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RESEARCH

Dual targeting of Aurora Kinase A and poly (ADP-ribose) polymerase as a therapeutic option for patients with ovarian cancer: preclinical evaluations

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Abstract

Purpose Epithelial ovarian cancers (EOCs) are often diagnosed at an advanced stage, leading to poor survival outcomes despite chemotherapeutic and surgical advances. Precision oncology strategies have been developed to treat EOCs characterized by *BRCA1* and *BRCA2* inactivation with consequent homologous recombination (HR) repair defects. HR deficiency enhances tumor sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis), approved for EOCs as maintenance therapy, although they have been discontinued as recurrent EOC monotherapy. However, combination treatment with PARPis may be a viable alternate strategy for EOCs. Moreover, EOC patients with wild-type *BRCA* are ineligible for PARPs, necessitating novel approaches. We previously discovered that inhibiting Aurora kinase A (AURKA) downregulates PARP and BRCA1/2 expression in EOCs and may constitute a viable approach for EOCs.

Methods Herein, we evaluated combined PARPi olaparib with the selective AURKA inhibitor (AURKAi) VIC-1911 in six different patient-derived xenograft (PDX) EOC models, including two with mutant *BRCA1*, two with mutant *BRCA2*, one with mutant *BRCA1/2*, and one with wild-type *BRCA1*/2.

Results We found that combined olaparib + VIC-1911 treatment reduced tumor volumes and weights by up 90% in some PDX models, with synergistic effect compared to olaparib and VIC-1911 monotherapy. Additionally, combined olaparib + VIC-1911 treatment improved survival of mice harboring both mutant *BRCA1* and wild-type *BRCA1/2* PDXs. Generally, mice tolerated the drug combinations well during treatment, though loss of body weight was observed at higher drug dosages and with intensive treatment regimens.

Conclusion Our studies indicate a synergistic benefit from combined PARPi and AURKAi in mutant and wild-type *BRCA* EOC tumors.

Keywords Aurora kinase A · VIC-1911 · Olaparib · Poly (ADP-ribose) polymerase · *BRCA1* · *BRCA2* · Patient-derived xenograft model

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Introduction

Ovarian cancer (OC) is the fifth leading cause of cancer-related mortality among women in the United States (US) (Siegel et al. 2023). Epithelial ovarian cancers (EOCs), the most common type accounting for 90% of cases (Torre et al. 2018), are aggressive and frequently detected only at advanced stages, resulting in the highest mortality among gynecological malignancies (Siegel et al. 2023). The 5-year relative survival rates for OC are 51% overall and only around 29% for cases diagnosed at late stage (Lheureux et al. 2019). Therefore, better treatment options are needed over the current standard-of-care, which comprises primary

cytoreductive surgery followed by platinum-based chemotherapy (Lheureux et al. 2019; Gadducci et al. 2019).

Germline mutations in the breast cancer susceptibility genes, DNA-damage repair *BRCA1* and *BRCA2*, predispose carriers to EOC by impairing DNA homologous recombination (HR) repair (Lheureux et al. 2019). *BRCA1/2* mutations are present in about 14% of EOC cases (Gadducci et al. 2019; Moschetta et al. 2016), of which the largest proportion, around 60 to 70%, develop high-grade serous EOC (HGSOC) (Mavaddat et al. 2012; Pal et al. 2005). *BRCA1/2* mutations also occur more frequently in patients with platinum sensitive (38%) versus platinum resistant (17%) EOCs (Ledermann et al. 2014; Mylavarapu et al. 2018). Apart from genetic mutations, epigenetic silencing or promoter methylation of *BRCA1/2* also contributes to HR deficiency (Cancer Genome Atlas Research Network 2011; Esteller et al. 2000; Prieske et al. 2017).

After decades of few therapeutic advances for women diagnosed with EOC, inhibitors of the DNA repair protein poly (ADP- ribose) polymerase (PARP) recently emerged as important therapeutics for HGSOC (Ashworth and Lord Sep 2018; Tew et al. 2020; Lau et al. 2022). PARP inhibitors (PARPis) function according to the concept of synthetic lethality (Lord and Ashworth 2017), by exploiting vulnerabilities in tumors harboring loss-of-function *BRCA1* or *BRCA2* mutations, which become reliant on PARP for DNA repair. PARPis block PARP-mediated repair, leading to accumulated DNA damage and tumor cell death, while sparing normal cells (Pommier et al. 2016; Rose et al. 2020).

The FDA approved the first oral PARPi, olaparib (AZD2281), in 2014 for EOC patients harboring germline *BRCA* mutations who had received > 3 prior lines of chemotherapy (Tew et al. 2020). Since then, olaparib and additional first-generation PARPis, rucaparib and niraparib, have been approved for additional indications, including front-line (Moore et al. 2018; González-Martín et al. 2019) and second-line (Ledermann et al. 2012; Mirza et al. 2016; Coleman et al. 2017) maintenance therapy (Tew et al. 2020). The landmark SOLO1/GOG 3004 clinical trial demonstrated substantial benefit from maintenance olaparib therapy on progression-free survival at 7-year follow-up among women with newly diagnosed advanced OC with *BRCA1/2* mutations (DiSilvestro et al. 2023). Nevertheless, shorter overall survival in several pivotal trials, SOLO3 (olaparib), ARIEL4 (rucaparib), and ENGOT-OV16/NOVA (niraparib) recently led to the withdrawal of the recurrent monotherapy indication for mutant *BRCA* OC (Tew et al. 2022; Shahzad et al. 2024).

Combination treatment with olaparib may be a viable alternate strategy for EOCs. Indeed, maintenance olaparib with bevacizumab, an anti-angiogenic monoclonal antibody, is FDA-approved for mutant *BRCA* ovarian cancer (Ray-Coquard et al. 2019). Combination treatment can overcome concerns about the development of tumor chemoresistance to PARPi (Bhatia et al. 2024; Klotz and Wimberger 2020). There is also a therapeutic need for EOC patients with HR proficient tumors that harbor neither germline nor somatic *BRCA* mutations, currently ineligible for PARPis. Further, there are sparse therapeutic options left available to EOC patients that recur while on PARPi maintenance therapy.

Herein, we build on our prior work that identified Aurora kinase A (AURKA) as a potential avenue for unlocking novel combination therapies and options for wild-type *BRCA* EOC patients (Do et al. 2017). AURKA is a serine threonine kinase essential for mitosis (Du et al. 2021; Turaga et al. 2023), which also performs several non-mitotic functions, including a role in the DNA damage response (Bertolin and Tramier 2020) and interactions with BRCA (Hirst and Godwin 2017; Tang et al. 2017; Blanco et al. 2015; Maxwell et al. 2011). EOCs overexpress AURKA, associated with poorer overall survival and prognosis (He et al. 2015). We discovered that AURKA regulates PARP and BRCA expression and activity, and that a pharmacological AURKA inhibitor (AURKAi), alisertib, stimulates the error prone non-homologous end joining (NHEJ) repair pathway (Do et al. 2017). AURKA inhibition mimics BRCAness (Hirst and Godwin 2017), constituting an approach for wild-type *BRCA* EOCs with potential synergism combined with PARPis, satisfying unmet needs in the current arsenal of EOC therapies.

