**ABSTRACT**

Combination therapy resulted in decreased clonogenic survival in ovarian cancer cells. Ovarian cancer (OC) is initially chemoresponsive but the majority of patients relapse after first-line platinum, taxane-based chemotherapy. Recurrence has been shown to be associated with increased DNA damage response (DDR) mediated by poly-(ADP)-ribose polymerase 1/2 (PARP1/2), which can be therapeutically targeted by PARP inhibitors (PARPi). Although PARPi are indicated for platinum-resistant, BRCA-mutated OC, most OC patients have BRCA-proficient disease.

On our previous studies supporting a role for DNA methylation in chemoresistant OC, mediated by the enzyme DNA methyltransferase 1 (DNMT1), and reports on a functional role for DNMT1 in DNA double strand break repair mediated by BRCA1/2, we hypothesize that combining the DNMT1i SGI-110 and the PARPi talazoparib (BMN673) will impair BRCA-mediated DDR, resulting in cytotoxicity.

**RESULTS**

**FIG. 1** Schematic for combination treatments

- **Co-Administration Treatment**
  - Day 0: Plate Cells (40-50% confluent)
  - Day 1: Daily SGI-110 Treatment (5, 20, 100mM)
  - Day 1: Talazoparib Treatment (1 or 10nM)
  - Day 4: Examine For Colony Growth, Proliferation, WB, Lucerase

- **Sequential (“Framing”) Treatment**
  - Day 0: Plate Cells (40-50% confluent)
  - Day 1-3: Daily SGI-110 Treatment (5, 20, 100mM)
  - Day 4: Wash Cells, Recover 24hrs
  - Day 5: Talazoparib Treatment (1 or 10nM)
  - Day 8: Examine For Colony Growth, Proliferation, WB, Lucerase

**FIG. 2** Combination of the DNMT inhibitor SGI-110 and PARPi talazoparib demonstrate increased efficacy in ovarian cancer cell lines

**FIG. 3** Combination DNMT inhibitor SGI-110 and PARPi talazoparib demonstrate increased efficacy in breast cancer cell lines MCF7, MDA-MB-231 and SKBR3

**FIG. 4** SGI-110 plus talazoparib is effective in BRCA2-deficient (Peo1) and BRCA2-proficient (Peo5/OC) cell lines

**FIG. 5** Low-dose SGI-110 increases PARP expression, while low-dose talazoparib increases DNMT1 expression

**FIG. 6** Low-dose talazoparib reduces PARP enzymatic activity, while SGI-110 induces PARylation

**CONCLUSIONS**

1. Combination therapy resulted in decreased clonogenic survival in BRCA-deficient or proficient ovarian cancer and breast cancer cell lines, suggesting that combinations of SGI-110 and talazoparib are effective irrespective of BRCA status.
2. Combination therapy resulted in decreased proliferative capacity and increased apoptosis in paired BRCA deficient and –proficient ovarian cancer cell lines.
3. SGI-110 increased PARP expression, as well as PARP enzymatic activity (PARylation).
4. Talazoparib reduced PARylation through PARP stabilization

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