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Clinical epigenetic resensitization of platinum-resistant, recurrent ovarian cancer patients with SGI-110, a novel, second-generation, subcutaneously administered hypomethylating agent (HMA)

Gini Fleming[1], Sharad Ghamande[2], Yvonne Lin[3], Angeles Alvarez Secord[4], John Nemunaitis[5], Merry-Jennifer Markham[6], Kenneth Nephew[7], Fang Fang[7], Shweta Gupta[8], Sue Naim[8], Gavin Choy[8], Simone Jueliger[8], Pietro Taverna[8], Yong Hao[8], Harold Keer[8], Aram Oganesian[8], Mohammad Azab[8], Daniela Matei[7]

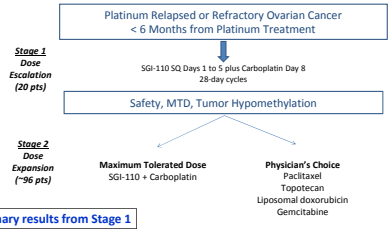
University of Chicago, Chicago, IL[1], Georgia Health Sciences, Augusta, GA[2],University of Southern California, Los Angeles, CA[3], Duke University, Durham, NC[4], Crowley Cancer Research Centers, Dallas, TX[5], University of Florida, Gainsville, FL[6], Indiana University, Bloomington, IN[7], Astex Pharmaceuticals Inc., Dublin, CA[8]

BACKGROUND

- In the past 20 years there has been little change in the 1-, 3-, and 5- year survival rates for patients with ovarian cancer
- 5-year survival is ~25% for patients diagnosed with advanced stage disease
- Recurrence is common and patients develop resistance to chemotherapy
- Platinum resistant ovarian cancer is uniformly fatal and epigenetic changes have been implicated in the development of platinum resistance
- Previous experience with decitabine, a hypomethylating agent, in combination with carboplatin demonstrated activity in recurrent platinum resistant ovarian cancer patients (Matei et al. Cancer Research 2012)
- SGI-110 is a dinucleotide of decitabine and deoxyguanosine, affords increased in vivo exposure of decitabine by protecting it from deamination due to slow release upon SQ injection
- In Phase 1 studies, SGI-110 provides longer exposure and more potent hypomethylation compared to decitabine. Combining SGI-110 with carboplatin in this population may improve upon the encouraging preliminary results

STUDY DESIGN

Figure 1: Study Design



Here we present the preliminary results from Stage 1

Major Study Objectives (Stage 1)

- **Primary:**
  - To assess the safety and tolerability of SGI-110 + carboplatin and determine MTD for Stage 2
- **Secondary:**
  - To determine objective response rate (ORR) based on both measurable disease and detectable disease
  - To assess PFS at 6 months, to determine the clinical benefit rate (CBR) and duration of response (DOR) Where CBR is defined as subjects achieving a response of CR, PR or SD ≥ 3months during the study
  - To determine CA-125 reduction by ≥ 50%
  - To determine PK of SGI-110 and decitabine in subjects with ovarian cancer and determine if there is a PK interaction between SGI-110 and carboplatin
- **Exploratory:**
  - To explore predictive and pharmacodynamic (PD) biomarkers as related to global DNA (LINE-1) methylation, and methylation status of selected genes in tumor tissue before and after treatment

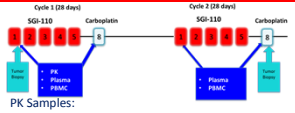
Major Inclusion and Exclusion Criteria

- **Major Inclusion Criteria:**
  - High-grade serous epithelial ovarian cancer, primary peritoneal carcinomatosis or fallopian tube cancer
  - Platinum-resistant disease (relapsed within 6 months of last platinum-containing regimen, no limit on number of prior therapies)
  - Measurable or detectable disease
  - ECOG 0-1
  - Acceptable organ function
- **Major Exclusion Criteria:**
  - Prior treatment with hypomethylating agent
  - Patients primarily refractory to platinum
  - LVEF < 50% by ECHO or MUGA
  - Grade 2 or higher neuropathy
  - Known brain metastases

