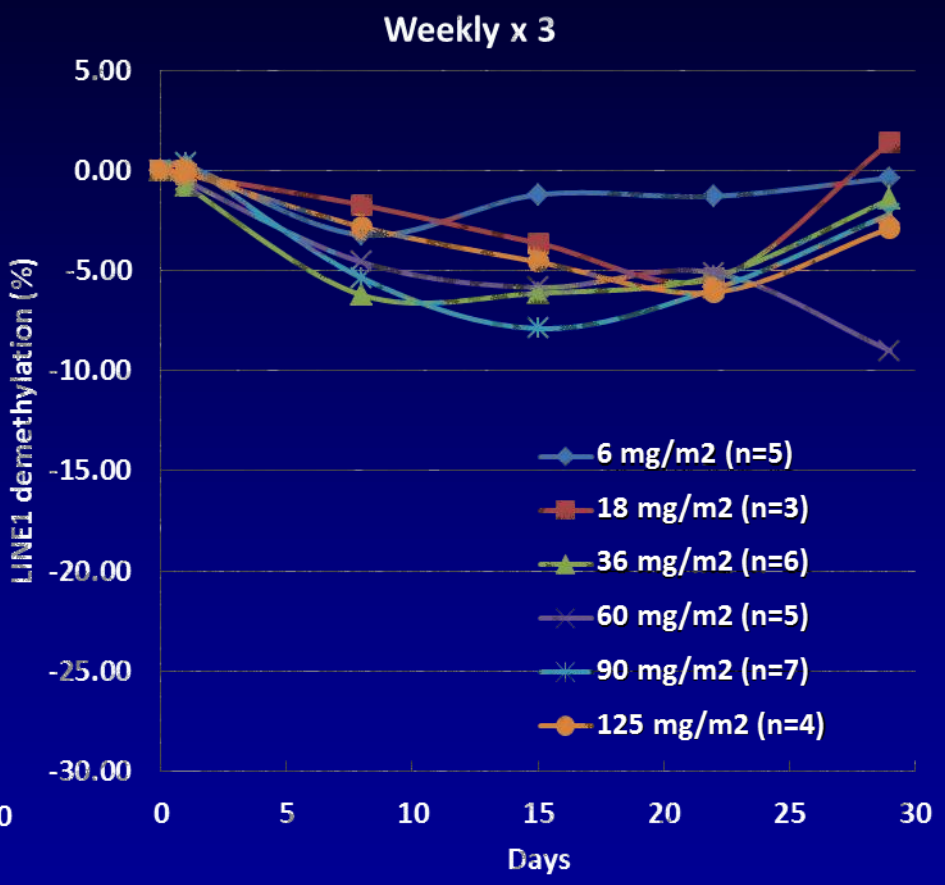




- **Equivalent or higher AUCs reached with lower Cmax compared to reference levels from decitabine IV (20 mg/m²)**

