11th International Congress on **Targeted Anticancer Therapies**

Paris, March 4-6, 2013

IMMUNOMODULATORY ACTIVITY OF SGI-110, A SECOND GENERATION HYPOMETHYLATING AGENT

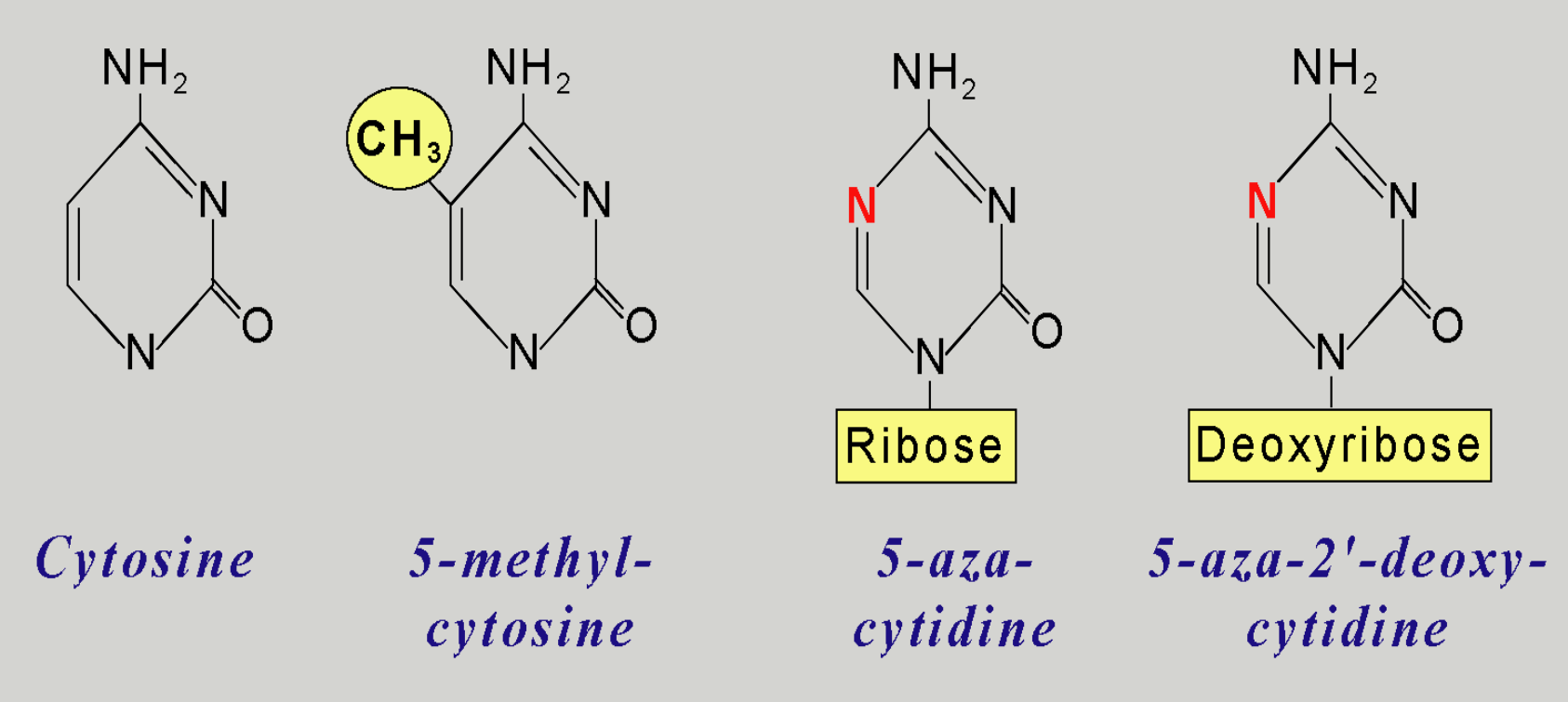
Michele Maio[1], Alessia Covre[1,2], Giulia Parisi[1], Hugues JMG Nicolay[1,2], Ester Fonsatti[1], Sandra Coral[1,2], Pietro Taverna[3], Hagop Kantarjian[4], **on behalf of SGI-110-1 Study Investigators**

[1]Medical Oncology and Immunotherapy, Department of Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [2]Epigen Therapeutics, Pordenone, Italy; [3]Astex Pharmaceuticals Inc. Dublin, California, USA, [4]MD Anderson Cancer Center, Houston, TX, USA

DNA Methylation as a Therapeutic Target

- DNA methylation is abnormal in most cancers and affects the expression of key genes and pathways
- DNA methylation and epigenetic readers and writers are often mutated in cancer
  - In leukemias: DNMT3a, TET2, EZH2, ASXL1, MLL1-3, CBP etc.
- The cancer phenotype can be reversed by DNA methylation reprogramming
- DMNT inhibitors or Hypomethylating Agents (HMAs) demonstrated efficacy in the treatment of MDS and AML

Cytosine Analogues as HMAs



Azacitidine (2004)[1]

Decitabine (2006)[1] (2012)[2]