In this study, we assessed the in vivo efficacy of olaparib PARPi combined with VIC-1911 (formerly known as TAS-119) AURKAi in mutant *BRCA1/2* and wild-type *BRCA* patient-derived xenograft (PDX) EOC models. VIC-1911 is a novel selective AURKAi with anti-tumor activity in preclinical cancer models either as monotherapy or combined with other drugs (Turaga et al. 2023; Miura et al. 2021; Sootome et al. 2020). VIC-1911 has also been tested in humans for several advanced tumors in a phase I dose escalation study, demonstrating a favorable safety profile compared to prior AURKAis (Robbrecht et al. 2021). To our knowledge, neither VIC-1911 nor combined olaparib + VIC-1911 has been preclinically tested for EOC and this is the first study to report the findings in an extensive panel of PDX models of mutant and wild-type *BRCA1/2* EOC.

Materials and methods

Patient-derived xenografts

We conducted six studies of PDX EOC models, including two with mutant *BRCA1*, two with mutant *BRCA2*, one with mutant *BRCA1/2*, and one with wild-type *BRCA1/2*. Study 1 was of PDTX0205004, derived from a patient with endometrioid adenocarcinoma (grade II) combined with clear cell carcinoma harboring mutant *BRCA2*. The model

was sampled after the patient received 6 courses of paclitaxel liposome + nedaplatin chemotherapy after surgery. Study 2 was performed on PDTX0101005, derived from a patient with high-grade serous carcinoma, harboring mutant *BRCA1*. The model was sampled after the patient underwent platinum-based chemotherapy (paclitaxel + carboplatin) 6 times post-surgery. Study 3 was conducted using the ovarian PDX model OV-10–0060 with *BRCA2* mutation, originally established from a surgically resected clinical sample implanted in nude mice, defined as passage 0 (P0), which was followed by serial passages. Tumor revived from frozen P2 tumor, defined as FP3, was further passaged by serial implantation in mice; OV-10–0060 FP6 was used for this study. Study 4 employed the ovarian PDX model OV10-0079 with *BRCA1* and *BRCA2* mutations, originally established from a surgically resected clinical sample and implanted in nude mice defined as P0. P4 tumor tissue was used for this study. Study 5 was performed on the ovarian PDX model PDX 14138, originally established using tumor tissue collected from the primary site and the omentum of a patient with stage IIIc high-grade serous carcinoma with a common pathogenic germline nonsense mutation in *BRCA1* and implanted in NSG mice defined as P0. The P4 tumor tissue from these mice was used for this study. Finally, Study 6 used the ovarian PDX model PDX 12707, initiated from tumor tissue obtained from the primary site of a patient with stage IIIc high-grade serous carcinoma with wild-type *BRCA1/2* and implanted in NSG mice defined as P0. The P5 tumor tissue was used for this study.

Test product preparation

Vehicle control was 20% (2-hydroxypropyl)-β-cyclodextrin (catalog no. C485578, Aladin Scientific, Riverside, CA) in 25 mM PBS. For VIC-1911 (6 mg/mL) preparation, 36 mg of the test product (VITRAC Therapeutics, Natick, MA) was dissolved in 6.0 mL of vehicle, vortexed and sonicated until it completely dissolved. For olaparib (10 mg/mL) preparation, 0.3 mL DMSO was added to 30 mg of test product (catalog no. HY-10162, MedChem Express, Monmouth Junction, NJ), vortexed, sonicated, and placed in a 70 °C water bath until completely dissolved; 0.3 mL PEG300 was added and the solution placed in the 70 °C water bath again until complete dissolution; finally, 2.4 mL of 10% (2-hydroxypropyl)-β-cyclodextrin in PBS was added and the solution vortexed until complete dissolution. For Studies 5 and 6, VIC-1911 (75 mg/kg) was prepared in 0.5% hydroxypropyl methylcellulose, catalog no. 09963, Sigma Aldrich, St Louis, MO) and olaparib (50 mg/kg) in 10% (2-hydroxypropyl)-β-cyclodextrin). Test products were prepared before each dosing and stored at 4 °C until needed.

Experimental animals

For Studies 1 and 2 with PDTX0205004 and PDTX0101005, female NCG mice (NOD/ShiLtJGpt Prkdcem26Cd52IL-2rgem26Cd22/Gpt; GemPharmatech Co., Ltd, China) aged 5–8 weeks and weighing 18–22 g were used. For Studies 3 and 4 of PDX OV-10–0060 and PDX OV-10–0079, female NOD SCID mice (NOD.Cg-Prkdcscid/J; Zhejiang Vital River Laboratory Animal Technology, Beijing, China) aged 6–8 weeks and weighing 17–22 g were obtained. Lastly, for Studies 5 and 6 with PDX 12707 and PDX 14138, female NSG mice (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) aged 8–10 weeks and weighing 22–24 g were obtained from an in-house breeding colony at the University of Kansas Medical Center (KUMC). All in vivo efficacy studies were approved by the Institutional Animal Care and Use Committee (IACUC). IACUC protocol numbers are as follows: Studies 1 & 2 (IACUC# 1706003–4), Studies 3 & 4 (IACUC# SZ20210421-Mice-A and IACUC# ON01-003-2021v1.0, respectively), Studies 5 & 6 (IACUC# 2020–2549).

Tumor implantation and animal dosing

For Studies 1 and 2, tumor tissue ($2 \times 2x2$ mm^3) was subcutaneously inoculated into the right forelimb of each mouse. When the average tumor volume reached about 100–200 mm^3, mice were divided into four groups, control, VIC-1911, olaparib, combined VIC-1911 + olaparib (5 mice/group), by stratified randomization based on tumor volume and body weight for test product administration. Mice were continuously administered treatment for 28 days, per a dosing schedule (Supplementary Table S1). For Studies 3 and 4, each mouse was subcutaneously implanted with tumor slices (20–30 mm^3) in the right flank. When the average tumor volume reached about 180 mm^3 for OV-10–0060 and 150 mm^3 for OV-10–0079, mice were assigned into four groups, control, VIC-1911, olaparib, combined VIC-1911 + olaparib (5 mice/group), by stratified randomization based on tumor volumes. Treatment was started on day 16 and 32 after OV-10–0060 and OV-10–0079 implantation, respectively, and the testing article was administrated according to a predetermined regimen (Supplementary Table S1).

Finally, for Studies 5 and 6, each animal was subcutaneously injected with a mixture of tumor slurry (~ 1×10^6 cells) and Matrigel (catalog no. 356234, Corning) unilaterally within the dorsal flank of each animal. Once the tumors attained an average volume of ~ 200 mm^3, mice were assigned into four groups, control, VIC-1911, olaparib, combined VIC-1911 + olaparib (10 mice/group), by stratified randomization based on tumor volume. Mice were treated once daily for 31 days (PDX 14138, mutant *BRCA1* model) and 21 days (PDX 12707, wild-type *BRCA* model) according to a predetermined regimen (Supplementary Table S1).

Tumor measurements and endpoints

For all studies, animal health was monitored throughout, including weekly body weights. Animals were euthanized on the day that tumors first attained ≥ ~2000 mm^3 for Studies 1–4 and ≥ ~4000 mm^3 for Studies 5–6, as required by respective IACUC protocols or if animals showed signs of pain or distress. Otherwise, mice were sacrificed at study end, on Day 28 (for Studies 1–3) and Day 42 (for Study 4) by carbon dioxide (CO_2) asphyxiation and until survival endpoint for Studies 5–6, by CO_2 asphyxiation followed cervical dislocation and bilateral thoracotomy.

