

The Novel, Small Molecule DNA Methylation Inhibitor SGI-110 as an Ovarian Cancer Chemosensitizer

**J. Tang, F. Fang, Y. Wang, P. Taverna, D. Miller, J. Pilrose, G. Choy, M. Azab, D. Matei, K. Pawelczak, P. VanderVere-Carozza, M. Wagner, J. Turchi, and
K. P. Nephew**

AACR 104th Annual Meeting
April 6-10, 2013

Minisymposium: Therapies Targeting Epigenetic Mechanisms



INDIANA UNIVERSITY

Disclosure Information

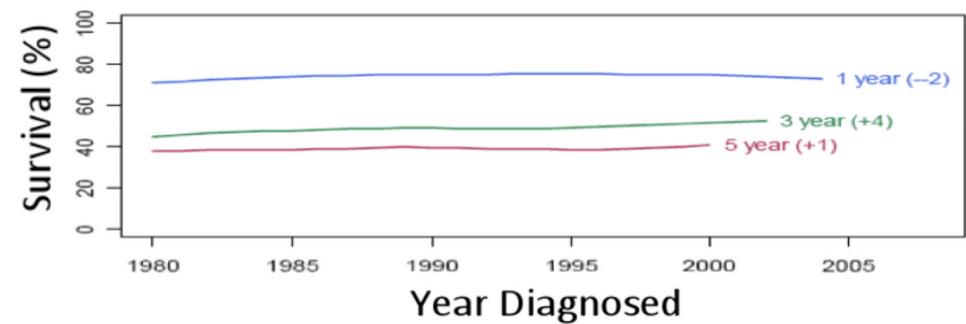
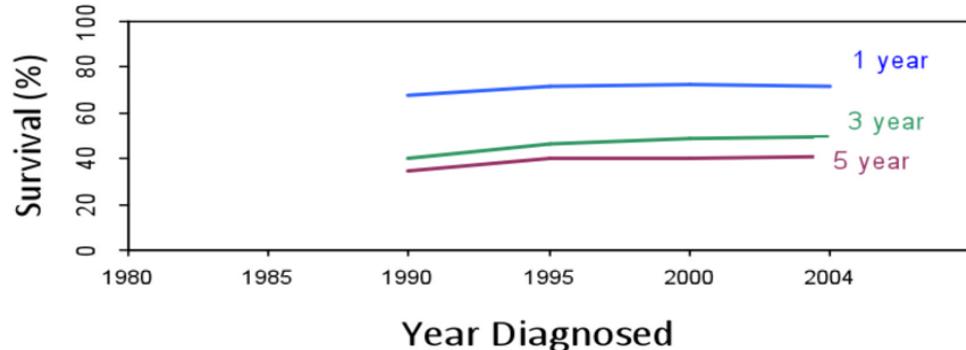
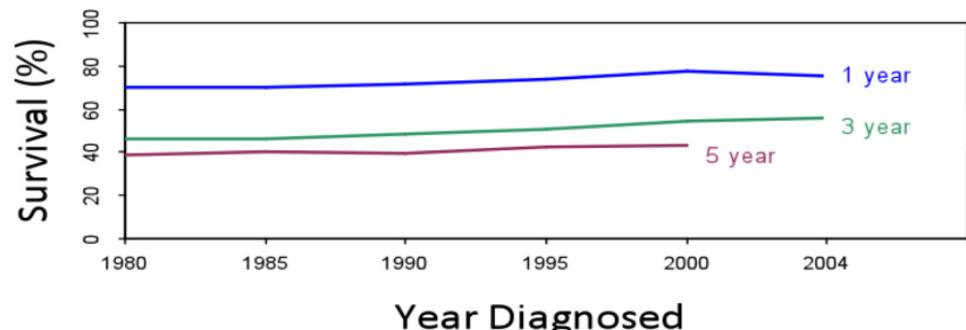
Therapies Targeting Epigenetic Mechanisms
Jessica Tang

I have no financial relationships to disclose.

I will not discuss off label use or investigational use in my presentation.

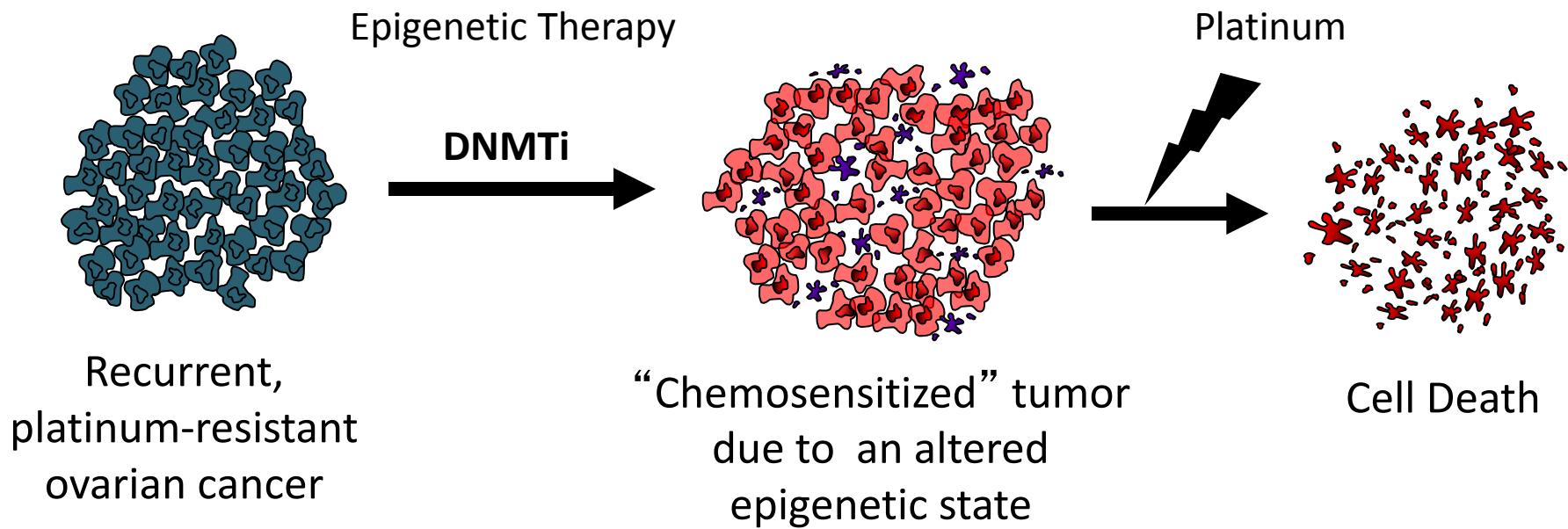
Survival in Ovarian Cancer

- Little change in 1-, 3- and 5-year survival rates over the past 20 years
- 5-year survival is ~25% for patients diagnosed with advanced-stage disease
- Recurrence is common and patients develop chemotherapy resistance
- Platinum resistant ovarian cancer is uniformly fatal



