Abst. No. 5547

# Epigenetic resensitization to platinum in recurrent, platinum-resistant ovarian cancer (OC) using guadecitabine (SGI-110), a novel hypomethylating agent (HMA): results of a randomized Phase 2 study

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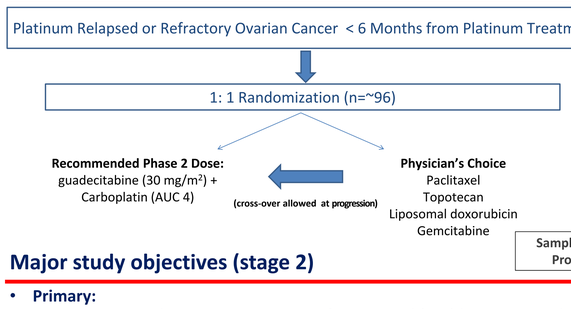
## BACKGROUND

- 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)
- Guadecitabine 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, guadecitabine provides longer exposure and more potent hypomethylation compared to decitabine. Combining guadecitabine with carboplatin in this population may improve upon the encouraging preliminary results and an acceptable dose for phase 2 was previously established (Fleming, et al AACR 2014)

## STUDY DESIGN

### Figure 1: Study Design




### Major study objectives (stage 2)

- **Primary:**
  - To assess and compare progression-free survival (PFS) between guadecitabine + carboplatin (C) and Treatment Choice (TC) Arms
- **Secondary:**
  - To determine and compare objective response rate (ORR) for guadecitabine + C and TC arms based on both measurable disease and detectable disease
  - To assess and compare PFS at 6 months for guadecitabine + C and TC arms
  - To determine and compare OS for guadecitabine + C and TC arms and compare the, 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 guadecitabine and decitabine in subjects with ovarian cancer and determine if there is a PK interaction between guadecitabine 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

### 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 (RECIST or Rustin criteria)
- ECOG 0-1
- Acceptable organ function

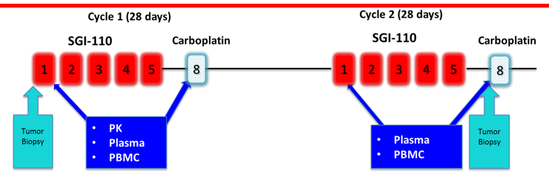
**Major Exclusion Criteria:**

- 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:
  - Guadecitabine daily days 1 to 5 (dose of 30 mg/m$^2$) + Carboplatin IV D8 (initial dose AUC 4)
  - TC options:
    - Topotecan: 3.5-4.0 mg/m$^2$/week D 1,8,15
    - Pegylated liposomal doxorubicin: 40-50 mg/m$^2$ on D 1
    - Paclitaxel: 60-80 mg/m$^2$/week D 1,8, 15, 22
    - Gemcitabine 800-1000 mg/m$^2$/week D 1, 8, 15
- Dose reduction based on tolerability and G-CSF support allowed
- PD/PK sampling pre and post dosing
- Disease Assessment: every 8 weeks

### Figure 2: Schema




- PK Samples:
  - Guadecitabine: 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:
  - Tumor biopsies: Gene specific methylation and expression
  - Blood: LINE-1

### Table 1: Demographics & prior therapies

| Characteristic | Guadecitabine + C (n=51) | TC (n=49) |
|---|---|---|
| Age | 62.0 (9.2) | 62.1 (9.6) |
| ECOG | | |
| 0 | 18 (35%) | 23 (47%) |
| 1 | 33 (65%) | 25 (51%) |
| 2 | 0 (0%) | 1 (2%) |
| **Prior Systemic Treatment** | | |
| Prior Platinum | 51 (100%) | 49 (100%) |
| Prior Taxanes | 48 (94%) | 48 (98%) |
| Number of Prior Regimens | | |
| 1-2 | 12 (24%) | 14 (29%) |
| 3-4 | 22 (43%) | 16 (33%) |
| ≥5 | 17 (33%) | 19 (39%) |