Tumor volume was the major endpoint to determine whether treatments slowed or regressed tumor growth. Tumor dimensions were measured twice and thrice weekly for Studies 1–4 and Studies 5–6, respectively, using a caliper. Volumes were expressed in mm^3 using the formula $V = 0.5\ a\ x\ b^2$, where a and b were the length and width of the tumor, respectively. Tumor volume to control ratios (T/C) were calculated from mean tumor volumes in treatment to control groups (%) on a given day, as an indicator of antitumor effectiveness. Tumor growth inhibition in tumor volume (TGI_{TV}) was calculated for each group using the formula $TGI_{TV}\ (\%) = [1-(T_i-T_0)/(V_i-V_0)] \times 100\%$, where T_i represents mean tumor volume in the treatment group on day i of test product administration, T_0 represent mean tumor volume in the treatment group on day 0 of test product administration, V_i represents mean tumor volume in the vehicle control group on day i of test product administration, and V_0 represents mean tumor volume in the vehicle control group on day 0 of test product administration. Tumor growth inhibition in tumor weight (TGI_{TW}) was recorded at study end after euthanizing surviving animals and excising and weighing tumor tissues. TGI_{TW} was calculated for each treatment group using the formula $TGI_{Tw}\ (\%) = (1-W_{\text{Mean treatment group}}/W_{\text{Mean vehicle control group}}) \times 100\%$, where $W_{\text{Mean treatment group}}$ and $W_{\text{Mean vehicle control group}}$ represent average tumor weights in the treatment and vehicle control groups, respectively.

Finally, survival was assessed in Studies 5–6.

Statistical analyses

The mean ± standard error of the mean (SEM) was plotted for tumor volumes with time. Tumor volumes and weights (at study end) in each group were expressed as mean ± SEM and compared by Kruskal–Wallis with Dunn's multiple comparisons test. Median survival was assessed by Log-rank rest from survival curves. All analyses were performed in SPSS 19.0 or Prism 8 (GraphPad, San Diego, CA) and p-values < 0.05 were considered significant.

Results

PARPi and AURKAi inhibit mutant BRCA2-PDTX0205004 tumor growth

In Study 1, PDTX0205004 tumor-bearing mice exhibited normal activity throughout the study with terminal weights that did not differ significantly by vehicle or treatment, suggesting good tolerance to the test products. VIC-1911 was dosed at 60 mg/kg BID (twice daily) for 2 weeks followed by 30 mg/kg BID for the last 2 weeks, 100 mg/kg QD (once daily) for olaparib, and combined (Fig. 1A). Tumor volumes were measured over the 28-day regimen (Fig. 1B) and, on Day 28, were significantly lower in the VIC-1911 + olaparib (353.2 mm^3; TGI_{TV} 80.6%) compared to the control (1303.3 mm^3), whereas VIC-1911 (664.3 mm^3; TGI_{TV} 54.2%) and olaparib group (1182 mm^3; TGI_{TV} 10.4%), did not differ significantly from control (Table 1). Post-treatment, tumors were excised and weighted (Fig. 1C) and were lower for VIC-1911 + olaparib (609.8 mg; TGI_{TW} 78.0%) versus control (2776 mg) while VIC-1911 (1317 mg; TGI_{TW} 52.6%) and olaparib groups (2357 mg; TGI_{TW} 15.1%) did not differ significantly from control (Table 1). Overall, VIC-1911 + olaparib treatment exerted significant synergistic effect on tumor growth inhibition against mutant *BRCA2-PDTX0205004* tumors with an intensive treatment regimen (Supplementary Table S1).

PARPi and AURKAi do not inhibit mutant BRCA1-PDTX0101005 tumor growth

In Study 2, the laboratory animals were in a good state of activity and terminal weight did not differ by vehicle or treatment group, indicating that the test products were well tolerated at 60 mg/kg BID for VIC-1911, 100 mg/kg QD for olaparib, and combined (Fig. 1D). However, tumor volume did not differ significantly in treatment versus control groups (Fig. 1E, Supplementary Table S2). TGI_{TV} was 18.7% for olaparib, 16.5% for VIC-1911, and 1.2% for VIC-1911 + olaparib groups. Post the 28-day regimen at study end, tumors were excised (Fig. 1F) and TGI_{TW} computed in VIC-1911 (24.7%), olaparib (22.0%), and VIC-1911 + olaparib (19.6%) groups (Supplementary Table S2). These treatment regimens (Supplementary Table S1) did not seem to be effective in inhibiting tumor growth.

PARPi and AURKAi inhibit mutant BRCA2-PDX-OV-10–0060 tumor growth

In Study 3, animals were dosed continuously for a period of 28 days; VIC-1911 60 mg/kg BID + olaparib 100 mg/kg