SGI-110: Average LINE1 Demethylation by Cohort





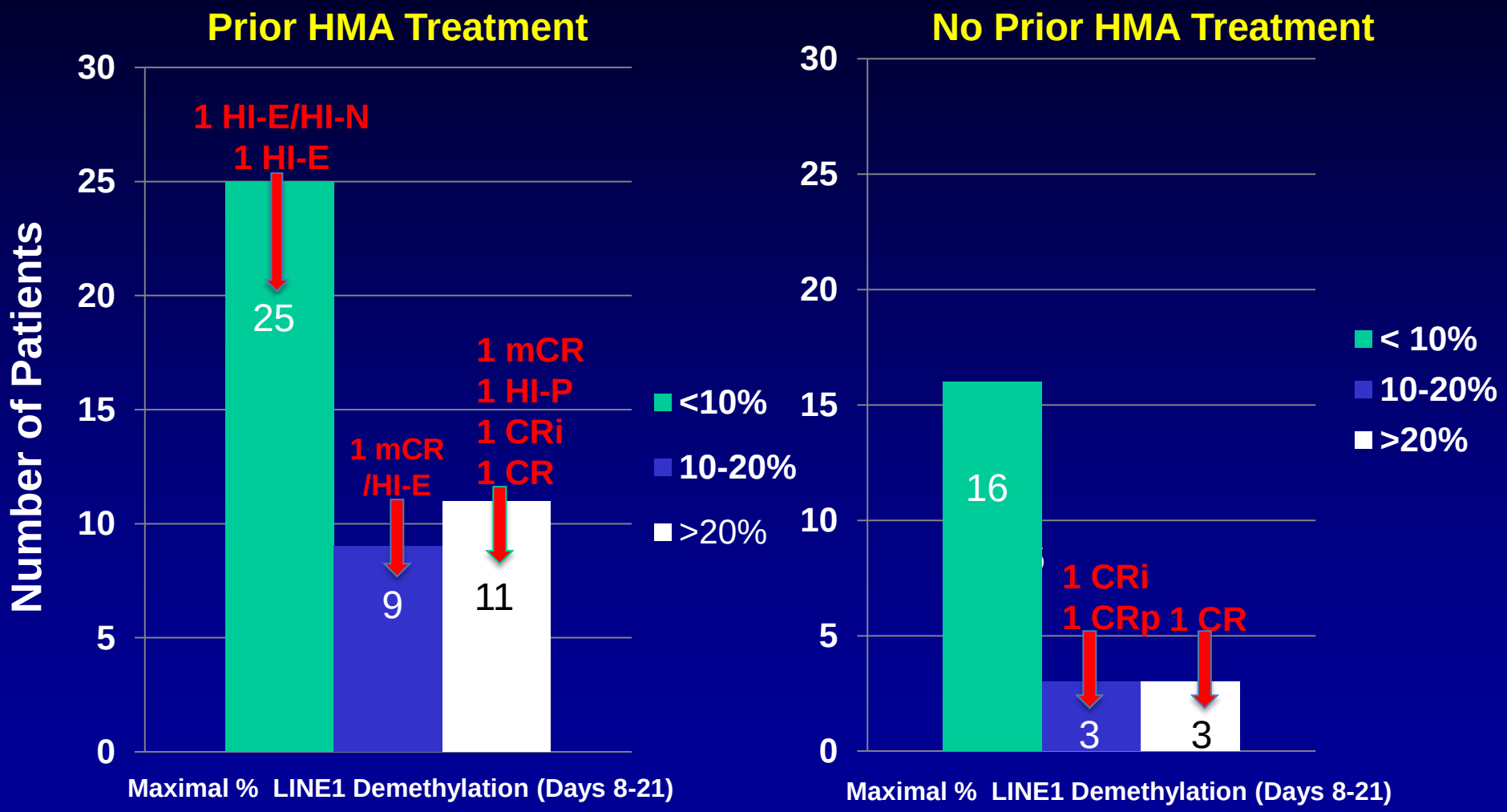
- Dose-dependent increase in demethylation up to 60 mg/m^2 dailyx5
- Similar demethylation of 60, 90, and 125 mg/m^2 dailyx5
- BED established at 60 mg/m^2 dailyx5

SGI-110: Efficacy

Daily x 5 Regimen			
Cohort	AML	MDS	Responses
3 mg/m^2	3	1	NR
9 mg/m^2	4	0	NR
18 mg/m^2	3	2	1 mCR/HI-E (MDS-HR)
36 mg/m^2	5	1	1 CRi (AML)
60 mg/m^2	7	0	1 CR (AML), 1 CRi (AML)
90 mg/m^2	5	1	NR
125 mg/m^2	9	3	mCR (MDS-2)

Weekly x 3 Regimen			
Cohort	AML	MDS	Responses
6 mg/m^2	4	1	1 HI-E/HI-N (MDS-HR)
18 mg/m^2	1	3	NR
36 mg/m^2	6	0	NR
60 mg/m^2	6	0	1 CR (AML)
90 mg/m^2	6	2	1 HI-E (MDS HR), 1 HI-P (MDS-1)
125 mg/m^2	6	0	CRp (AML)