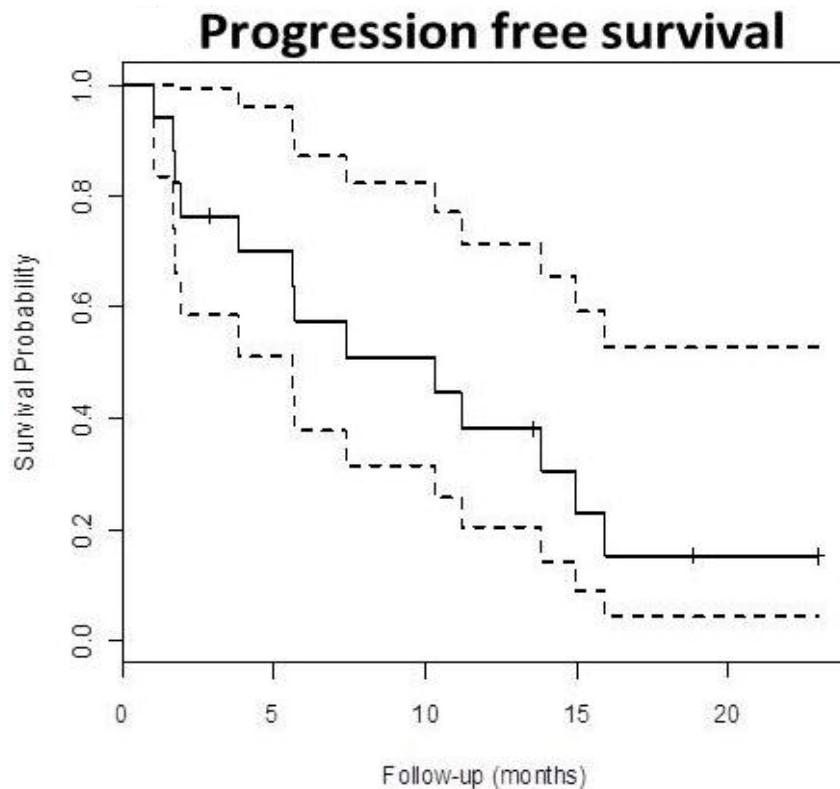
Vaughan et al. 2011, Nat Rev Cancer

Hypothesis: Epigenetic “re-setting” using low dose DNMTi will re-sensitize recurrent ovarian cancer to platinum



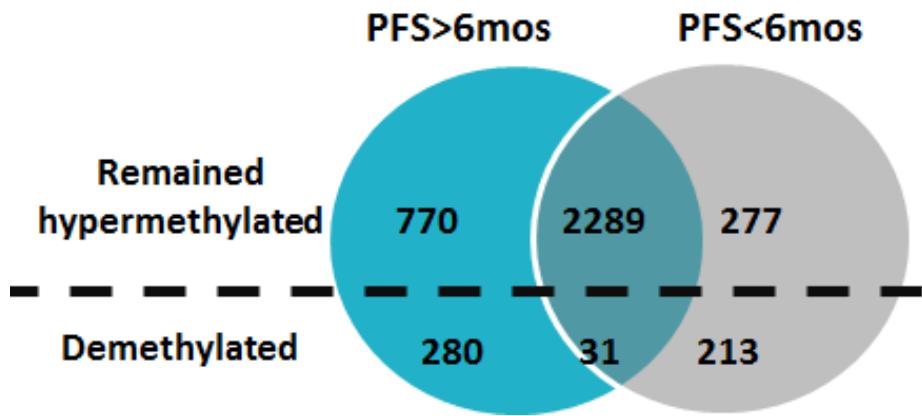
Phase I/II Trial of Decitabine and Carboplatin in Platinum Resistant Recurrent Ovarian Cancer

Matei *et al.*, 2012. *Cancer Research*



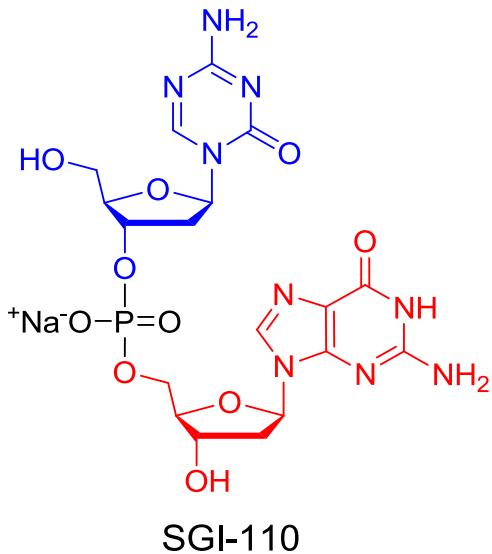
Median progression free survival was 10.2 months

Changes in DNA methylation after decitabine in biopsy ($\beta>0.5$)

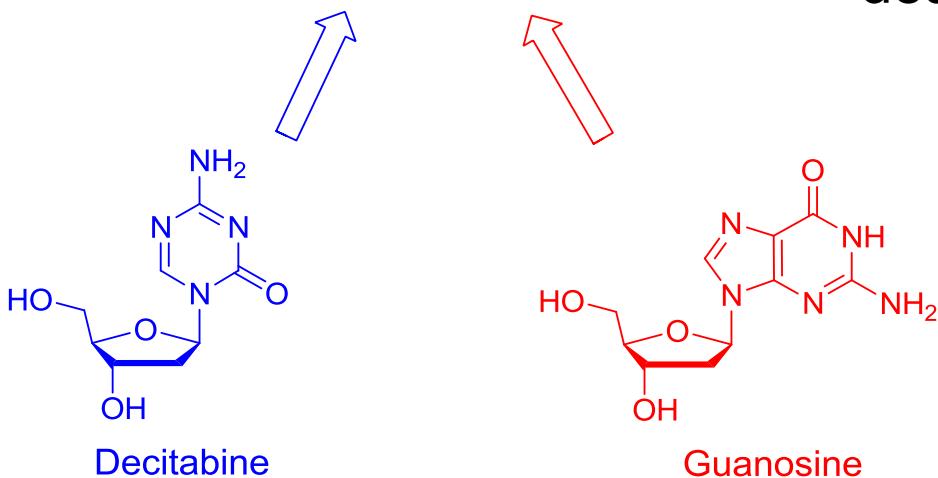


Greater number of decitabine-induced demethylated genes in responders

SGI-110: A New DNMT Inhibitor (Astex Pharmaceuticals)

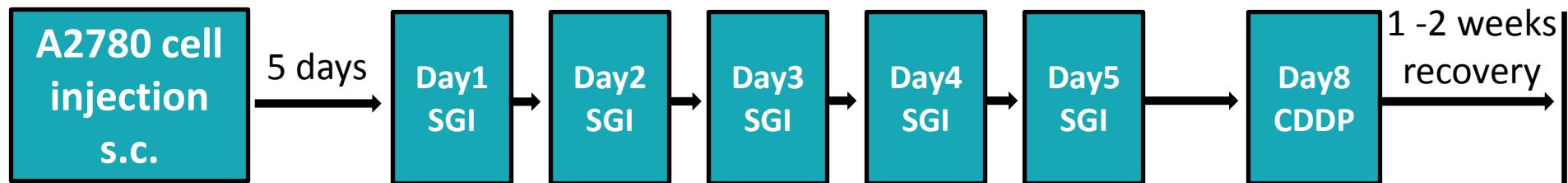


- Decitabine is rapidly eliminated by cytidine deaminase, limiting drug exposure time to cancer cells *in vivo*
- **SGI-110** is a dinucleotide of decitabine and deoxyguanosine that increases the *in vivo* exposure of decitabine by protecting it from deamination



Experimental Design

QD5 schedule:



Biweekly schedule:

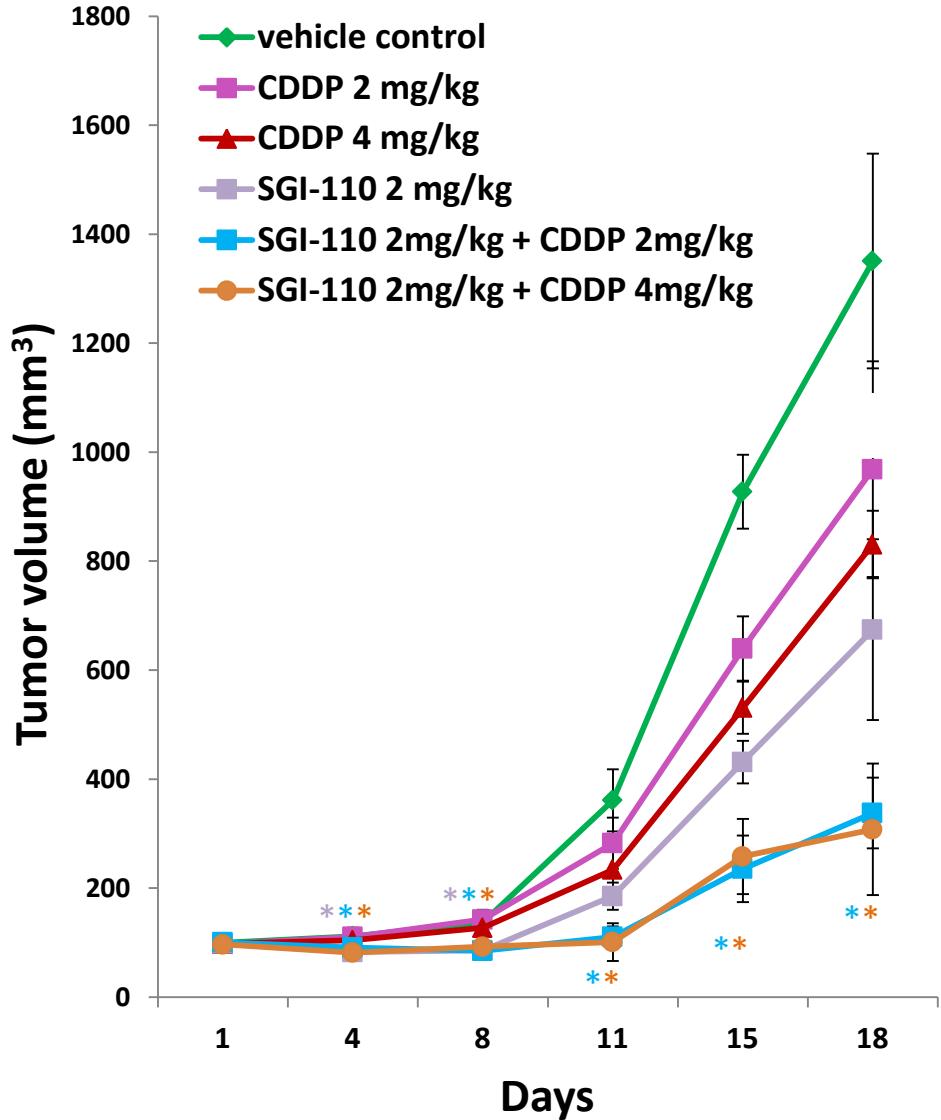


Xenografts of parental and cisplatin (CDDP)-resistant A2780 ovarian cancer cells were examined for:

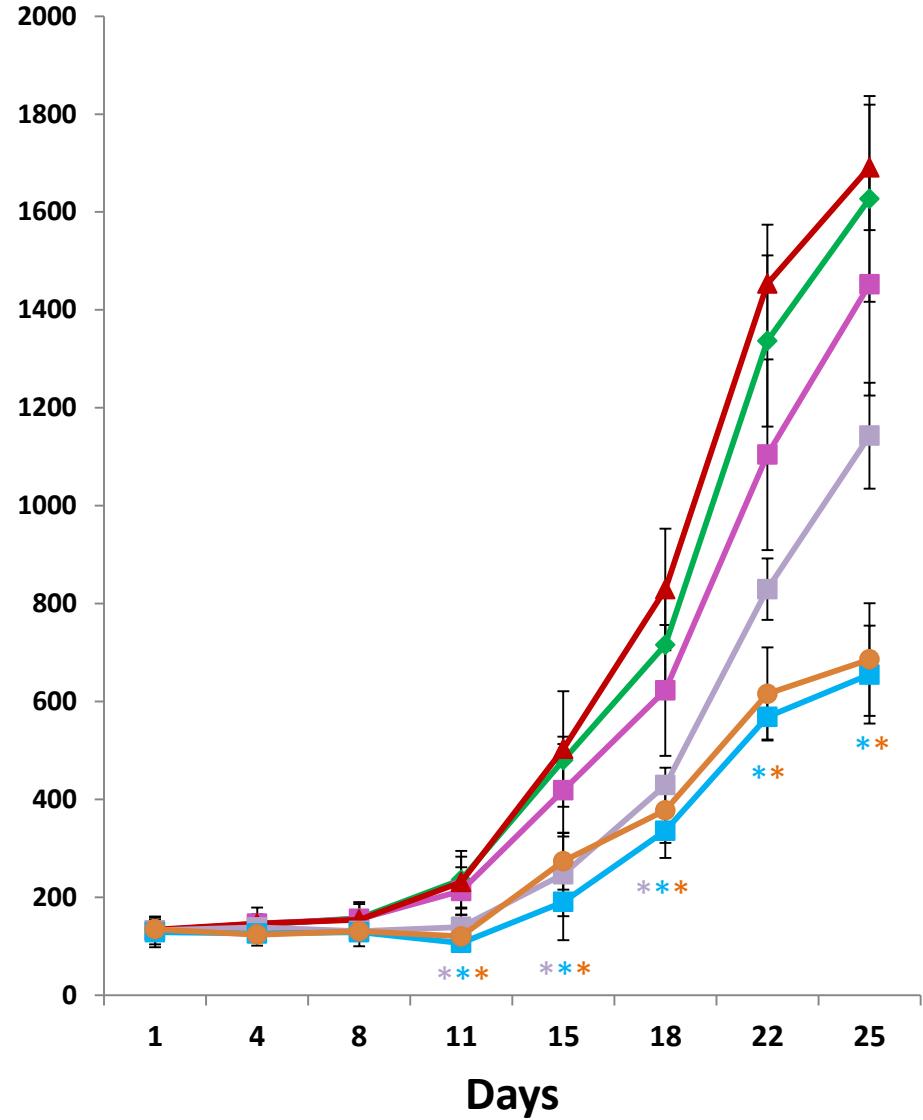
- I. Tumor size and growth rate
- II. *LINE1* (global methylation) in PBMCs and tumor tissue
- III. Gene-specific methylation and expression levels