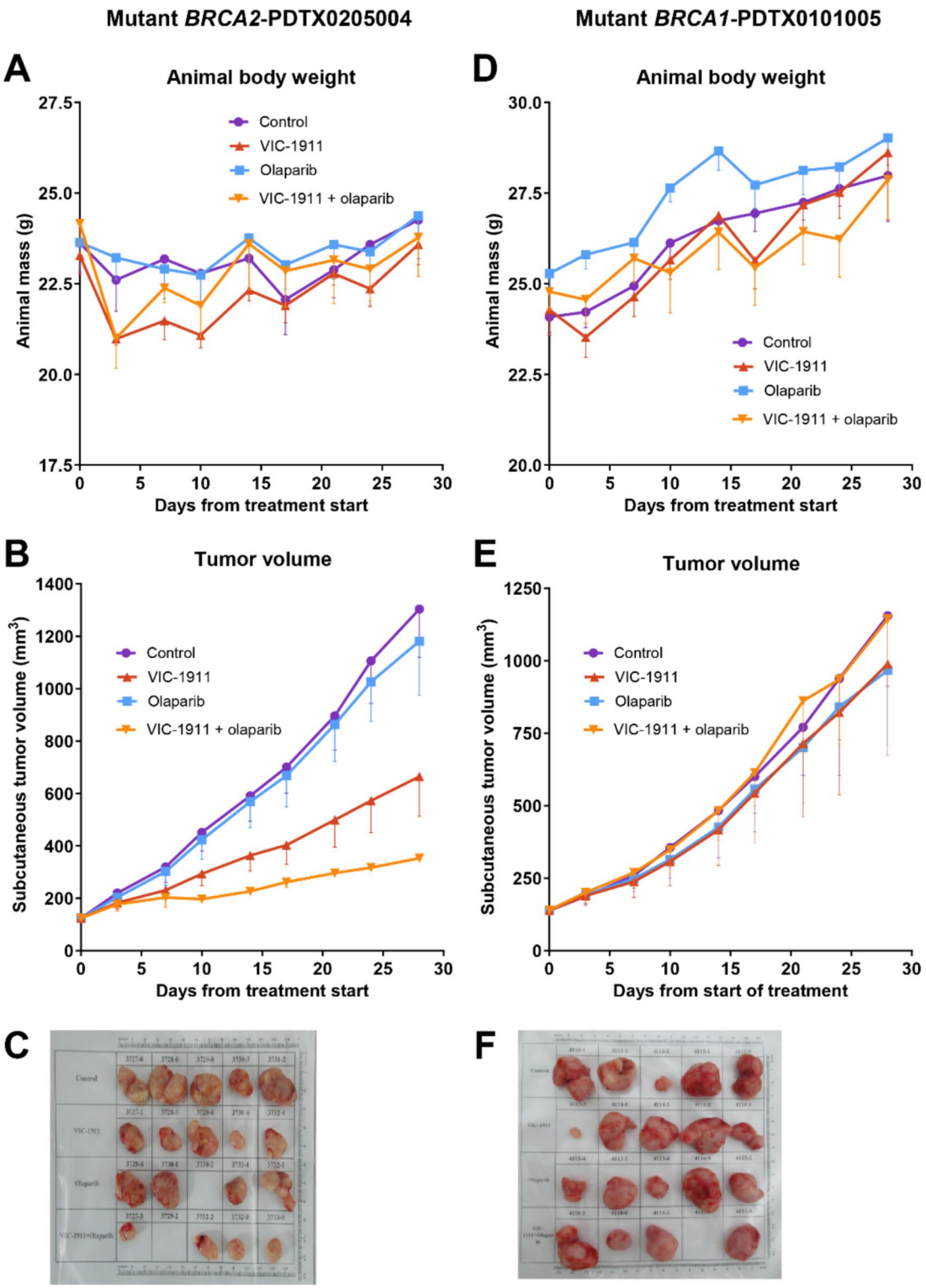

Fig. 1 Tumor efficacy study of VIC-1911, olaparib, and combined treatment on mutant *BRCA2*-PDTX0205004 and *BRCA1*-PDTX0101005 tumor-bearing mice. Longitudinal (**A**) body weights and (**B**) tumor volumes and (**C**) terminal excised tumors from mutant *BRCA2*-PDTX0205004 tumor-bearing mice in control, olaparib, VIC-1911, and combined VIC-1911 + olaparib groups. Longitudinal (**D**) body weights and (**E**) tumor volumes and (**F**) terminal excised tumors from mutant *BRCA1*-PDTX0101005 tumor-bearing mice in control, olaparib, VIC-1911, and combined VIC-1911 + olaparib groups. Data represented as mean ± SEM; n = 4–5 mice per group

Table 1 Effect of the test products on tumor volumes and weights in mutant *BRCA2*-PDTX0205004 tumor-bearing mice (Study 1)

Effect of test products on tumor volumes						
Treatment	Tumor volume (mm^3) on Day 28[a]	T/C (%)	TGI_{TV} (%)	P-value[b] (vs. control)	P-value[b] (vs. VIC-1911)	P-value[b] (vs. olaparib)
Control	1303.3 ± 183.8		–	–	–	–
VIC-1911	664.3 ± 151.3	50.9	54.2%	0.348	–	–
Olaparib	1182 ± 206.5	90.7	10.4%	> 0.999	–	–
VIC-1911 + olaparib	353.2 ± 14.2	27.1	80.6%	0.024*	> 0.999	0.085
Effect of test products on tumor weights						
Treatment	Tumor weight (mg) at study end[a]	TGI_{Tw} (%)	P-value[b] (vs. control)	P-value[b] (vs. VIC-1911)	P-value[b] (vs. olaparib)	
Control	2776 ± 472.2	–	–	–	–	
VIC-1911	1317 ± 329.4	52.6%	0.303	–	–	
Olaparib	2357 ± 345.8	15.1%	> 0.999	–	–	
VIC-1911 + olaparib	609.8 ± 57.3	78.0%	0.020*	> 0.999	0.102	

TGI_{TV}, tumor growth inhibition in tumor volume; TGI_{TW}, tumor growth inhibition in tumor weight

[a]Mean ± SEM

[b]Statistical comparison of tumor volumes on Day 28 and weights at study end between groups by Kruskal–Wallis test with Dunn's multiple comparisons, $*p < 0.05$; $n = 4–5$ mice per group

QD (Supplementary Table S1) (Fig. 2A), therefore some animals did not tolerate the treatment well. Tumor volumes were recorded over the 28-day regimen of daily treatments (Fig. 2B) and, on Day 28, volumes were decreased in VIC-1911 + olaparib (357 mm^3; TGI_{TV} 92.7%) relative to control vehicle group (2604 mm^3), but the VIC-1911 (1464 mm^3; TGI_{TV} 47.0%) and olaparib group (2286 mm^3; TGI_{TV} 13.1%) was not significantly distinct from control (Table 2). Following treatment, mice were sacrificed, and tumors were excised (Fig. 2C) and weighed; VIC-1911 + olaparib (405 mg; TGI_{TW} 84.7%) mice harbored tumors that were of significantly lower weight than control (2656 mg), although the VIC-1911 (1549 mg; TGI_{TW} 41.6%) and olaparib group (2389 mg; TGI_{TW} 10%) did not differ significantly from control (Table 2). Moreover, combined VIC-1911 + olaparib outperformed the olaparib monotherapy group in inhibiting tumor volume and weight growth. In summary, the test compound VIC-1911 combined with olaparib (28 days of 60 mg/kg VIC-1911 p.o, BID + 100 mg/kg Olaparib p.o, QD) produced significant and synergistic anti-tumor activity against the mutant *BRCA2* OV-10–0060 human ovarian PDX model.

PARPi and AURKAi do not inhibit mutant BRCA1/2-PDX-OV-10–0079 tumor growth

As for prior studies, animal body weights were monitored regularly as a surrogate of toxicity in Study 4. Mice in the single-agent VIC-1911 at (60 mg/kg BID) and combined VIC-1911 (60 mg/kg BID) and olaparib (100 mg/kg QD) groups exhibited obvious loss of body weight from the test article administration (Fig. 2D), indicating some lack of tolerability. Tumor volumes were quantitated over the 28-day regimen of daily treatments (Fig. 2E), and, on Day 28, combined VIC-1911 + olaparib (586 mm^3; TGI_{TV} 73.7%), monotherapy VIC-1911 (730 mm^3; TGI_{TV} 65.0%) group and olaparib monotherapy (1506 mm^3; TGI_{TV} 18.0%) groups did not differ significantly from control (1803 mm^3) (Supplementary Table S3). At study termination, tumors were isolated from each group (Fig. 2F) and weighed; VIC-1911 + olaparib (919.6 mg; TGI_{TW} 54.8%), VIC-1911 (1168 mg; TGI_{TW} 42.7%) and olaparib (1795 mg; TGI_{TW} 11.9%) did not differ significantly from control (2039 mg) (Supplementary Table S3). In sum, no significant differences were observed with monotherapy or combination therapy in the mutant *BRCA1/2* OV-10–0079 human PDX OC model.