### Assessment of responses and progression

- **Progression based on RECIST, Rustin, and clinical progression as assessed by Investigators**
  - Subjects were encouraged to remain on treatment for 6 cycles in the absence of toxicity or clinical progression (i.e. only RECIST progression)
  - For subjects without measurable disease (evaluable disease), progression was assessed by Rustin criteria
  - If subjects had RECIST measurable disease without a follow up scan and also had PD by CA-125 criteria, the earliest point of progression was used for both arms

### Table 2: Clinical activity by RECIST

| | Guadecitabine + C (N=51) | | | TC (N=49) | | | TC_guadecitabine* (N=27) | | |
|---|---|---|---|---|---|---|---|---|---|
| | # | % | 95% CI | # | % | 95% CI | # | % | 95% CI |
| n | 51 | | | 49 | | | 27 | | |
| CR/FR | 1 | 2 | ( 0.0, 10.4) | 0 | 0 | ( 0.0, 7.3) | 0 | 0 | ( 0.0, 12.8) |
| PR | 7 | 14 | ( 5.7, 26.3) | 3 | 6 | ( 1.3, 16.9) | 2 | 7 | ( 0.9, 24.3) |
| SD | 11 | 22 | ( 11.3, 35.3) | 10 | 20 | ( 10.2, 34.3) | 4 | 15 | ( 4.2, 33.7) |
| PD | 26 | 51 | ( 36.6, 65.2) | 26 | 53 | ( 38.3, 67.5) | 15 | 56 | ( 35.3, 74.5) |
| NE | 6 | 12 | ( 4.4, 23.9) | 10 | 20 | ( 10.2, 34.3) | 6 | 22 | ( 8.6, 42.3) |

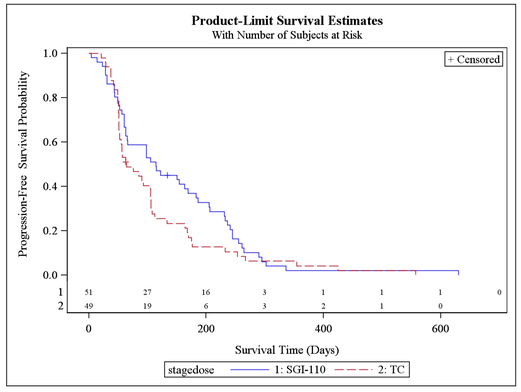
*Column represents subjects who crossed over to carboplatin + guadecitabine after progression on TC

- Objective Response Rates (ORR) were similar between guadecitabine + C and TC arms though a significant number of subjects did not have evaluable disease
- Using CA-125 measurements, 15 (29%) of subjects in the Guadecitabine + C treated group had 50% or more reduction in CA-125 compared to baseline vs. 19 (39%) in the TC group. In subjects crossing over from TC to guadecitabine + C, 12 (44%) had a 50% reduction). None of these values were significantly different from each other.

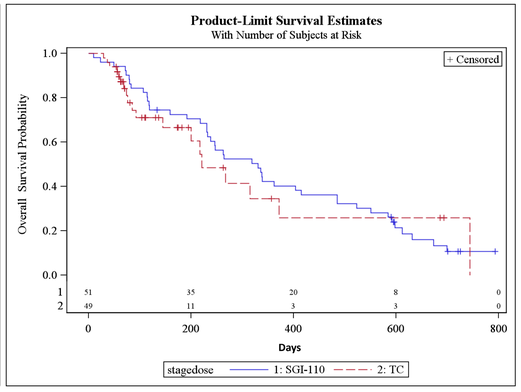
### Table 3: Grade 3 or above AEs, assessed as related at ≥ 5% incidence

| Event | Guadecitabine + C (N=51) | TC (N=49) |
|---|---|---|
| - Neutropenia | 34 (67%) | 9 (18%) |
| - Leukopenia | 13 (25%) | 2 (4%) |
| - Anaemia | 7 (14%) | 7 (14%) |
| - Thrombocytopenia | 3 (6%) | 4 (8%) |
| - Febrile neutropenia | 1 (2%) | 0 |
| - Fatigue | 4 (8%) | 4 (8%) |