SGI-110 delays CDDP-resistant tumor growth

QD5

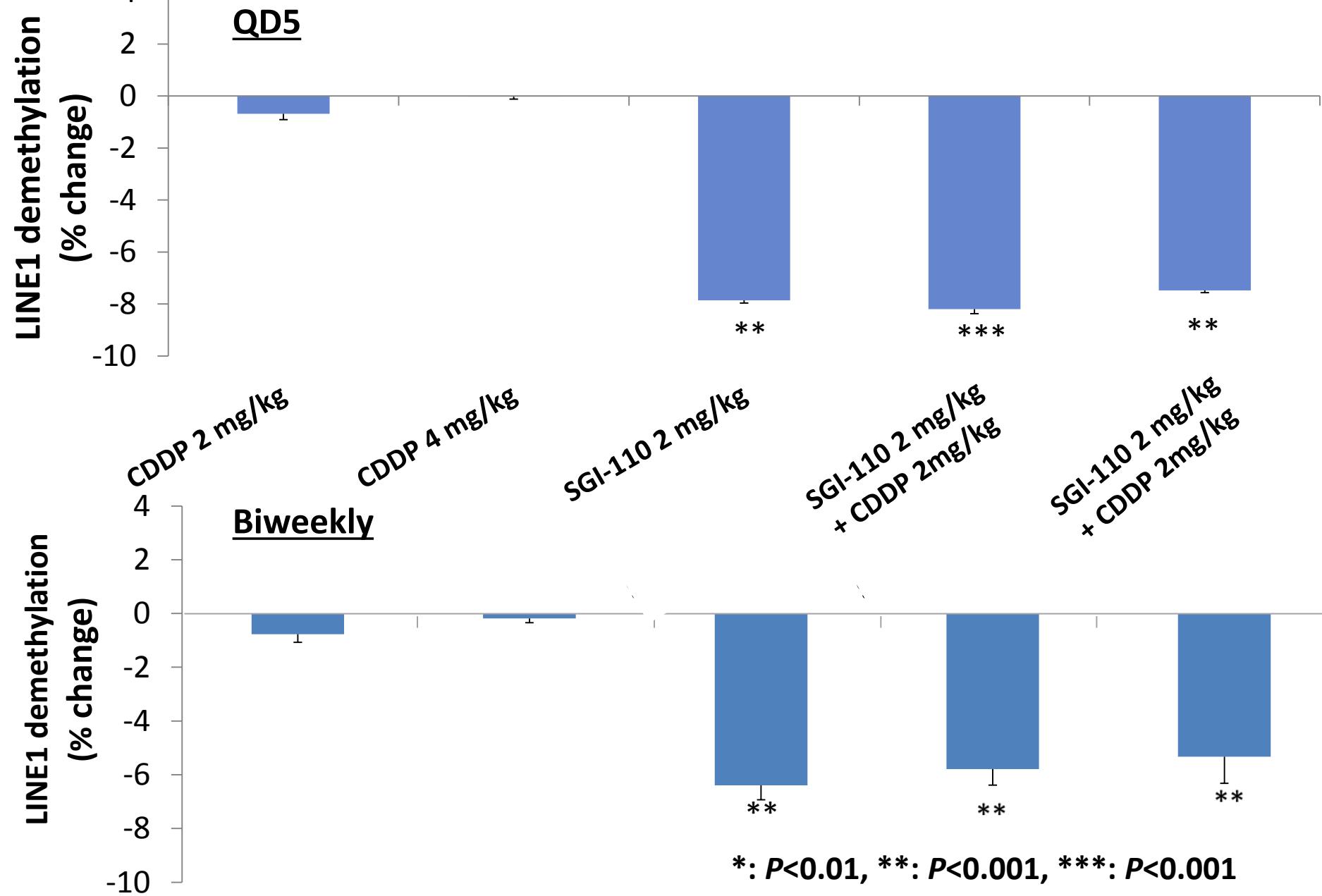


Biweekly

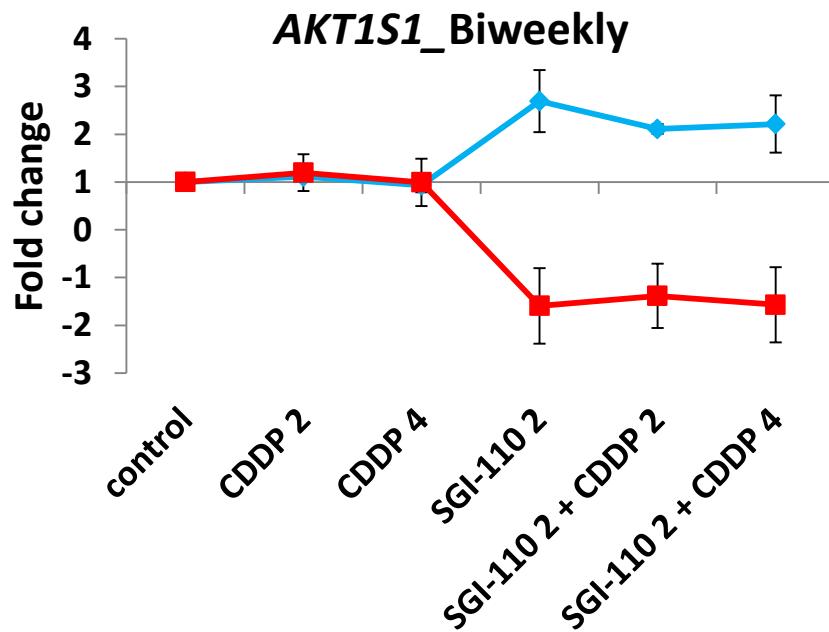
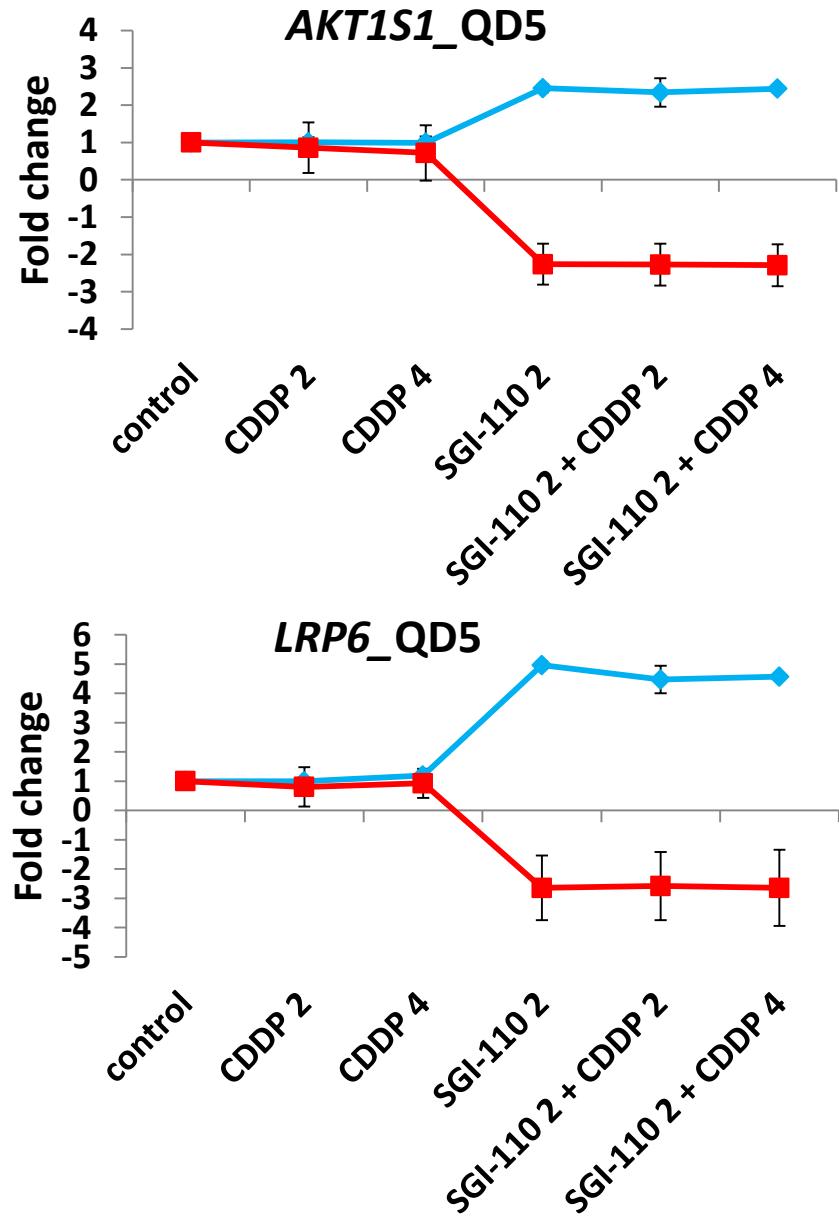