PARPi and AURKAi inhibit mutant BRCA1-PDX 14138 tumor growth and improve survival

For Study 5, mice were treated daily with test products or vehicle until Day 31 when the regimen ended, and overall survival was assessed till study end. Animal weights did not differ significantly across the control and experimental groups, indicating the test products were well tolerated during (Fig. 3A) and after (Supplementary Fig. S1A) treatment. At the end of treatment (Day 31) combined VIC-1911 (75 mg/kg QD) and olaparib (50 mg/kg QD) (474.8 mm^3; TGI_{TV} 65.7) significantly decreased tumor volume growth although neither single-agent VIC-1911 (867.1 mm^3; TGI_{TV}

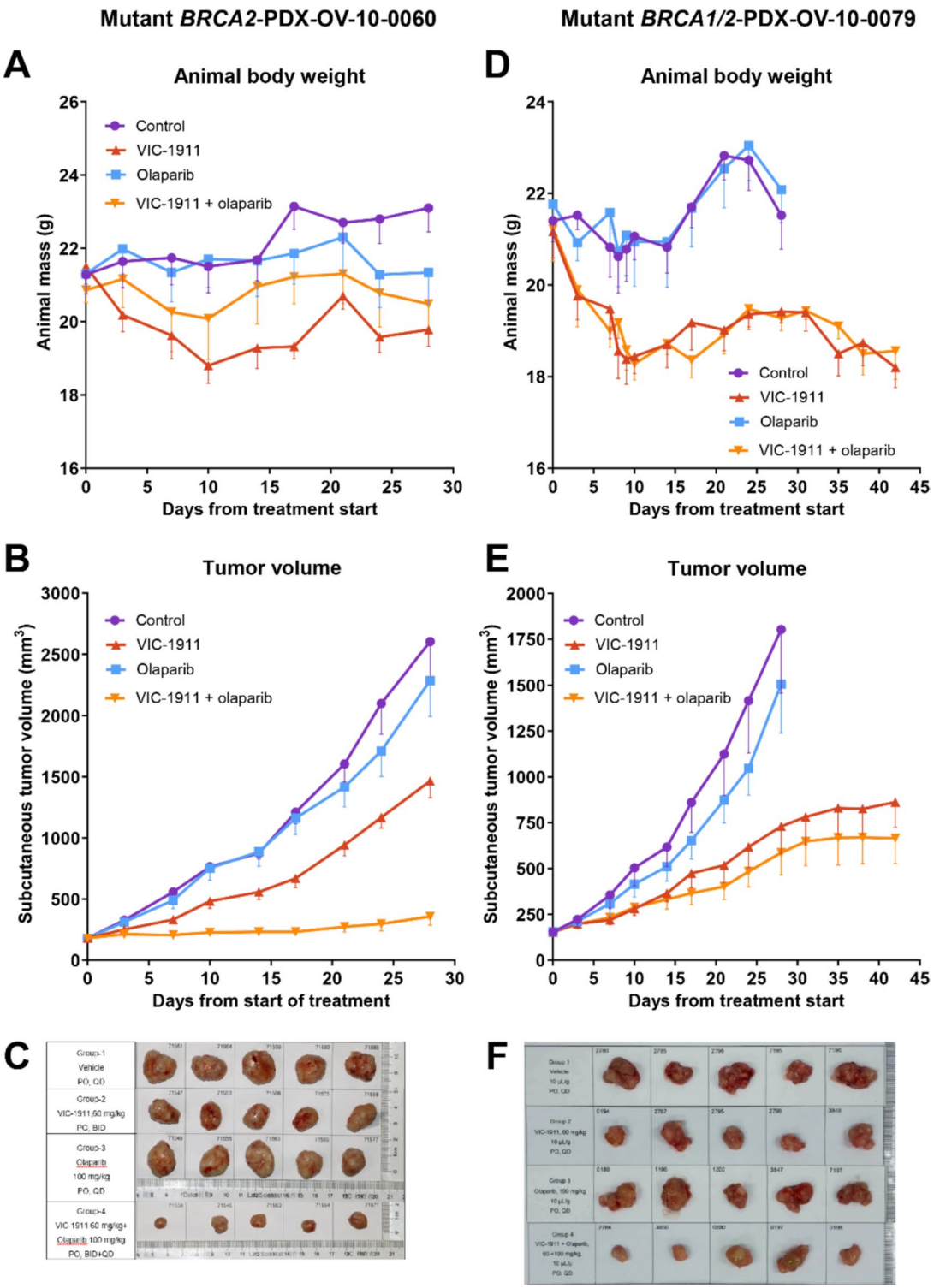

Fig. 2 Tumor efficacy study of VIC-1911, olaparib, and combined treatment on mutant *BRCA2*-PDX-OV-10–0060 and mutant *BRCA1/2*-PDX-OV-10–0079 tumor-bearing mice. Longitudinal (**A**) body weights and (**B**) tumor volumes and (**C**) terminal excised tumors from mutant *BRCA2*-PDX-OV-10–0060 tumor-bearing mice in control, olaparib, VIC-1911, and combined VIC-1911 + olaparib groups. Longitudinal (**D**) body weights and (**E**) tumor volumes and (**F**) terminal excised tumors from mutant *BRCA1/2*-PDX-OV-10–0079 tumor-bearing mice in control, olaparib, VIC-1911, and combined VIC-1911 + olaparib groups. Data represented as mean ± SEM; n = 5 mice per group

Table 2 Effect of the test product on tumor volumes and weights in mutant *BRCA2*-PDX-OV-10–0060 tumor-bearing mice (Study 3)

Effect of test products on tumor volumes						
Treatment	Tumor volume (mm^3) on Day 28[a]	T/C (%)	TGI_{TV} (%)	P-value[b] (vs. control)	P-value[b] (vs. VIC-1911)	P-value[b] (vs. olaparib)
Control	2604 ± 332.0	–	–	–	–	–
VIC-1911	1464 ± 136.6	56.2	47.0	0.253	–	–
Olaparib	2286 ± 293.6	87.7	13.1	> 0.999	–	–
VIC-1911 + olaparib	357 ± 71.3	13.7	92.7	0.002**	0.806	0.016*
Effect of test products on tumor weights						
Treatment	Tumor weight (mg) at study end[a]	TGI_{Tw} (%)	P-value[b] (vs. control)	P-value[b] (vs. VIC-1911)	P-value[b] (vs. olaparib)	
Control	2656 ± 333.7	–	–	–	–	
VIC-1911	1549 ± 140.5	41.6	0.253	–	–	
Olaparib	2389 ± 295.4	10.0	> 0.999	–	–	
VIC-1911 + olaparib	405 ± 84.7	84.7	0.002**	0.806	0.016*	

T/C, tumor volume to control ratios; TGI_{TV}, tumor growth inhibition in tumor volume; TGI_{TW}, tumor growth inhibition in tumor weight

[a]Mean ± SEM

[b]Statistical comparison of tumor volumes on Day 28 and weights at study end between groups by Kruskal–Wallis test with Dunn's multiple comparisons, *$p < 0.05$, **$p < 0.01$; $n = 5$ mice per group

30.2) nor olaparib (681.4 mm^3; TGI_{TV} 47.6) were effective compared to the control (1177 mm^3). In addition, combined therapy significantly inhibited tumor volume in comparison to VIC-1911 monotherapy (Fig. 3B, Table 3). After the treatment was stopped at Day 31, mice were followed for 144 days, until end-point symptoms or the maximum allowable tumor volume was attained (Supplementary Fig. S1B). Combined treatment significantly increased overall survival versus all other groups, control, olaparib only, and VIC-1911 only (Fig. 3C, Table 3). Representative tumors from each group excised at study Day 31 when the treatment ended are shown (Supplementary Fig. S1C). Thus, overall, combined VIC-1911 and olaparib effectively decreased tumor volume within the treatment window (31 days of 75 mg/kg VIC-1911 p.o., QD + 50 mg/kg Olaparib i.p., QD) and improved overall survival of mice bearing mutant *BRCA1*-PDX 14138.