### Figure 3: PFS analysis



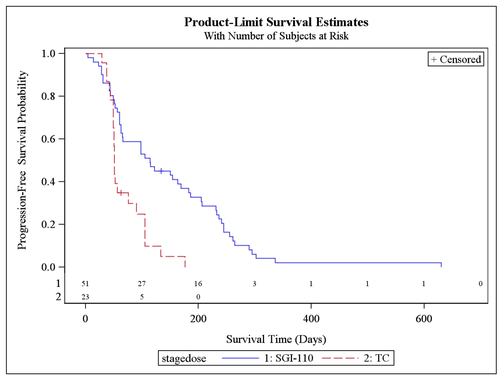

### Figure 4: OS (with censoring)



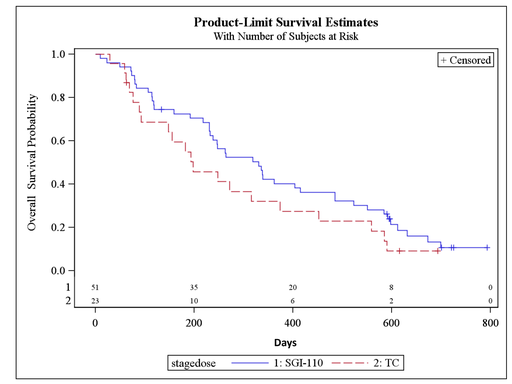

**Progression-Free Survival and Overall Survival Analyses**

- PFS analysis was based on 98% of events (2% censored)
- PFS analysis showed 16.3 weeks in the guadecitabine + C arm compared to 9.1 weeks for TC (HR of 0.74)
- PFS at 6 months was 37% and 13%, respectively for guadecitabine + C vs. TC
- OS analysis was performed censoring for subjects crossing over from TC to guadecitabine + C and was based on 62 events (38% censored)
- OS for guadecitabine + C vs TC were 11.0 vs. 7.4 months respectively (HR= 0.88)

### Figure 5: PFS in guadecitabine + C vs TC of topotecan or gemcitabine




### Figure 6: OS (without censoring) in guadecitabine + C vs TC of topotecan or gemcitabine




**Additional subgroup analyses**

- Additional analyses were performed based on the selected TC used, comparison vs topotecan or gemcitabine are presented in Figs 5 & 6. Because most patients crossed over to guadecitabine + carboplatin, OS is presented without censoring of crossover patients.
- Demographics showed no major differences between the groups
- PFS analysis showed 16.3 weeks vs. 7.3 weeks for TOPO/GEM, respectively (HR= 0.37)
- Uncensored OS analysis showed 11.0 vs 6.6 months survival for guadecitabine + carboplatin vs. TOPO/GEM, respectively, (HR= 0.69)

## Conclusions

- Guadecitabine + carboplatin is tolerated at the phase 2 doses of 30 mg/m$^2$ and AUC 4, respectively
- SGI-110-02 Data are encouraging with a signal favoring guadecitabine + carboplatin vs. TC, particularly against TC of TOPO or GEM
- The signal seen in this randomized phase 2 study is consistent with that seen in previous non-randomized studies (1, 2) and supports the hypothesis that HMA "priming" may render platinum-resistant ovarian cancer patients more sensitive to platinum-based therapy

## References

1) Matei, et al. Cancer. Res. 72(9); 2197-205 (2012)
2) Fleming, et al Cancer Res October 1, 2014 74:2320


Poster presented at: ASCO Annual Meeting, Chicago, IL June 3 – 7, 2016