Study Conduct

- **Dosing in 28 Day cycles:**
  - SGI-110 daily days 1 to 5 (initial dose 45 mg/m2)
  - Carboplatin IV D8 (initial dose AUC 5)
- **DLTs were defined as:**
  - Non-hematologic events ≥ Grade 3 despite optimal treatment
  - Hematologic events:
    - Complicated grade 4 neutropenia
    - Other grade 4 events
- **PD/PK sampling pre and post dosing**
- **Disease Assessment: every 8 weeks**

Figure 2: Schema



- PK Samples:
  - SGI-110: Cycle 1, Day 1: serial sampling up to 8 hours post-dose
  - Carboplatin: Cycle 1, Day 8: serial sampling up to 8 hours
- Pharmacodynamic Samples:
  - Biopsies and Plasma: Gene specific methylation and expression
  - PBMC: LINE-1

Table 1: Patient Characteristics and Dosing Cohorts

Characteristics	Cohort 1 (N=6)	Cohort 2 (N=14)	Total (N=20)
SGI-110	45 mg/m²	30 mg/m²	-
Carboplatin	AUC 5	AUC 4	-
Age (mean, range)	57 (38-72)	58 (38-71)	58 (38-72)
ECOG			
0	4 (67%)	6 (43%)	10 (50%)
1	2 (33%)	8 (57%)	10(50%)
Prior Treatment			
Platinum	6(100%)	14 (100%)	20 (100%)
Taxanes	6(100%)	14(100%)	20 (100%)
Number of prior regimens (median, range)	6 (2-9)	7 (1-9)	7 (1-9)
Disease			
Recurrent High-grade Ovarian Cancer	5 (83%)	13 (93%)	18 (90%)
Fallopian Tube Cancer	0 (0%)	1 (7%)	1 (5%)
Primary Peritoneal Carcinomatosis	1 (17%)	0 (0%)	1 (5%)

Dosing Cohorts and Recommended Dose for Stage 2

- Dosing was initiated (cohort 1, n=6) at SGI-110 at 45 mg/m2 + Carboplatin AUC 5
  - 4 DLTs (grade 4 thrombocytopenia, febrile neutropenia) were observed and the dose of both SGI-110 and Carboplatin were de-escalated for Cohort 2. Cohort 2 was dosed with SGI-110 at 30 mg/m2 + Carboplatin AUC 4 with the potential to increase the carboplatin dose to AUC 5 if well tolerated
- After initial safety of this combination was established(n=6), the safety was confirmed by enrolling an additional 8 subjects(total of 14) to evaluate for safety and activity. 1 DLT was observed in cohort 2 in one of the 8 additional subject enrolled
- Cohort 2 dose was selected for SGI-110 arm of stage 2

Table 2: Summary of Dose Limiting Toxicities

Cohort	Patient ID	Dose (SGI-110/ Carboplatin)	Event	Grade	Outcome
1	05-01	45mg/m²-AUC 5	Neutropenia	4	Recovered
1	07-01	45mg/m²-AUC 5	Neutropenia	4	Recovered
1	07-02	45mg/m²-AUC 5	Neutropenia & Thrombocytopenia	4	Recovered
1	07-03	45mg/m²-AUC 5	Neutropenia & Thrombocytopenia	4	Complicated by neutropenic sepsis and unrelated pulmonary embolus and CVA
2	0402	30mg/m2- AUC4	Febrile Neutropenia	3	Recovered

Table 3: Summary of All Related Grade 3 and Above Adverse Events to SGI-110 or Carboplatin for Stage 1

	45 mg/m² (N=6)		30 mg/m² (N=14)		Total (N=20)	
Events	# and % of Subjects		# and % of Subjects		# and % of Subjects	
ANY RELATED EVENT	6	(100.0%)	9	(64.3%)	15	(75.0%)
Neutropenia	6	(100.0%)	8	(57.1%)	14	(70.0%)
Leukopenia	2	(33.3%)	3	(21.4%)	5	(25.0%)
Anaemia	3	(50.0%)	1	(7.1%)	4	(20.0%)
Thrombocytopenia	2	(33.3%)	0		2	(10.0%)
Infusion related reaction	1	(16.7%)	1	(7.1%)	2	(10.0%)
Hyperbilirubinaemia	1	(16.7%)	0	(0%)	1	(5.0%)
Sepsis	1	(16.7%)	0	(0%)	1	(5.0%)