[1]Year approved by FDA for MDS treatment

[2]Year approved by EMA for AML treatment

Santini V, et al. *Ann Intern Med.* 2001;134(7):573-86

IMMUNOMODULATORY ACTIVITY OF DECITABINE

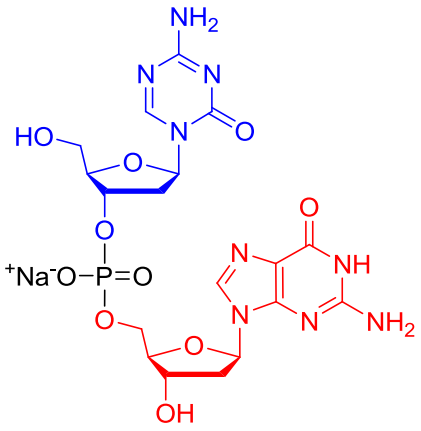
Pre-clinical

- Induction/up-regulation of CTA expression in tumor cells of different histotype (Coral, Clin Cancer Res 2002)
- Up-regulation of the expression of HLA class I antigens and co-stimulatory molecules in tumor cells of different histotype (Fonsatti, Clin Cancer Res 2007)
- Increased recognition of cancer cells treated with decitabine by TAA-specific CTL (Sigalotti, Cancer Res 2004)
- Persistent induction/up-regulation of CTA expression in tumor xenografts (Coral, J Cell Physiol 2006)
- Generation of circulating anti-CTA antibodies in mice injected with decitabine-treated human melanoma cells (Coral, J Cell Physiol 2006)

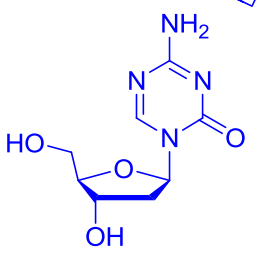
Clinical

- Induction of CTA expression in AML and MDS patients (Sigalotti et al, Blood 2003)
- Post-treatment generation of circulating anti-CTA antibodies in patients with thoracic malignancies (Schrump, Clin Cancer Res 2006)
- Complete remission following decitabine/dendritic cell vaccine in a case of relapsed neuroblastoma (Krishnadas, Pediatrics, 2012)