SGI-110: Maximum % LINE1 Demethylation vs. Response (Cohorts 1–7)



67 patients with LINE1 results, Cohorts 1–7; Daily 3–125mg/m^2 and Weekly 6–125 mg/m^2

SGI-110: r/r AML Responses vs. Demethylation[1]

LINE1 Demethylation	Number Treated	Responders (CR/CRi/CRp)	Percent
< 10%	32	0	0%
≥ 10%	17	5	29%
Total	49	5	10%

[1] All 49 r/rAML patients with LINE1 data

SGI-110: Related AEs (≥ 5%) – Dailyx5 regimen (n=44)

Adverse Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Injection Site Pain	18%	0	0
Thrombocytopenia	16%	2%	9%
Anemia	14%	11%	0
Nausea	11%	0	0
Neutropenia	9%	2%	7%
Fatigue	9%	0	0
Decreased Appetite	9%	0	0
Diarrhea	9%	0	0
Leukopenia	7%	2%	2%
Asthenia	7%	0	0
Dry Mouth	7%	0	0
Febrile Neutropenia	5%	2%	2%
Injection Site Events	5%	0	0
Epistaxis	5%	0	0
Vomiting	5%	0	0
Constipation	5%	0	0

SGI-110:
Related AEs (≥ 5%)- Weekly x3 regimen (n=34)

Adverse Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Injection Site Pain	29%	0	0
Nausea	9%	0	0
Fatigue	9%	0	0
Anemia	6%	6%	0
Febrile Neutropenia	6%	6%	0
Diarrhea	6%	0	0
Asthenia	6%	0	0
Pyrexia	6%	0	0
Arthralgia	6%	0	0
Cough	6%	0	0

SGI-110: DLTs

- No DLTs with weeklyx3 regimen
- Two patients with DLTs on dailyx5 at 125 mg/m^2 (12 patients treated: 3 MDS and 9 AML)
  - Both MDS (2/3 MDS):
    - 1 patient febrile neutropenia + bacteremia
    - 1 patient febrile neutropenia + sepsis Gr5, thrombocytopenia Gr4
  - No DLTs in 9 patients with AML at that dose

SGI-110: Summary

- SGI-110 delivers extended exposure of decitabine
  - Longer exposure window of decitabine up to 8+ hours
  - $T_{1/2}$ of decitabine from SGI-110 is 4-fold longer than decitabine IV
  - Lower C_{max} than decitabine IV
- Excellent hypomethylation induction with dailyx5; less adequate hypomethylation with weeklyx3
- Major responses observed in relapsed/refractory AML when adequate hypomethylation achieved regardless of regimen
- BED 60 mg/m^2 dailyx5
- 90 mg/m^2 dailyx5 highest tolerable dose for both MDS and AML
- Most common AEs: Injection site pain (mostly Grade 1), and myelosuppression
- Phase 2 Expansion: randomization to 60 or 90 mg/m^2 dailyx5; new arm of 60 mg/m^2 dailyx10 is also now open

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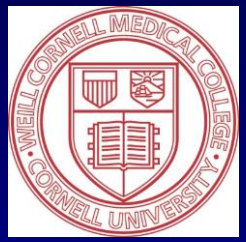

Gail Roboz, MD
Eric Feldman, MD
Ellen Ritchie, MD

Steve Baylin, MD
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Mohammad Azab, MD
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Aram Oganesian, PhD
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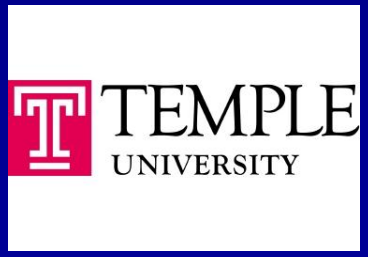

Jean Pierre Issa, MD
Woonbok Chung