SY-1365, a selective CDK7 inhibitor, enhances carboplatin activity in ovarian cancer cell lines and xenografts, and inhibits effectors of homologous recombination repair

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**Introduction**

- Homologous Recombination Deficiency (HRD) forms the basis for synthetic lethality interactions with agents that directly cause DNA damage (e.g. carboplatin) or agents that inhibit DNA repair (e.g. PARP inhibitors).
- HRD is caused by alterations in effectors of homologous recombination repair (HRR), such as mutation of BRCA1/2 and ATM. These mutations result in loss of function of HRR proteins, leading to cells’ inability to repair the DNA damage caused by platinum agents.
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**SY-1365 is synergistic with carboplatin in ovarian cancer cell lines and enhances carboplatin activity in ovarian cancer xenografts**

In *vivo* (top): Dose-response curves were generated in TOV21G (DMSO only) and OVCAR3 (DMSO only) in combination with SY-1365 and CP. The combination with SY-1365 and CP shows synergy with CP in both cell lines.

In *vivo* (bottom): Growth of ovarian cancer xenografts (TOV21G and OVCAR3 treated with CP alone or in combination with SY-1365) was monitored. SY-1365 combined with CP resulted in 100% complete regressions, in OC patient-derived xenograft models.

**Conclusions**

- SY-1365, a selective CDK7 inhibitor, is synergistic with CP in OC preclinical models.
- SY-1365 inhibits transcription of HRR genes and inhibits DNA repair in OC cancer cell lines.
- These results suggest that SY-1365-mediated inhibition of HRR induces an HRD-like state resulting in enhanced sensitivity to DNA damaging agents and/or DNA repair inhibitors.
- These data support the ongoing clinical investigation of SY-1365 in combination with carboplatin in a phase 1 trial (NCT03134638).