Inhibition of ovarian and endometrial cancer cell proliferation by an anti-ROR1 monoclonal antibody

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Dongli Liu[1], Gunnar F. Kaufmann[2], James B. Breitmeyer[2], Kristie-Ann Dickson[3], Deborah J. Marsh[3], Caroline E. Ford[1*]

1 Gynaecological Cancer Research Group, Lowy Cancer Research Centre, School of Women's and Children's Health, Faculty of Medicine & Health, University of New South Wales, Australia; 2 Oncternal Therapeutics, Inc., San Diego CA, USA; 3 School of Life Sciences, University of Technology Sydney, Australia. *Contact Caroline.ford@unsw.edu.au @DrCFord

Introduction

The non-canonical Wnt signalling receptor **ROR1** has been shown to be aberrantly expressed in numerous cancers, including ovarian and endometrial cancer [1,2]. We previously reported that silencing ROR1 could inhibit proliferation and metastatic potential of ovarian and endometrial cells *in vitro* [2,3]. **Cirmtuzumab** is a humanised monoclonal antibody against ROR1 that blocks Wnt5a-induced ROR1 signalling [4]. It has demonstrated safety and efficacy in several Phase I/II clinical trials for patients with chronic lymphocytic leukemia (CLL) [5], mantle cell lymphoma (MCL) (NCT03088878) and Her2-negative breast cancer (NCT02776917).

Method

- **Cell lines**: High grade serous ovarian cancer (HGSOC: **CaOV3**, **CaOV3CisR**, **PEO1**, **PEO4**) and Endometrial cancer (**Ishikawa**, **KLE**).
- The half maximal inhibitory concentration (IC50) for **cisplatin**, **paclitaxel** and the PARP inhibitor **olaparib** in each cell line at 72h was determined using the cell counting kit 8 (CCK-8).
- Cells were treated with **cirmtuzumab** at 25μg/ml or 50μg/ml for 4h prior to the addition of the chemotherapeutic agents at IC70 concentration. The effect of cirmtuzumab +/- agents for 72h was quantified using the IncuCyte S3 Live Cell Analysis System.
- Two-way ANOVA (factors: cell line and drug dose) with Tukey post-hoc test for multiple comparison adjustment was performed to analyse single dose effect of cirmtuzumab.

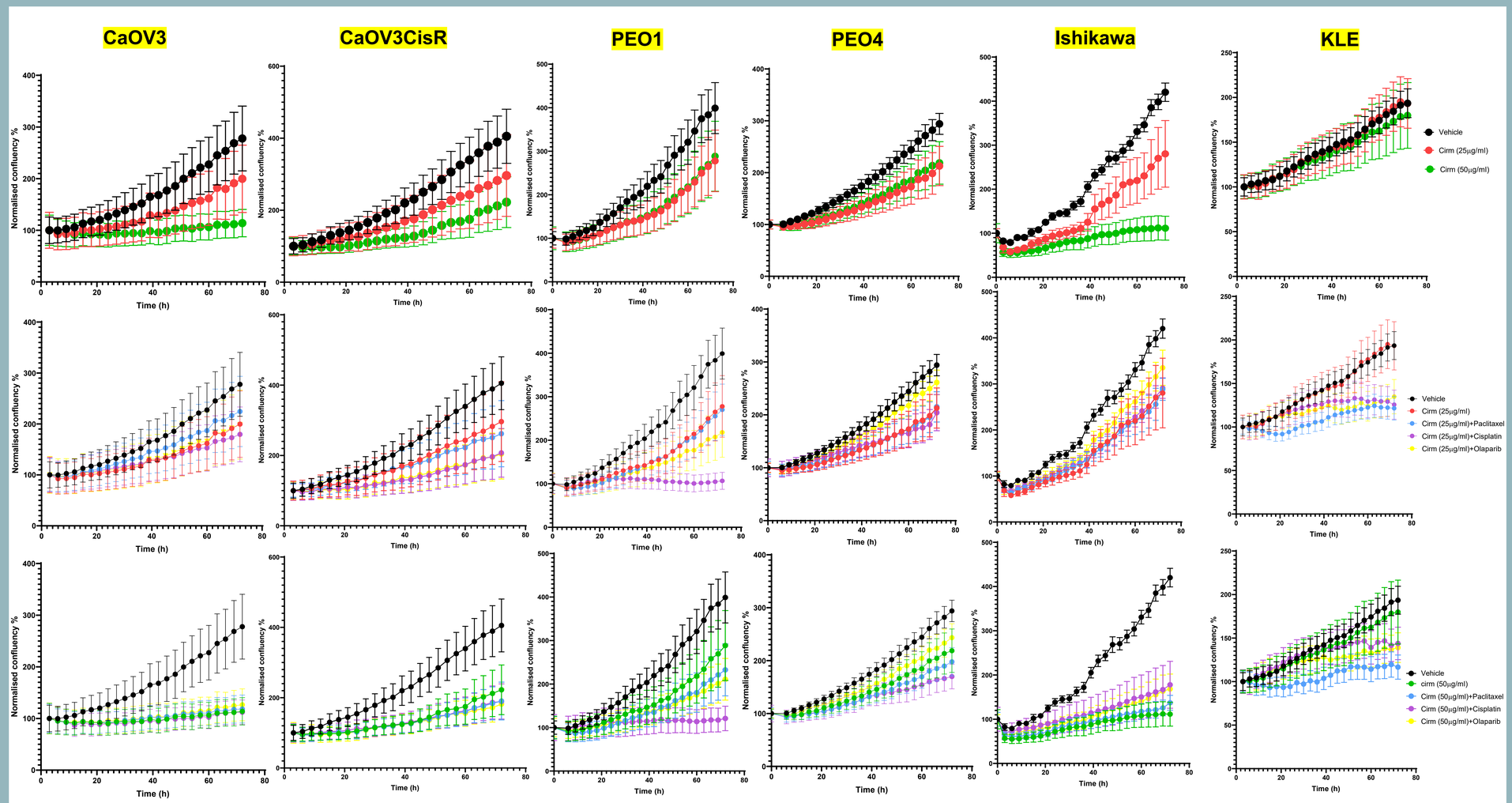

Figure 1. The effect of cirmtuzumab +/- paclitaxel, cisplatin, olaparib on high grade serous ovarian cancer cell lines CaOV3, CaOV3CisR, PEO1, PEO4 and endometrial cancer cell lines Ishikawa and KLE. For each panel, n=5, error bar SEM.

References

[1] Henry, C. E. et al., (2017). Translational oncology. [2] Liu, D. et al., (2020). Scientific reports.[3] Henry, C. et al., (2017). Oncotarget. [4] Choi, M. Y. et al., (2015). Clinical Lymphoma Myeloma and Leukemia. [5] Choi, M. Y. et al., (2019).

TAKE-HOME Messages

- Single agent of activity of cirmtuzumab was observed in HGSOC (*padj*=0.019 at 25μg/ml and 0.002 at 50μg/ml) and endometrial cancer (*padj*=0.040 at 25μg/ml and <0.001 at 50μg/ml) cell lines, including models of platinum resistance.
- Addition of cirmtuzumab enhanced the anti-proliferative effect of commonly-used chemotherapies in HGSOC and endometrial cancer cell lines.
- Further experiments investigating the synergistic effects of cirmtuzumab and other agents are underway in order to direct combination therapy in ovarian and endometrial cancer.