PARPi and AURKAi do not inhibit wild-type BRCA1/2-PDX 12707 tumor growth but combined treatment improves overall survival

Finally, for Study 6, we administered test products or vehicle to mice daily until Day 21 when the regimen ended, and we evaluated overall survival till study end. Mice were weighted during that time, and no significant between group differences were noted, neither during (Fig. 3D) nor after (Supplementary Fig. S2A) treatment, indicative test products were tolerated. In this model, at the end of treatment (Day 21) no significant differences in tumor volumes were observed in combined VIC-1911 and olaparib treatment (343.4 mm^3; TGI_{TV} 69.5%), single-agent VIC-1911 (75 mg/kg; 260.4 mm^3; TGI_{TV} 84.9%) and olaparib (50 mg/kg; 255.4 mm^3; TGI_{TV} 83.5%) groups in comparison to the control (747.7 mm^3) (Fig. 3E, Table 4). After the treatment was stopped at Day 21, mice were followed for 103 days until end-point symptoms or the maximum allowable tumor volume was reached (Supplementary Fig. S2B). Combination treatment resulted in a significant overall survival benefit compared to control group (Fig. 3F, Table 4), but not from either single-agent VIC-1911 or olaparib alone. Representative tumors from each group excised at Day 21 when treatment was ended are shown (Supplementary Fig. S2C). Thus, in conclusion, combined VIC-1911 and olaparib and single-agents did not reduce tumor volume during the treatment window whereas combined VIC-1911 and Olaparib (21 days of 75 mg/kg VIC-1911 p.o., QD + 50 mg/kg Olaparib i.p., QD) enhanced overall survival of mice bearing wild-type *BRCA1/2*-PDX 12707.

Discussion

PARP inhibitors have become indispensable therapeutics for treating women diagnosed with advanced high-grade serous/endometrioid ovarian cancer whose tumors display homologous recombination deficiency. PARPis are available to patients, in both the first-line and recurrent platinum-sensitive disease settings; however, the majority of

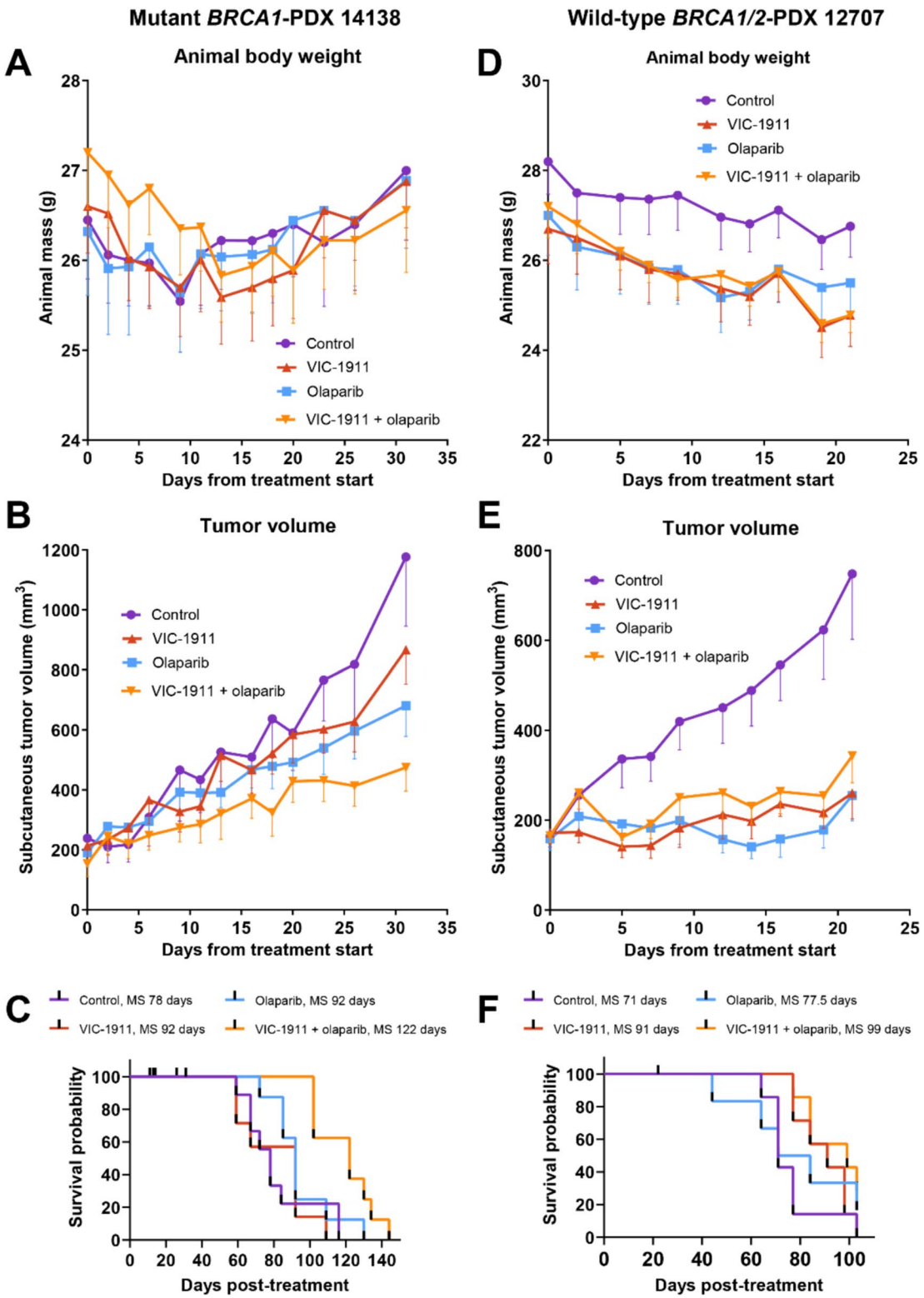

Fig. 3 Tumor efficacy study of VIC-1911, olaparib, and combined treatment on mutant *BRCA1*-PDX 14138 and wild-type *BRCA1/2*-PDX 12707 tumor-bearing mice. Longitudinal (**A**) body weights and (**B**) tumor volumes and (**C**) survival of mutant *BRCA1*-PDX 14138 tumor-bearing mice in control, olaparib, VIC-1911, and combined VIC-1911 + olaparib groups. Longitudinal (**D**) body weights and (**E**) tumor volumes and (**F**) survival of mutant wild-type *BRCA1/2*-PDX 12707 tumor-bearing mice in control, olaparib, VIC-1911, and combined VIC-1911 + olaparib groups. Data represented as mean ± SEM; n = 8–10 mice per group

Table 3 Effect of the test product on tumor volumes and survival in mutant *BRCA1*-PDX 14138 tumor-bearing mice (Study 5)