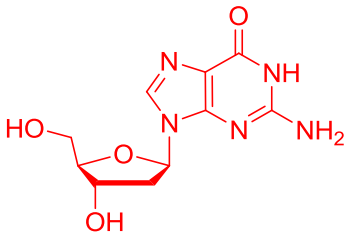
New DNMT Inhibitor: SGI-110



SGI-110



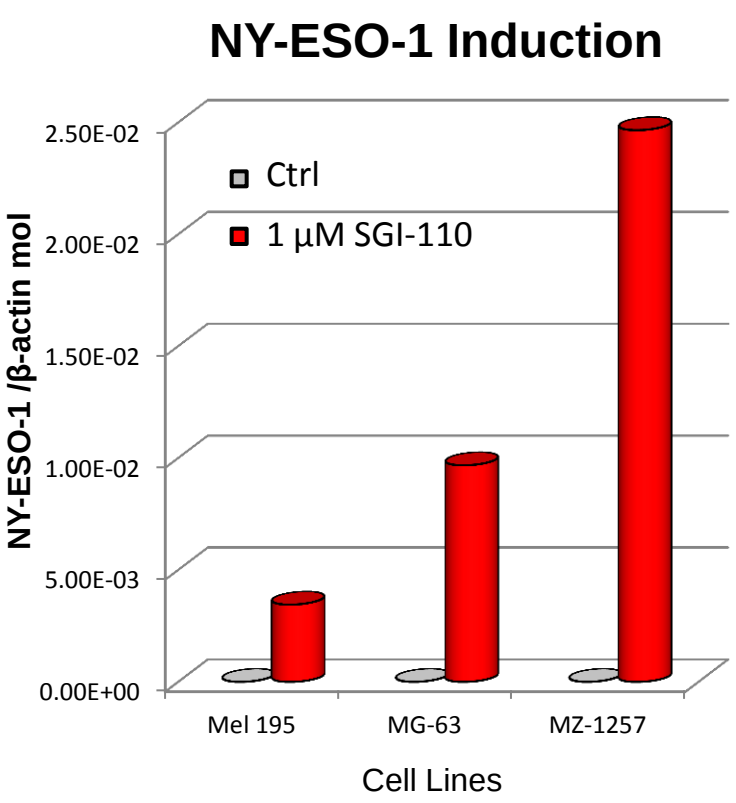
Decitabine

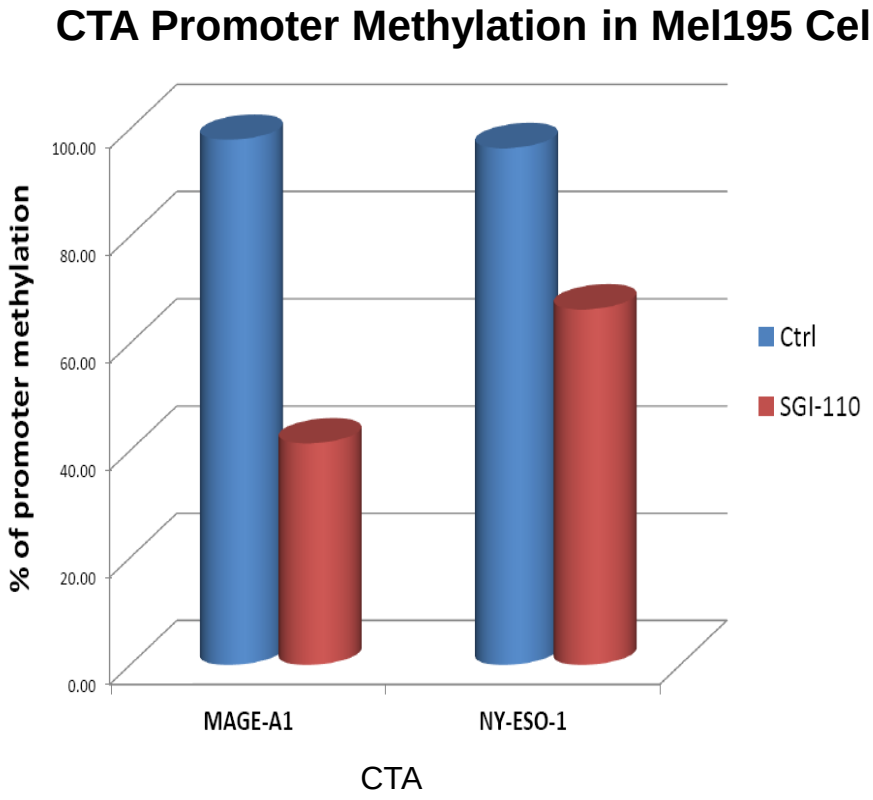


Guanosine

- 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 increases the *in vivo* exposure of decitabine by protecting it from deamination

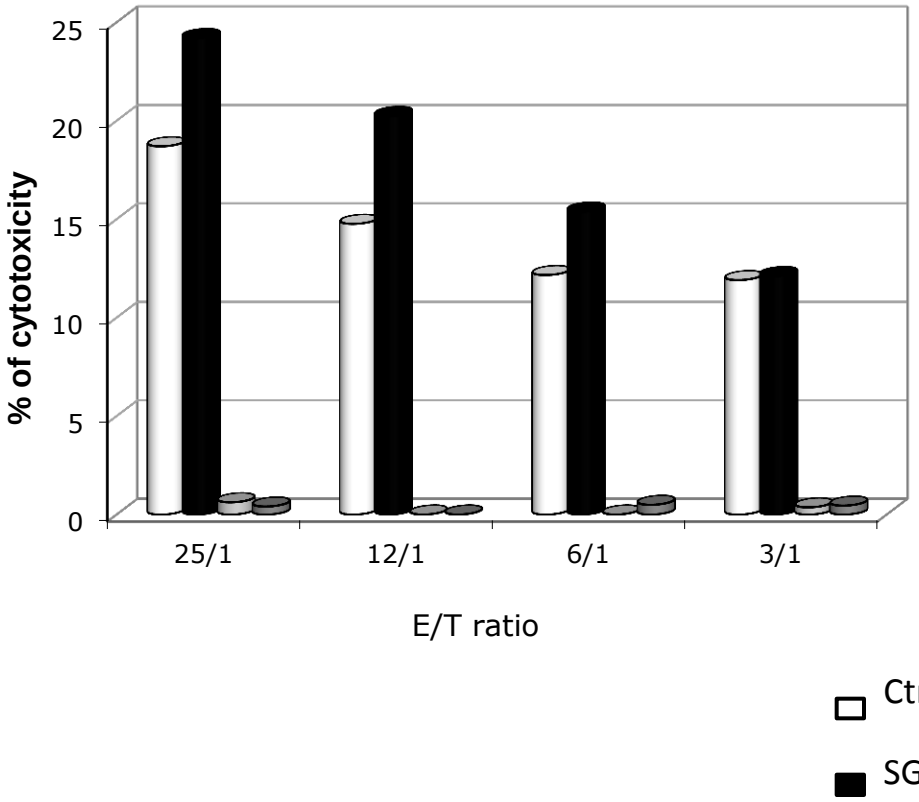
SGI-110 Modulates CTA Expression and Methylation in Cancer Cells