- Events reported at frequency of 10% or greater are listed

Table 4: Clinical Activity (responses, disease control)

Best Response Per RECIST 1.1	Cohort 1 (n=6)	Cohort 2 (n=14)	Total (n=20)
CR	0	0	0
PR	0	3	3
SD	4	3	7
CBR	67%	43%	50%
ORR*	0	21%	15%

* ORR is defined as the % of subjects achieving a response rating of CR and PR by RECIST 1.1

- 17/20 patients had CA-125 values ≥ 2x the upper limit of normal at baseline, 3 had ≥ 50% decrease which was maintained for at least 28 days

LINE-1 Demethylation in Blood DNA Individual Patients Max LINE-1 Demethylation

Table 5:

SGI-110 Cohort (mg/m2 qd x5)	Max LINE-1 Demethylation
1 (45)	-17.4 ± 6.9% (n=6)
2 (30)	-19.5 ± 8.6 % (n=14)

- Potent global DNA demethylation was detected by LINE-1 assay
- DNA demethylation was similar for the two doses of SGI-110

Figure 3:

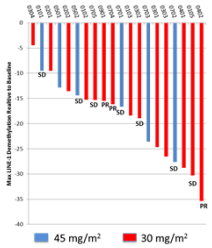


Figure 4: Gene Specific Methylation in Paired Tumor Biopsies or Ascites

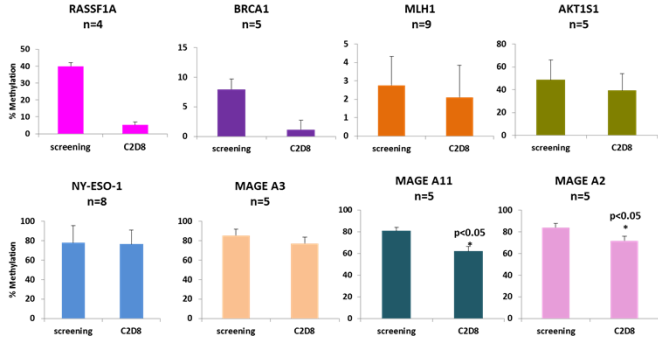
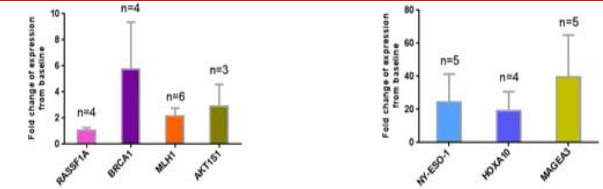
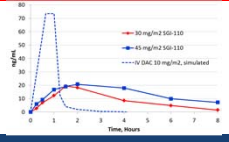


Figure 5: Fold Increase of Gene Expression in Paired Tumor Biopsies or Ascites



- Gene-specific demethylation in tumor biopsy DNA was evident in tumor suppressor (RASSF1A, BRCA1) and in cancer testis antigens genes (MAGE A2, A3, A11)
- Gene-specific demethylation was generally associated with increased expression of the related transcript

Figure 6 : Plasma Decitabine after SGI-110



Decitabine exposure window after SQ injection of SGI-110 is prolonged compared to previously published data of decitabine IV infusion

Conclusions

- Safety: The combination of SGI-110 at 30 mg/m2 with carboplatin at AUC 4 is well tolerated and is being used for Stage 2 of the study
- Activity: 3 PRs were seen with **7** SD resulting in a ORR of **15%** and CBR of **50%** for this part of the study
- SGI-110 can be used safely as a priming agent prior to carboplatin
- PD: Potent global DNA demethylation (LINE-1) and gene-specific demethylation and re-expression was evident in pre and post-treatment blood and tumor biopsies
- PK: no apparent drug-drug interactions between SGI-110 and carboplatin; decitabine exposure window after SQ injection of SGI-110 is prolonged compared to decitabine IV infusion
- Stage 2 (randomized part) is currently ongoing

Poster presented at: AACR Annual Meeting, San Diego, CA April 5 – 9, 2014