*: $P<0.01$, **: $P<0.001$, ***: $P<0.001$

SGI-110 demethylates *LINE1* in CDDP-resistant tumor

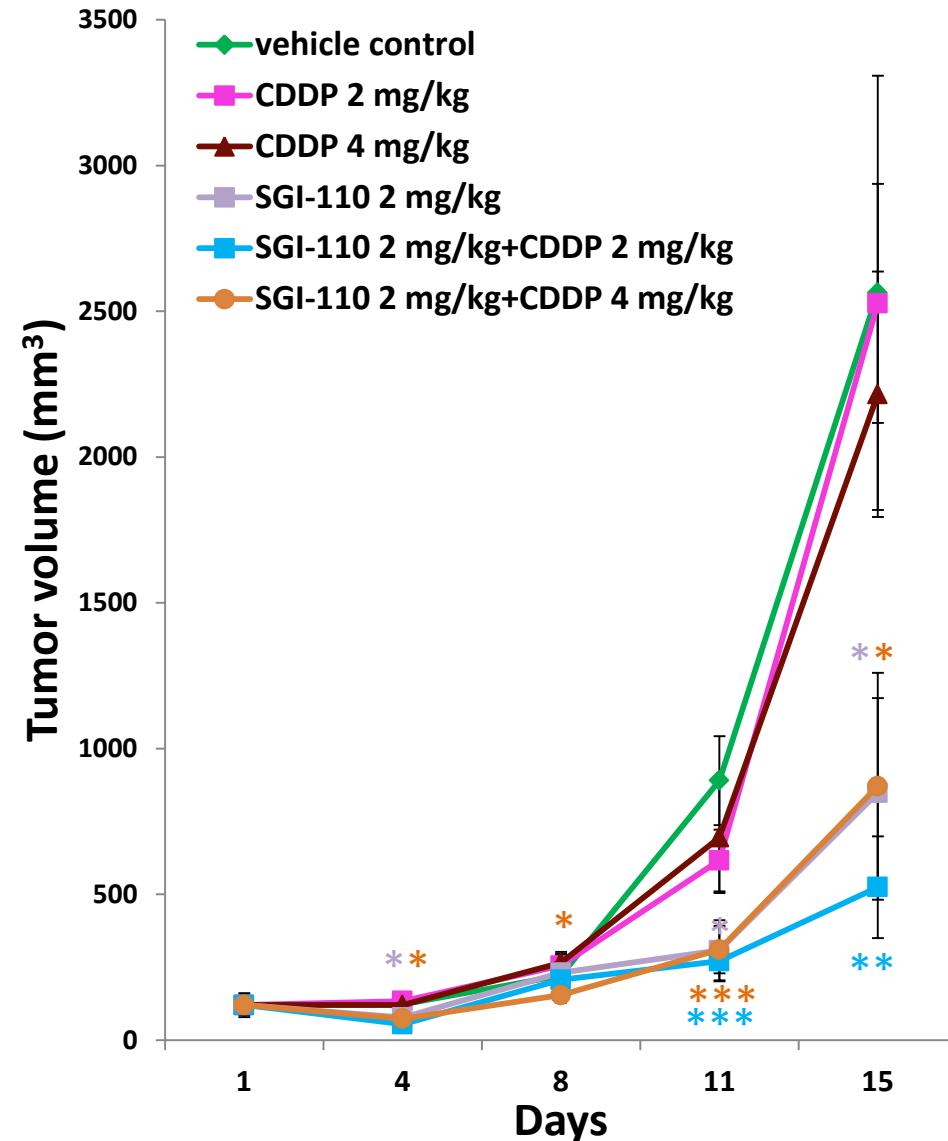


SGI-110 de-represses specific genes in QD5 and Biweekly schedule (xenografts from resistant A2780 cells)

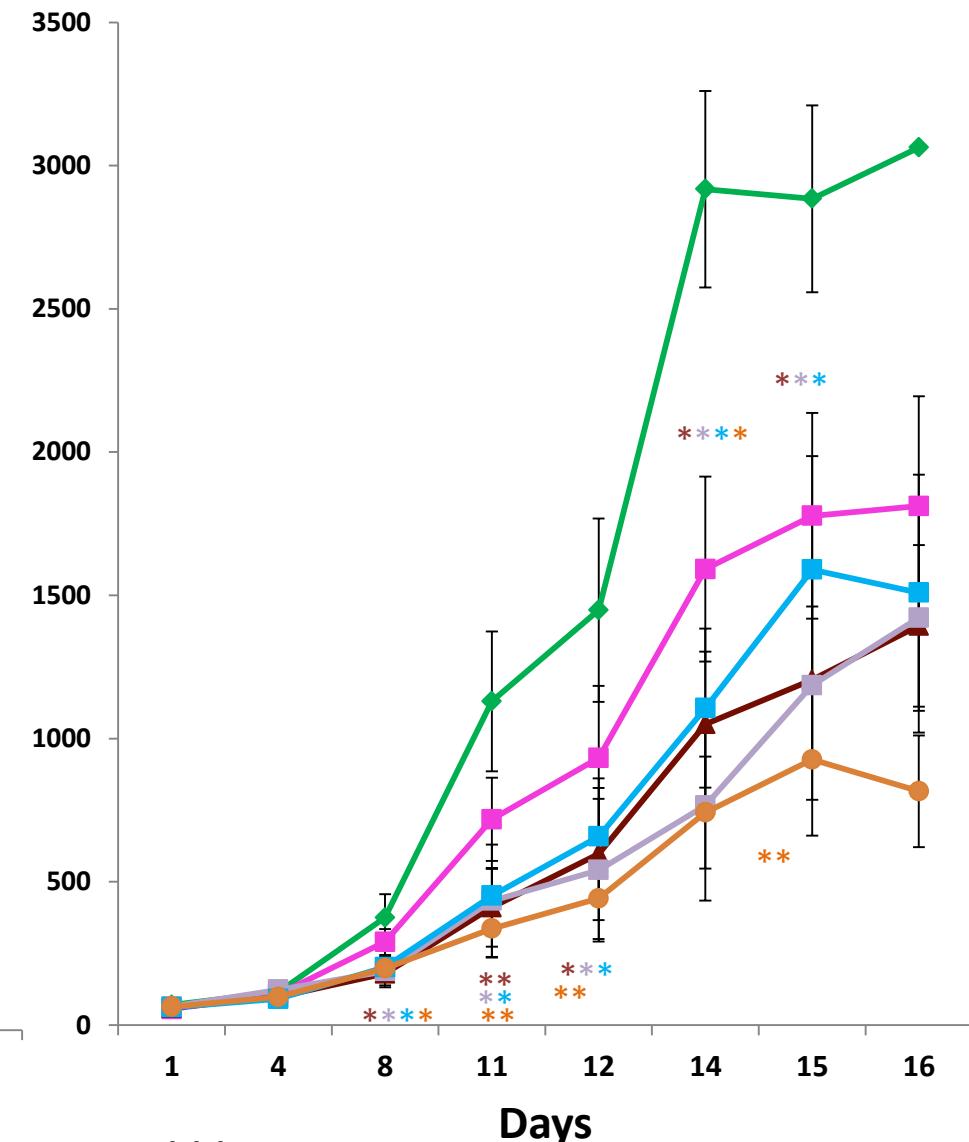


SGI-110 delays tumor growth (parental A2780 xenografts)