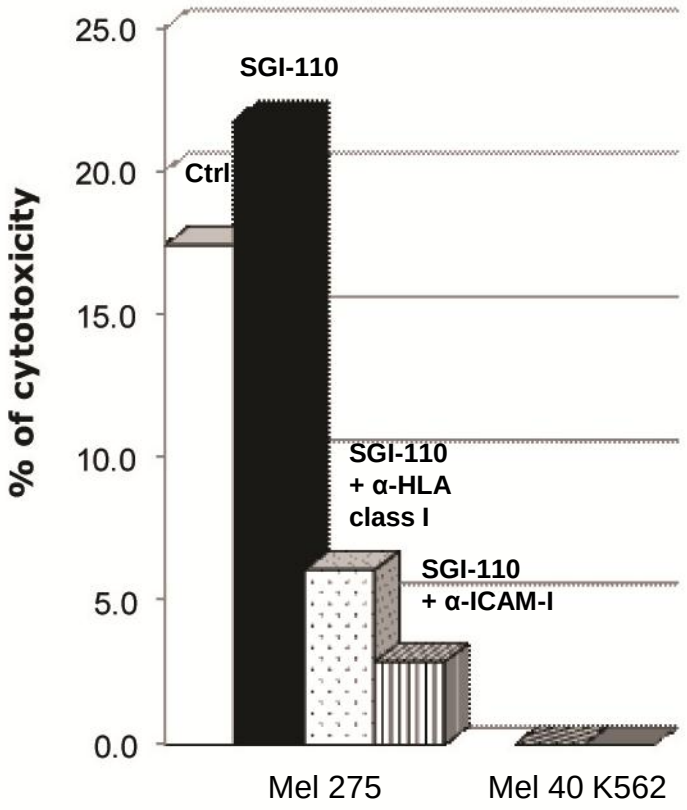




SGI-110 induces the demethylation of CTA promoters and induces their expression

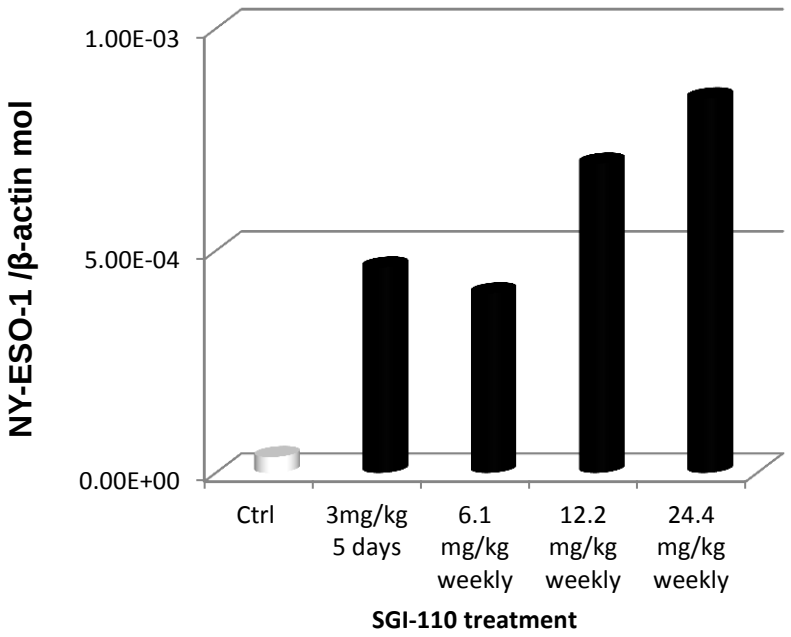
Recognition of SGI-110-treated Mel 275 melanoma cells by gp100-specific CTL



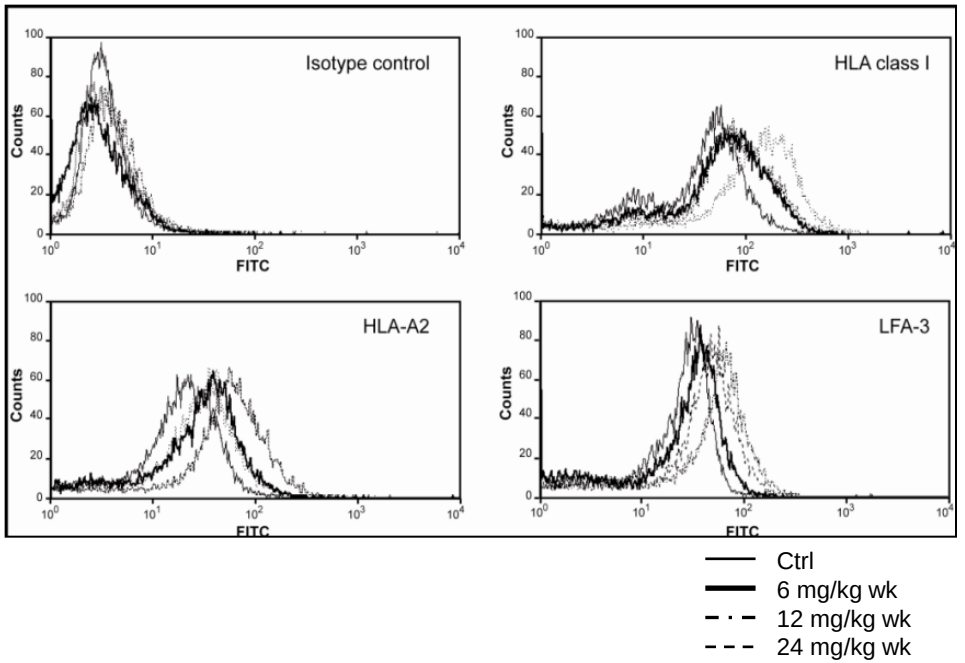


SGI-110 Modulates CTA Expression and Immune Phenotype of Melanoma Xenografts

NY-ESO-1 Induction in Mel313 xenografts



HLA Class I and co-stimulatory molecules induction in Mel195 xenografts



Tolerated doses and schedules of SQ SGI-110 induces CTAs, HLA class I antigens, HLA-A2 alleles, and the co-stimulatory molecules LFA-3 and ICAM-1 in melanoma xenografts

