THE DNA HYPOMETHYLATING AGENT SGI110 REVERSES THE PLATINUM RESISTANCE OF OVARIAN CANCER MODELS

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INTRODUCTION

• Patients with advanced stage ovarian cancer (OC) have a 5-year survival rate of less than 25%. The most common treatment strategy comprises debulking surgery followed by platinum-based chemotherapy. Patients commonly respond to frontline chemotherapy, but >70% relapse, developing platinum-resistance. There is evidence that the acquisition of platinum resistance is associated with the epigenetic silencing of specific genes by DNA methylation.

• SGI110 is a novel second generation DNA hypomethylating agent, which is currently in a Phase II clinical trial in combination with carboplatin, in platinum-resistant recurrent ovarian cancer patients (NCT01869323).

• SGI110 is a dinucleotide of decitabine and deoxyguanosine, which is resistant to modification by cytidine deaminase: a common pathway of decitabine metabolism and deactivation.

2. SGI110 REVERSES THE CISPLATIN-RESISTANCE OF A2780 CELLS IN VITRO

• Here we demonstrate that SGI110 reverses the cisplatin-resistance of the A2780 OC model, by abrogating the epigenetic silencing of MLH1. We demonstrate SGI110 activity in a panel of OC cell lines. We suggest that epigenetic silencing of ZIC1 is a mechanism of cisplatin resistance in the Ovcar8 and OAW28 cells and demonstrate that it is reversed by SGI110.

• SGI110 confers MLH1 demethylation and re-expression in A2780 xenografts.

3. SGI110 SENSITISES OVARIAN CANCER CELL LINES WITH DISTINCT MECHANISMS OF CISPLATIN RESISTANCE

• SGI110 confers re-expression of DOK2 and ZIC1 in both OAW28 and Ovcar8 cells (Table 1). DOK2 re-expression did not correlate with SGI110-induced sensitisation to cisplatin across the OC cell panel (Table 2). ZIC1 has previously been identified as a prognostic biomarker in OC (Huang et al., 2013).

• SGI110 confers ZIC1 demethylation.

SUMMARY AND CONCLUSIONS

• SGI110 reverses the known cisplatin resistance mechanism (epigenetic silencing of MLH1) of A2780 cells by conferring MLH1 promoter demethylation and re-expression.

• SGI110 sensitises Ovcar8 and OAW28 cells to cisplatin. This suggests that ZIC1, Ovcar3 and SKOV3 cells do not have an epigenetic mechanism of cisplatin resistance.

• We demonstrate that SGI110 reverses the cisplatin resistance of OC models by restoring expression of ovarian resistance genes.