Effect of test products on tumor volumes						
Treatment	Tumor volume (mm^3) on Day 31[a]	T/C (%)	TGI_{TV} (%)	P-value[b] (vs. control)	P-value[b] (vs. VIC-1911)	P-value[b] (vs. olaparib)
Control	1177 ± 231.0	–	–	–	–	–
VIC-1911	867.1 ± 114.8	73.6	30.2	> 0.999	–	–
Olaparib	681.4 ± 102.5	57.9	47.6	0.533	–	–
VIC-1911 + olaparib	474.8 ± 78.5	40.3	65.7	0.007**	0.049*	0.838
Effect of test products on survival						
Treatment	Median survival (days)		P-value[c] (control vs. other groups)	P-value[c] (vs VIC-1911)	P value[c] (vs Olaparib)	
Control	78		–	–	–	
VIC-1911	92		0.175	–	–	
Olaparib	92		0.832	–	–	
VIC-1911 + olaparib	122		0.001**	0.001**	0.016*	

T/C, tumor volume to control ratios; TGI_{TV}, tumor growth inhibition in tumor volume

[a]Mean ± SEM

[b]Statistical comparison of tumor volumes on Day 31 between treatment and control groups by Kruskal–Wallis test with Dunn's multiple comparisons, $*p < 0.05$, $**p < 0.01$; $n = 8$–10 mice per group

[c]Statistical comparison of survival by Log-rank (Mantel-Cox) test, $*p < 0.05$, $**p < 0.01$

Table 4 Effect of the test product on tumor volumes and survival in wild-type *BRCA1/2*-PDX 12707 tumor-bearing mice (Study 6)

Effect of test products on tumor volumes						
Treatment	Tumor volume (mm^3) on Day 21[a]	T/C (%)	TGI_{TV} (%)	P-value[b] (vs. control)	P-value[b] (vs. VIC-1911)	P-value[b] (vs. olaparib)
Control	747.7 ± 145.6	–	–	–	–	–
VIC-1911	260.4 ± 57.3	34.8	84.9	0.081	–	–
Olaparib	255.4 ± 56.6	34.1	83.5	0.081	–	–
VIC-1911 + olaparib	343.4 ± 59.9	45.9	69.5	0.510	> 0.999	> 0.999
Effect of test products on survival						
Treatment	Median survival (days)		P-value[c] (control vs. other groups)	P-value[c] (vs VIC-1911)	P-value[c] (vs olaparib)	
Control	71		–	–	–	
VIC-1911	77.5		0.503	–	–	
Olaparib	91		0.145	–	–	
VIC-1911 + olaparib	99		0.021*	0.170	0.350	

T/C, tumor volume to control ratios; TGI_{TV}, tumor growth inhibition in tumor volume

[a]Mean ± SEM

[b]Statistical comparison of tumor volumes on Day 21 between groups by Kruskal–Wallis test with Dunn's multiple comparisons, n = 10 mice per group

[c]Statistical comparison of survival by Log-rank (Mantel-Cox) test, $*p < 0.05$

patients eventually acquire resistance to PARP inhibitors and succumb to their disease. The goal of curative intent has become, for the first time, an achievable outcome in some ovarian cancer patients harboring germline or somatic *BRCA* mutations, in large part due to PARPis, a result that was unimaginable only a decade ago. Biomarker testing, including *BRCA* mutation status and testing for HRD and genomic instability, is critical to identify patients most likely to benefit from PARPi therapy and guide treatment decisions (Frey and Pothuri 2017). Although PARPis have

transformed the ovarian cancer treatment landscape, we are still far off from curing most patients. A recent systematic review and meta-analysis found that 5-year survival rates of *BRCA*-mutated OC patients have increased significantly, but that longer-term 10-year survival rates have not improved as much (Nahshon et al. 2022). Furthermore, the recurrent monotherapy indication for olaparib, rucaparib, and niraparib has recently been withdrawn based on disappointing overall survival results in several recent highly anticipated clinical trials (Tew et al. 2022; Shahzad et al. 2024). While maintenance PARPi therapy continues to demonstrate tangible and significant benefits to *BRCA*-mutant EOC patient outcomes (DiSilvestro et al. 2023), new approaches are needed, especially with recurrent EOC.

Additionally, most women with EOCs lack *BRCA* mutations, and account for approximately 86% of the patient population (Gadducci et al. 2019; Moschetta et al. 2016). The American Society of Clinical Oncology does not currently recommend PARPi monotherapy for ovarian cancer patients with wild-type *BRCA* (Tew et al. 2020, 2022). Rucaparib maintenance therapy is on a may-recommend basis upon first and second remission whereas niraparib is on a may-recommend basis upon first remission. Indeed, in the VELIA trial, veliparib did not confer any significant benefits to disease progression or survival in ovarian cancer patients with wild-type *BRCA* or with HRD-negative tumors (Coleman et al. 2019). Similarly, combined olaparib and bevacizumab maintenance therapy in the PAOLA-1 trial did not improve outcomes compared to bevacizumab maintenance therapy alone in OC patients with wild-type *BRCA* or with HRD-negative tumors (Ray-Coquard et al. 2019). Therefore, this EOC patient population needs additional therapeutic options.

The recent failures of PARPi recurrent monotherapy in women with mutant *BRCA* ovarian tumors prompts a realignment in treatment approaches, for instance by combination treatment to overcome potential concerns about the development of PARPi resistance (Bhatia et al. 2024; Klotz and Wimberger 2020). Further, novel approaches are needed to benefit patients with wild-type *BRCA* ovarian cancer. Herein, to address both needs, we examined PARPi olaparib combination therapy as a possible route forward, paired with an AURKA inhibitor, VIC-1911. This combination was based on our prior research in ovarian cancer cells, which discovered that AURKAi with alisertib promoted the activity of PARP, essential for NHEJ repair, an error-prone pathway of the cellular repair machinery, with a tandem drop in levels of BRCA1/2, vital for higher-fidelity HR repair (Do et al. 2017). This dual effect of AURKAi on DNA repair pathways rendered ovarian cancer cells incapable of effectively repairing DNA, with consequent increase in cell death. In cells already lacking *BRCA*, we expected an amplifying impact of additionally inhibiting AURKA. Indeed, alisertib most effectively curbed proliferation of PEO1, a mutant *BRCA2* and HRD ovarian tumor cell line susceptible to the PARPi rucaparib (Do et al. 2017).

In this study, we built on these earlier results, finding a positive synergistic effect from combined olaparib plus VIC-1911 on tumor growth, either volume or weight, or overall survival than either test article alone in three out of the five ovarian cancer PDXs harboring mutant *BRCA*, in support of our hypothesis. However, VIC-1911 monotherapy did not effectively inhibit tumor growth in vivo in the mutant *BRCA* OC PDXs assessed, in contrast with our earlier findings in ovarian cancer cell lines (Do et al. 2017). Additionally, single-agent olaparib did not curb tumor growth in any of the mutant *BRCA* OC PDXs.

We observed contrasting results between the two different studies with mutant *BRCA1* models (Studies 2 and Studies 5). This could be attributed to smaller sample size and shorter treatment regimen in Study 2, where we observed no significant differences, versus Study 5 with positive changes in tumor growth and overall survival. Similarly, with the double mutant *BRCA1/2* model (Study 4), we observed significant body weight loss indicating some toxicity from VIC-1911 monotherapy and combination treatment. We observed a trend in reduced tumor volumes in this Study 4, but lack of tolerability may have impacted tumor growth. Hence, additional studies are needed to evaluate whether the combined treatment has an effect in double mutant *BRCA1/2* models.