SGI-110-01 Phase 1/2 Clinical Trial 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 SC Days 1–5 of a 28-day course

Regimen 2
Weekly SC x 3 of a 28-day course

PK-PD guided dose escalation

Part B
Dose Expansion (~ 160 pts)

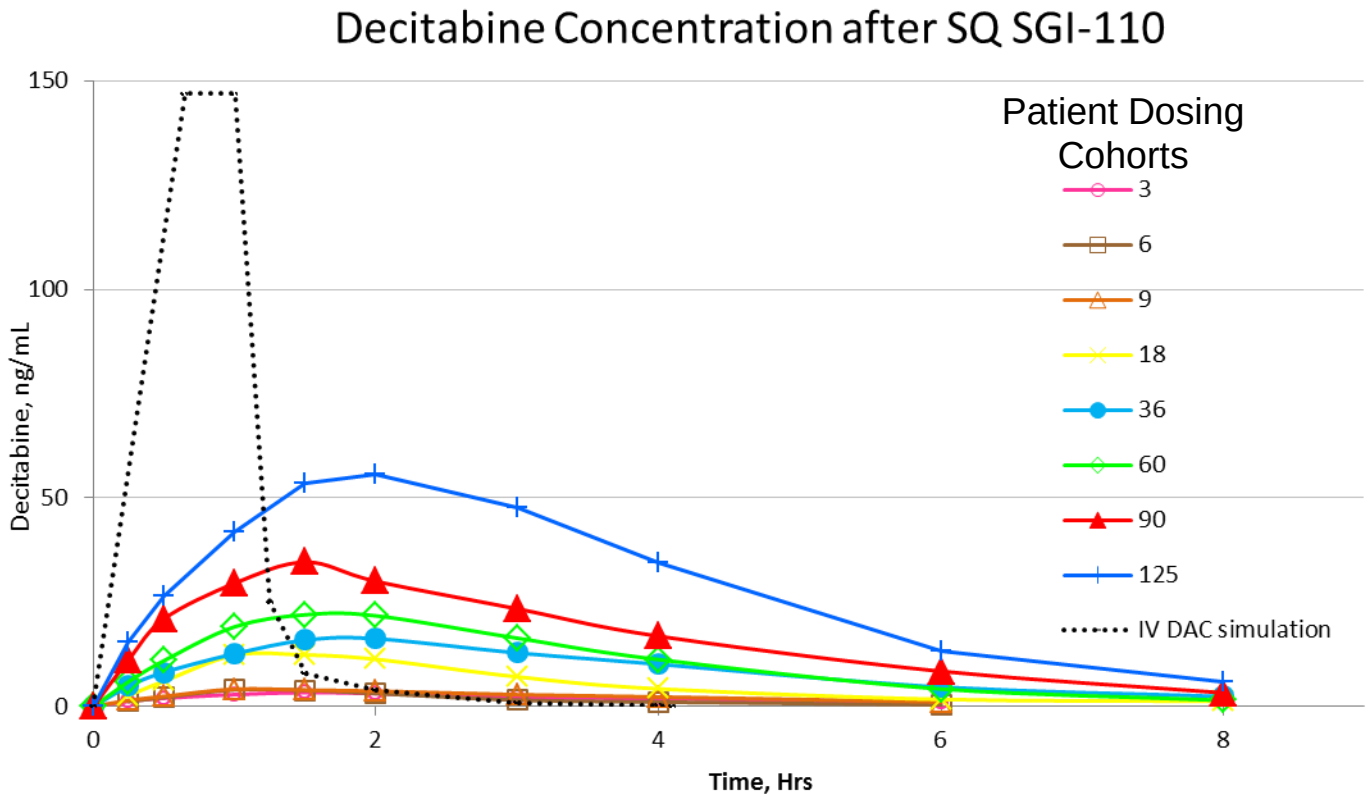
Safety, Efficacy, PK – PD Assessments
C_{max}, AUC, Global Hypomethylation