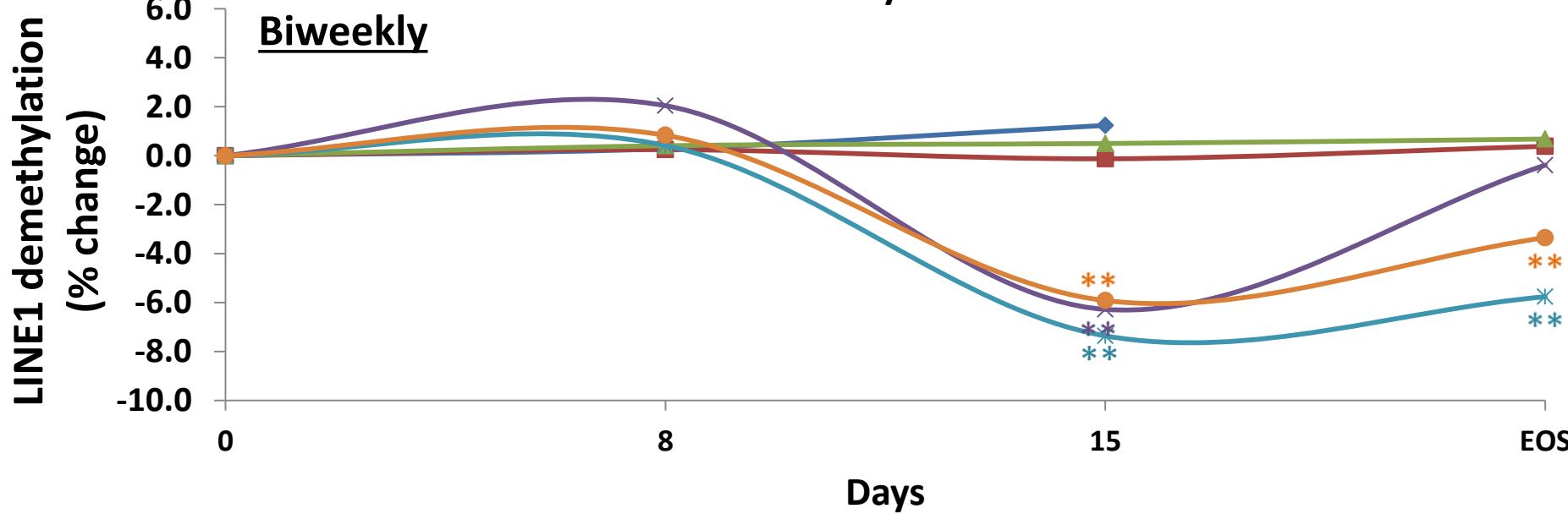
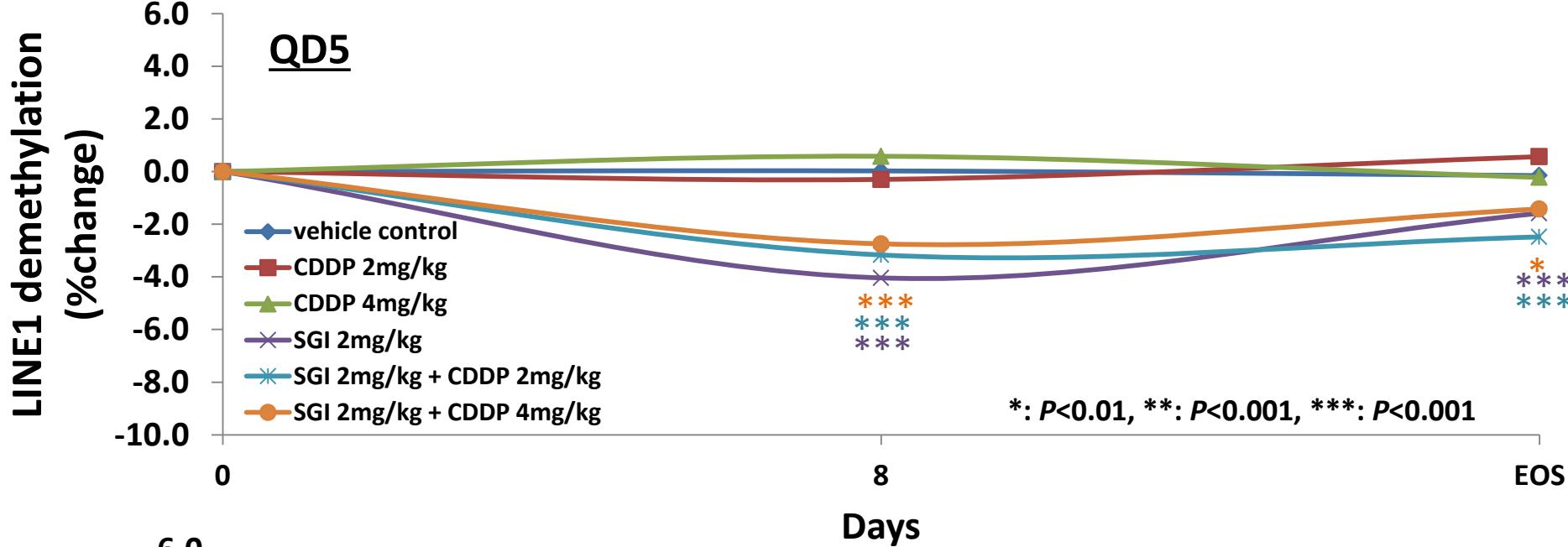
QD5