60 mg/m^2 dailyx5

90 mg/m^2 dailyx5

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

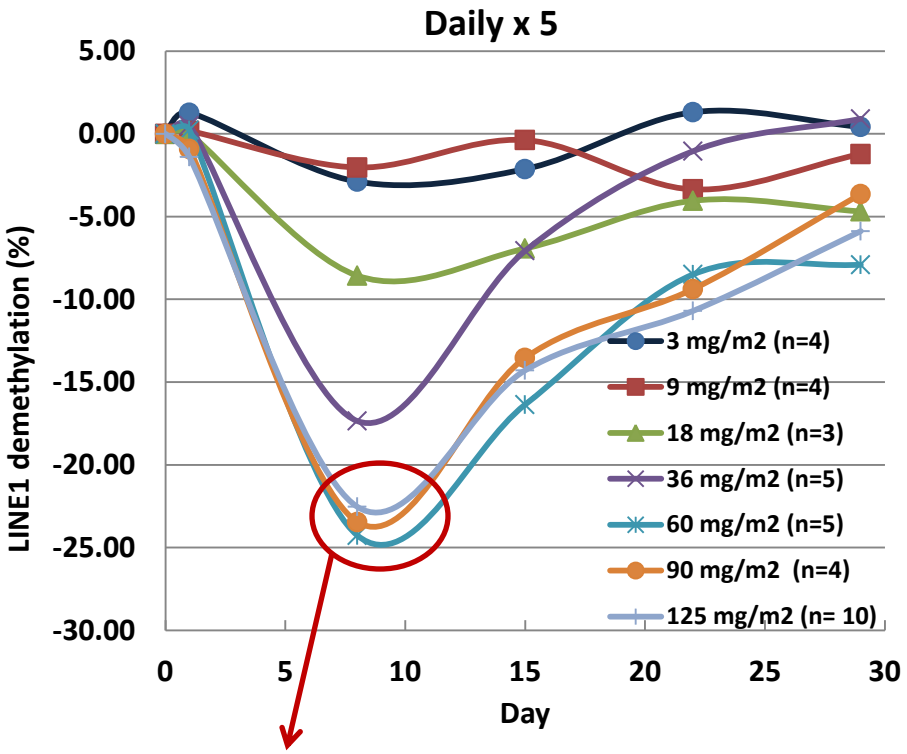
PK of decitabine delivered by SGI-110 SQ injection

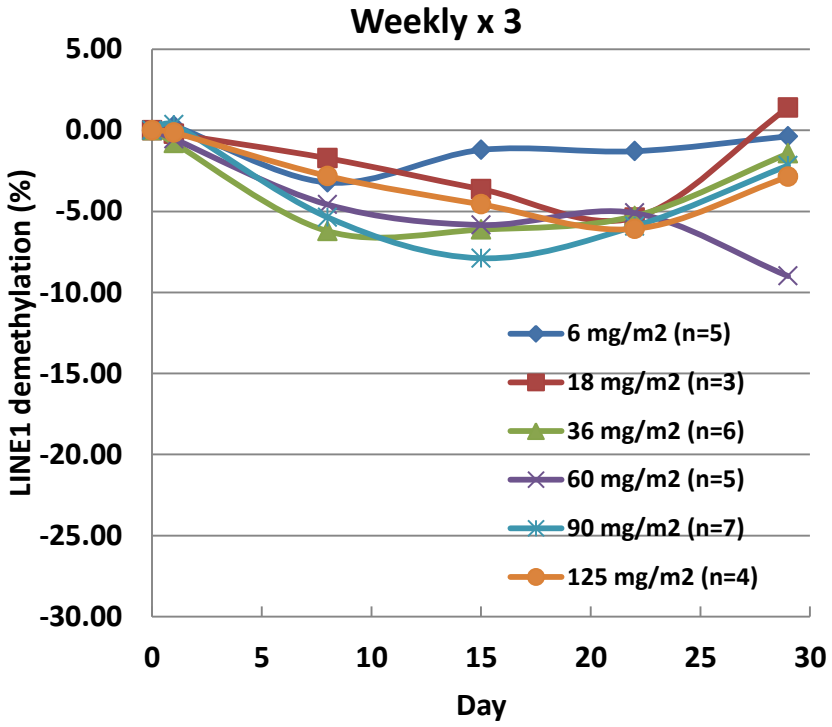


Compared to Dacogen IV (DAC IV):

- Doubled exposure window to decitabine (8+ hrs vs. 3-4 hrs)
- Up to 4-fold longer half life of decitabine (1.5-2.5 hrs vs. 35 minutes)
- Cmax less than half of decitabine

LINE1 Demethylation by Cohort





BED: 60 mg/m^2 dailyx5

The BED defined as the smallest dose
that achieves a maximum global hypomethylation
in at least three successive dose levels

AML Responses correlated with demethylation extent

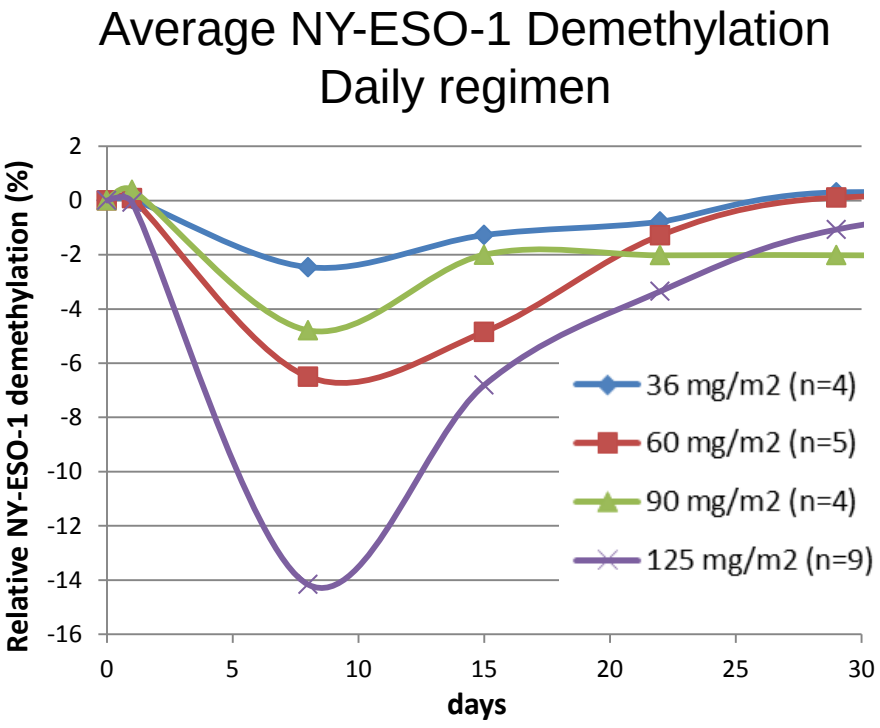
LINE1 Demethylation	Number Treated[1]	Responders (CR/CRi/CRp)	Percent
< 10%	31	0	0%
≥ 10%	19	5	26%
Total	50	5	10%

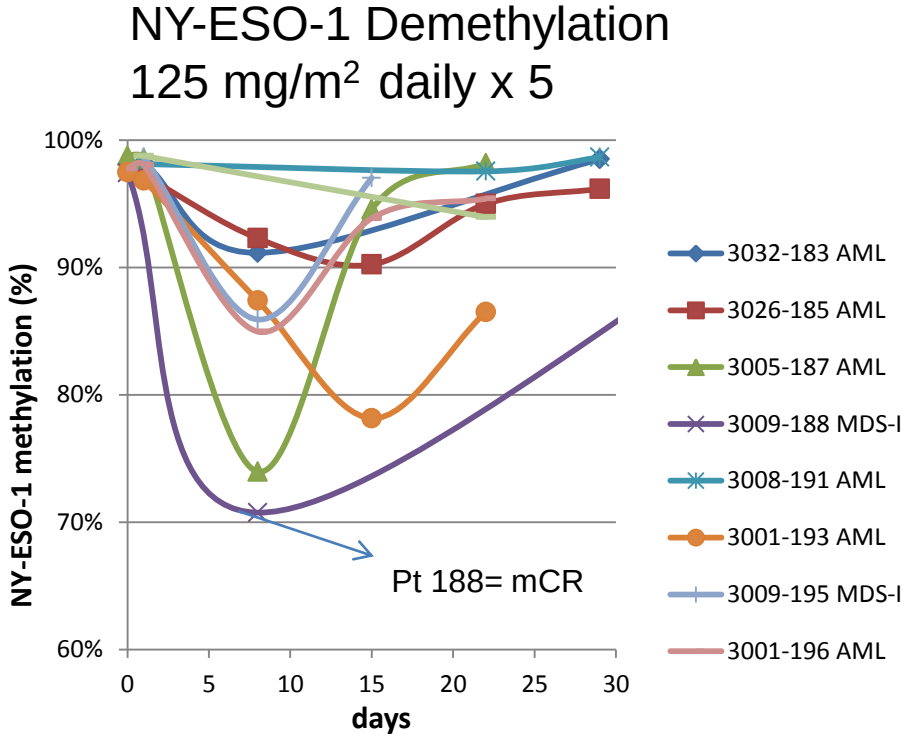
[1] All 50 r/r AML patients with LINE1 data

5 responses in MDS patients with prior HMA treatment
5 responses in AML patients regardless of prior HMA treatment