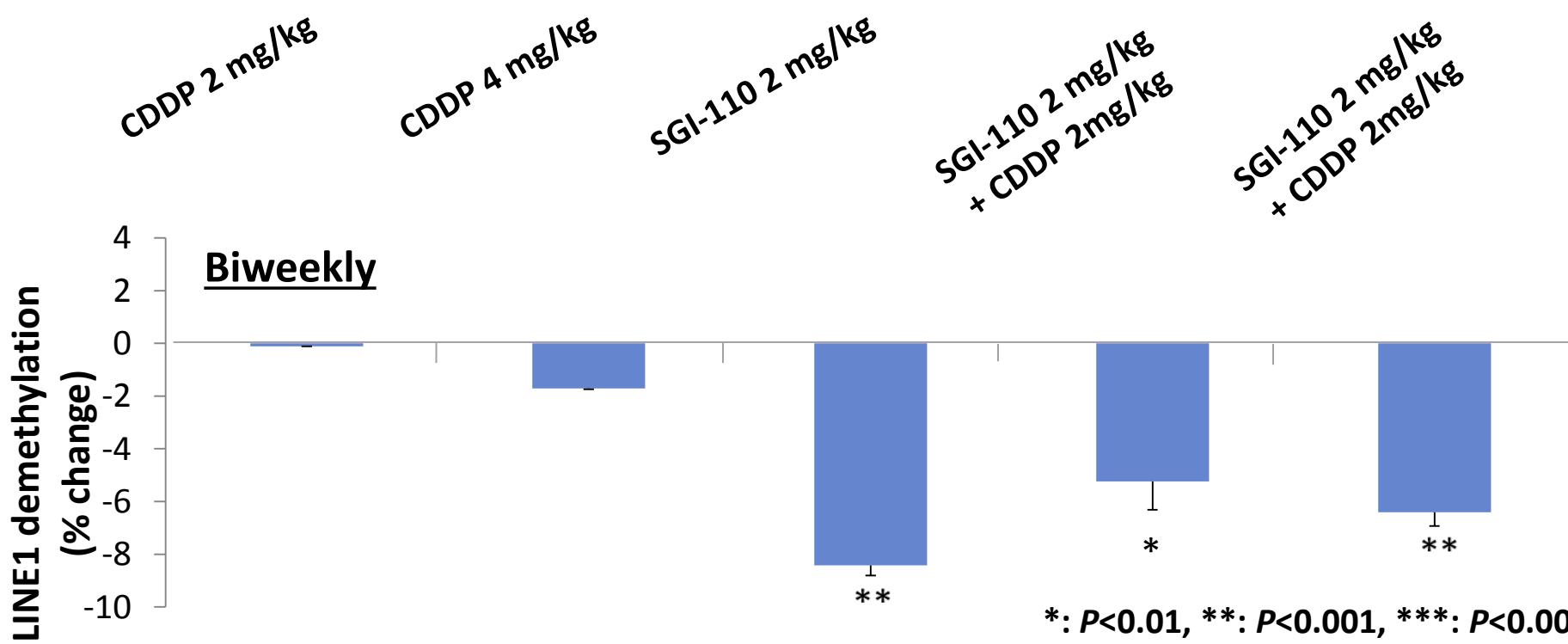
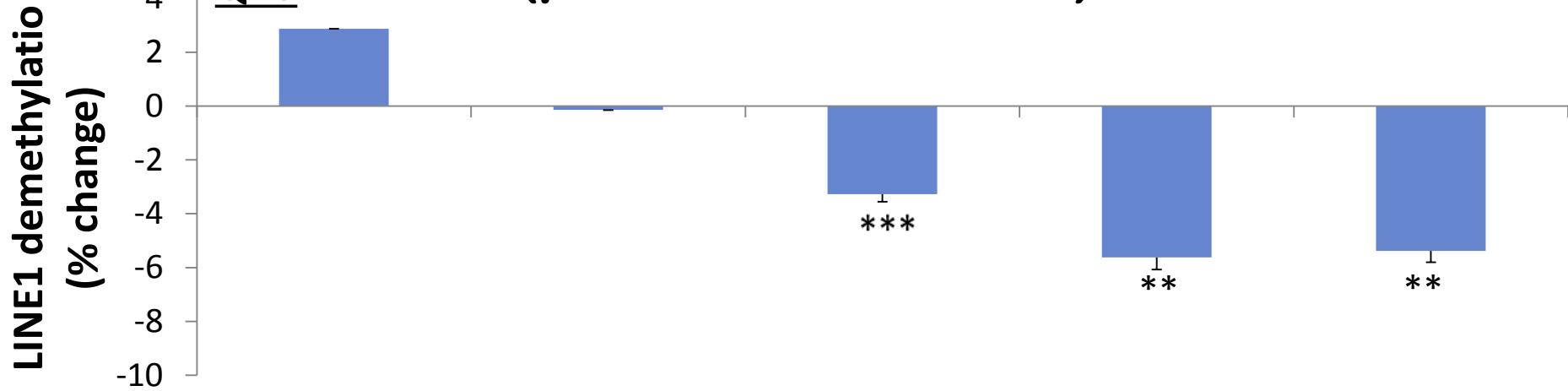
Biweekly



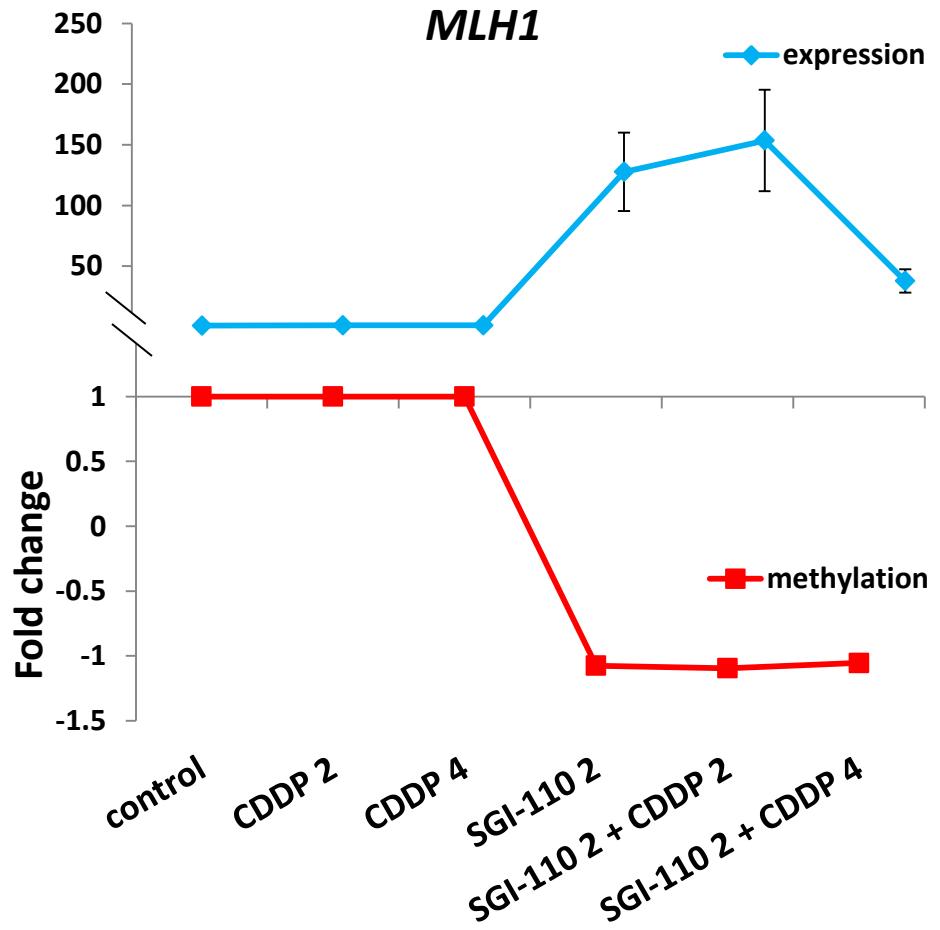
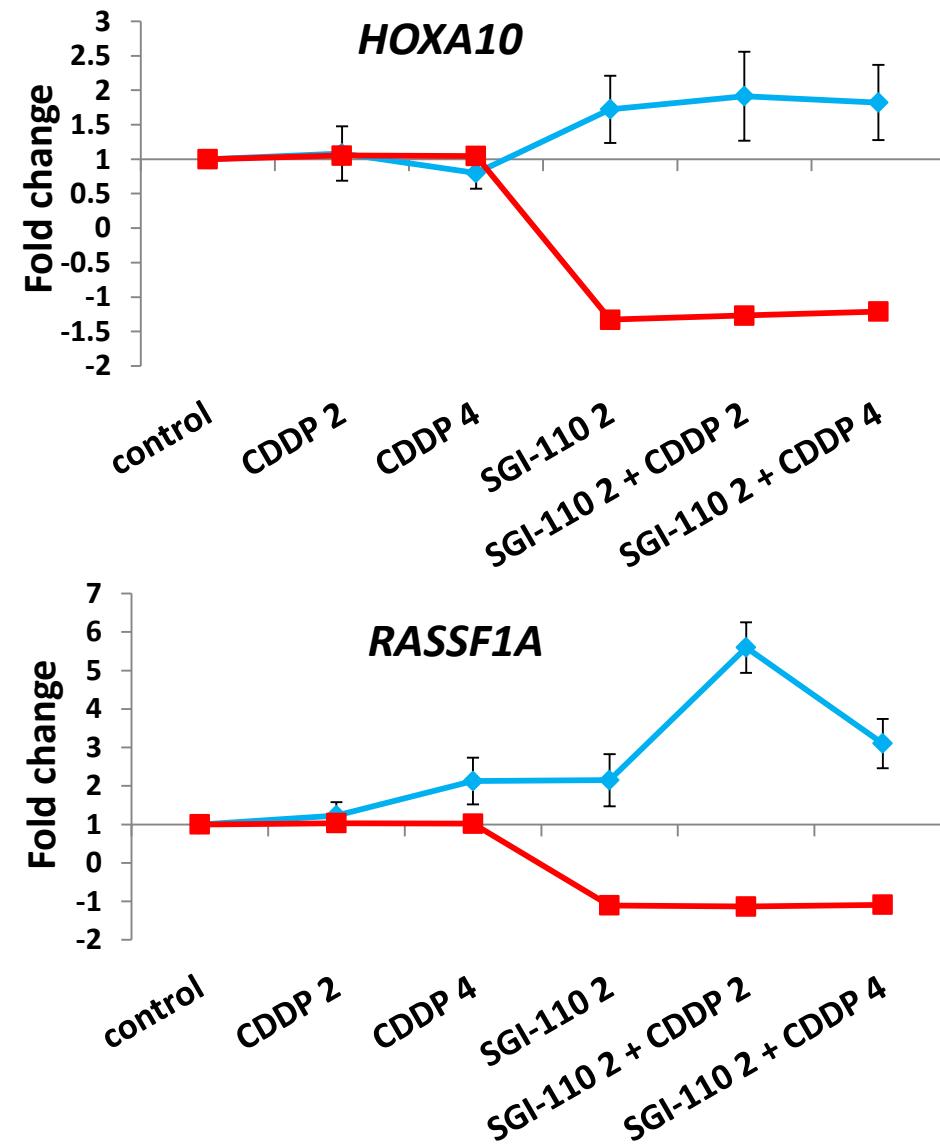
SGI-110 demethylates *LINE1* in PBMCs