EPIGENETIC MODULATION OF CTA IN BLOOD SAMPLES FROM PATIENTS ENROLLED IN STUDY SGI-110-01

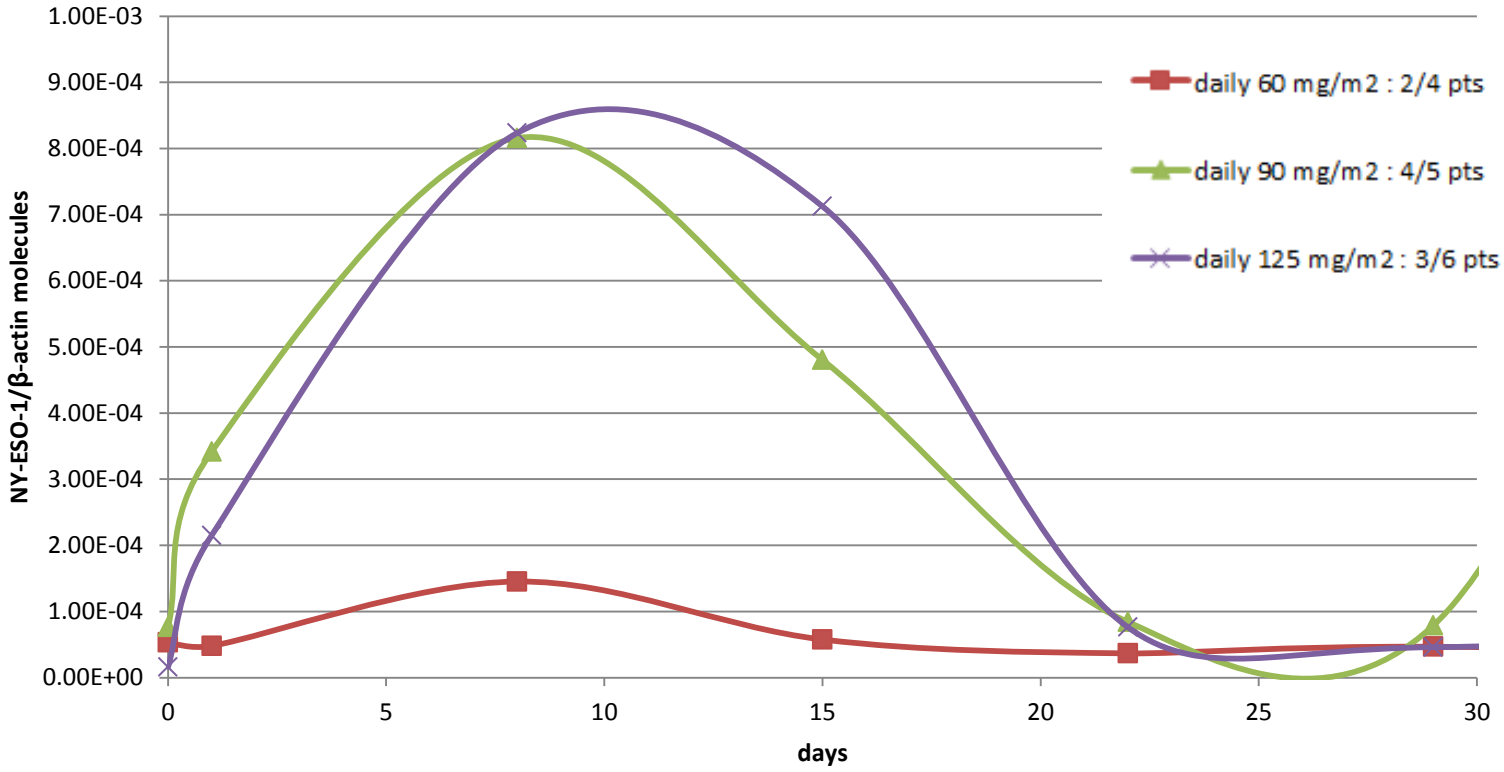
NY-ESO-1 Promoter Demethylation after SGI-110 in AML and MDS patients





- SGI-110 induces a dose-dependent demethylation of NY-ESO-1 promoter
- Similar extent of demethylation observed also for MAGE-A1 promoter

NY-ESO-1 Induction (cut-off ≥ 1E-05) after SGI-110 in AML and MDS patients



- NY-ESO-1 transcript was induced in 9 of 15 evaluable patients treated at SGI-110 BED
- 4 and 5 of the 15 patients induced also MAGE-A1 and -A3 respectively

Summary

- Excellent LINE1 hypomethylation induction with dailyx5; BED is 60 mg/m^2 dailyx5
- Well tolerated; most common AE's were Injection site pain (mostly Grade 1) and myelosuppression (neutropenia/neutropenic fever; anemia; thrombocytopenia)
- Major responses were observed in relapsed/refractory AML when adequate hypomethylation achieved (regardless of regimen)
- SGI-110 reduced the constitutive methylation levels in promoters of NY-ESO-1 and MAGE-A1 in a dose-dependent manner
- The induction and/or up-regulation of NY-ESO-1, MAGE-A1, MAGE-A3 expression was observed in 9/15, 4/15 and 5/15 patients treated with SGI-110 biologically effective doses
- These immunomodulatory properties and its favorable PK/PD profile make SGI-110 an active agent to implement new and more effective combined chemo-immunotherapeutic approaches

Acknowledgements: Clinical Study SGI-110-01

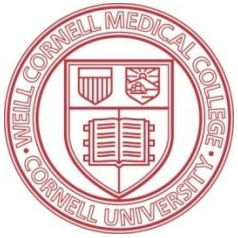
Hagop Kantarjian, MD
Guillermo Garcia-Manero, MD
Farhad Ravandi, MD

Casey O'Connell, MD
Anthony El Khoueiry, MD

David Rizzieri, MD
Arati Rao, MD
Carlos Decastro, MD

Katherine Walsh, MD
William Blum, MD

Raoul Tibes, MD, PhD
Ruben Mesa, MD



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

Steve Baylin, MD
Peter Jones, PhD
Jean Pierre Issa, MD

Wendy Stock, MD

Mohammad Azab, MD
Gavin Choy, PharmD
Sue Naim
Aram Oganesian, PhD
Sanjeev Redkar, PhD

Elizabeth Griffiths, MD

Karen Yee, MD
Aaron Schimmer, MD

Jean Pierre Issa, MD
Woonbok Chung PhD

Acknowledgements
Immunomodulatory Activity of SGI-110

MEDICAL ONCOLOGY AND IMMUNOTHERAPY
DEPT. OF MEDICAL ONCOLOGY
UNIVERSITY HOSPITAL OF SIENA

- Alessia Covre
- Giulia Parisi
- Hugues Nicolay
- Sandra Coral
- Ester Fonsatti

Epigen Therapeutics™
Innovative Medicines in Immuno Oncology

- Sandra Coral
- Alessia Covre
- Hugues Nicolay