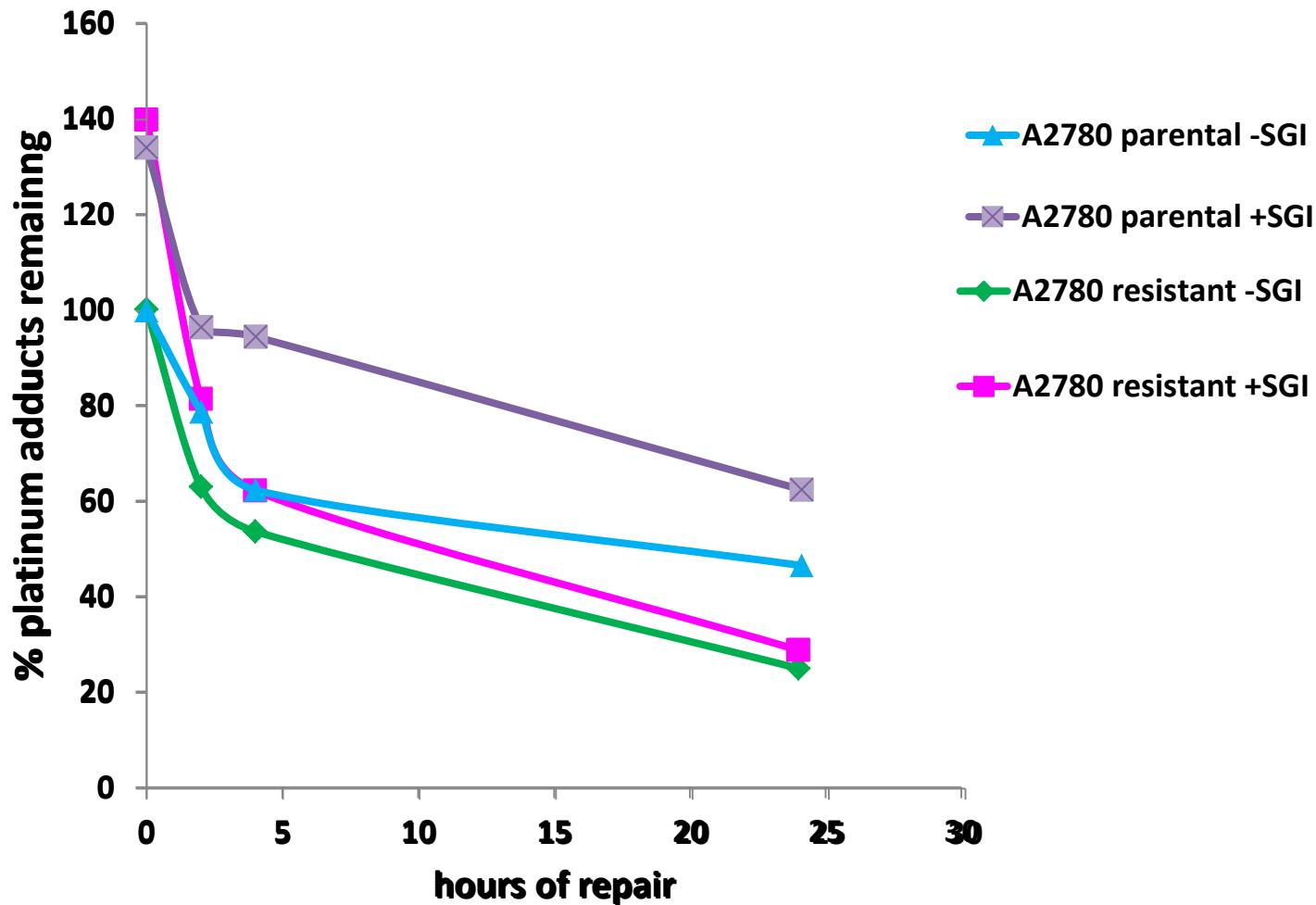
SGI-110 demethylates LINE1 in xenografts (parental A2780 cells)



SGI-110 de-represses specific genes in QD5 schedule (xenografts from parental A2780 cells)



SGI-110 slows repair of platinum DNA adducts *in vitro*



Conclusions and Future Directions

1. Low dose SGI-110 in combination with cisplatin inhibits growth of parental and CDDP-resistant ovarian cancer cells and xenografts
2. Low dose SGI-110 causes global (*LINE1*) and gene specific (e.g., *MLH1*) demethylation and re-expression
3. These preclinical studies support the use of SGI-110 as a safe and effective chemo-resensitizer in ovarian and perhaps other solid tumors.
4. *Current clinical development of SGI-110:*

Clinical Study	Phase	Description	Sponsor	Status
SGI-110-01	1 / 2	MDS / AML	Astex	Phase 1 complete Phase 2 ongoing
SGI-110-02	2	Ovarian Cancer	Astex	Ongoing
SGI-110-03	2	HCC	Astex	Ongoing

Acknowledgements

Indiana University

Fang Fang
Yinu Wang
David F.B. Miller
Jay Pilrose
Daniela Matei
Changyu Shen
Katherine S. Pawelczak
Pamela VanderVere-Carozza
Michael Wagner
John J. Turchi
Kenneth P. Nephew

Astex Pharmaceuticals Inc.

Mohammad Azab
John Lyons
Gavin Choy
Pietro Taverna
Simone Jueliger
Joanne Munck

EpigenDX: Liying Yan

Research Support

- NIH CA-85289
- NIH CA-133877
- NIH CA-11300 (The Integrative Cancer Biology Program, Centers for Cancer Systems Biology)
- Ovarian Cancer Research Fund (OCRF; *PPDIU01.2011*)



MELVIN AND BREN SIMON
CANCER CENTER

INDIANA UNIVERSITY