Nevertheless, olaparib synergized with VIC-1911, as we anticipated, indicating a potential role for PARPis in combination therapy, even in tumors not susceptible to olaparib alone. Although combined olaparib plus bevacizumab is approved to treat ovarian cancer patients with mutant *BRCA* as maintenance therapy (Ray-Coquard et al. 2019), our research herein highlighted the feasibility of PARPi combination treatment as well. Indeed, PAPRis continue to be evaluated in clinical trials in combination with a wide spectrum of additional agents of diverse mechanisms of action (Boussios et al. 2019). These approaches have included a PARPi combined with agents targeting alternate aspects of the DNA repair machinery, such as a phase I trial of prexasertib, an inhibitor of CHK1 (Do et al. 2021), a coordinator of the DNA damage response, and a phase II trial of ceralasertib, an inhibitor of ATR (Wethington et al. 2023), a DNA damage-sensing kinase that activates the DNA damage checkpoint. These clinical studies further bolster our approach of combining a PARPi with an AURKAi.

Other combination candidates that have been assessed in early-phase clinical trials have spanned PI3K inhibitors, such as BKM120 (Matulonis et al. 2017) and alpelisib (Konstantinopoulos et al. 2019), the AKT inhibitor AZD5563 (Westin et al. 2017), and the mTORC1 inhibitor vistusertib (Westin et al. 2018) combined with olaparib in phase I trials. Additionally, the VEGFR inhibitor cediranib (Nicum et al. 2024;

Liu et al. 2014) combined with olaparib has attained phase II trials. There is also interest in the intersection between PARPis and immunotherapy in OC (Maiorano et al. 2022), and the PD-1 inhibitor pembrolizumab (Konstantinopoulos et al. 2019) and PD-L1 inhibitor durvalumab (Drew et al. 2018) have been evaluated combined with PARPi in phase I and/or II trials. Although some of these combination therapies demonstrated some clinical benefit, including in ovarian cancer patients that had progressed on PARPi (Do et al. 2021), none have reached clinical use.

Another crucial insight gained from this present study was the impact of combined olaparib and VIC-1911 treatment on the wild-type *BRCA1/2*-PDX 12707 OC PDX. The rationale for assessing the efficacy of olaparib and VIC-1911 in the wild-type *BRCA* PDX arose from our earlier work, which found that AURKAi simulated BRCAness (Do et al. 2017). We posited, thereby, that AURKAi would also render wild-type *BRCA* ovarian tumors susceptible to PARPis despite the lack of deactivating *BRCA* mutations. Aligned with this notion, we had found that the AURKAi alisertib inhibited the proliferation of PEO4 (*BRCA2* revertant cells derived from the recurrent tumor of the same patient as PEO1) and SKOV3ip2 OC cell lines, both which possess functional BRCA1 and BRCA2 proteins and both of which are resistant to rucaparib (Do et al. 2017). Alisertib additionally hindered the wild-type *BRCA1/2* cell line OVCA429, also lacking deleterious *BRCA* mutations, but which was also modestly sensitive to rucaparib.

Here, we extend this concept in vivo in an ovarian cancer wild-type *BRCA* PDX model. We found that combined olaparib and VIC-1911 treatment significantly increased median survival of PDX 12707-harboring mice, in support of our hypothesis on AURKAi-induced BRCAness in wild-type *BRCA* ovarian tumors. Interestingly; however, the combined treatment did not curb tumor volume during the treatment phase. The reason for the differential results by tumor volume and survival remain unclear, and possibly point to effects beyond the primary tumor, although investigation is needed to definitively address this.

Combination of PARPi with other treatments have also been clinically evaluated for ovarian cancer patients with wild-type *BRCA*; (Matulonis et al. 2017; Westin et al. 2017; Nicum et al. 2024; Konstantinopoulos et al. 2019) interestingly, the PI3K inhibitor BKM120 achieved partial remission in half of wild-type *BRCA* ovarian cancer trial participants (n = 9) in a small phase I dose escalation trial (Matulonis et al. 2017). Similarly, the phase I/II trial of niraparib paired with the PD-1 inhibitor pembrolizumab noted comparatively better responses than anticipated in women with ovarian cancer that lacked tumor *BRCA* mutations or were HR proficient (Konstantinopoulos et al. 2019). Although small and very preliminary, these early-phase clinical trials indicate feasibility of PAPRi combination treatment. Additionally, preclinical investigation in OC models especially support coupling of a PARPi with another therapeutic targeting alternate DNA repair pathways (Xie et al. 2024), such as our strategy with AURKAi.

Our last important finding was on the safety profile of combined VIC-1911 and olaparib using body weight as a surrogate of tolerability. In most instances, the combination was tolerated well, with only marginal non-significant weight loss in most animals receiving treatment. Mice that received olaparib (100 mg/kg QD) and VIC-1911 (60 mg/kg BID) (Studies 3 and 4) were at greater risk of body weight loss than mice that received the same dose on an on–off schedule (Studies 1 and 2), as might be expected. Mice in Studies 5 and 6 were administered lower doses of olaparib (50 mg/kg QD) but higher doses of VIC-1911 (75 mg/kg QD) were well-tolerated. Although weight loss in mice is only a surrogate measure of drug tolerability, a phase I dose escalation study of VIC-1911 in participants with various advanced tumors deemed it to exhibit a more favorable safety profile compared to prior AURKAis (Robbrecht et al. 2021). Dose-limiting toxicities included nausea, ocular toxicity, and fatigue, and the recommended phase 2 dose was determined to be 200 mg, twice daily, following an on–off schedule. In sum, AURKAi via VIC-1911 may demonstrate a tolerable safety profile, and our mouse studies herein suggest combination with olaparib may be feasible, though first-in-human studies would be needed to definitely address this possibility.

This study had some limitations and strengths. Among the limitations was the small sample sizes in some of the PDX studies. Due to the lack of available tumor tissues, we were unable to assess additional mechanistic pathways that could have contributed to the observed changes across treatments (monotherapy versus combined) and between tumor models (mutational status and type of patient-derived tumor). Further studies are needed to understand these mechanistic changes and changes in key proteins with treatment. Nevertheless, among the strengths was the large number of diverse PDXs of varied *BRCA* status derived from OCs of various grades following different treatments, increasing the generalizability of our findings. Various mouse strains were used, and studies were conducted across different institutes, also bolstering generalizability. Furthermore, we evaluated a variety of dosing regimens for olaparib, VIC-1911, and combined treatment. Finally, our study tested a novel hypothesis for AURKAi studies by including an OC PDX harboring wild-type *BRCA*.

Overall, we report in vivo findings from combined olaparib and VIC-1911 treatment in six different EOC PDX models, harboring wild-type *BRCA1/2*, mutant *BRCA1*, mutant *BRCA2*, and double-mutant *BRCA1/2*. We found that combined olaparib and VIC-1911 treatment reduced tumor volumes and weights by up 90% in

some PDX models during the treatment phase, with synergistic effect compared to either olaparib or VIC-1911 monotherapy.

Additionally, combined olaparib and VIC-1911 treatment improved survival of mice harboring both mutant *BRCA1* and wild-type *BRCA1/2* PDXs. Our results herein pave the way forward for new avenues to treat women with advance forms of ovarian cancers, both mutant and wild-type *BRCA*, by further leveraging AURKAi-induced impairment in the cellular DNA repair machinery.

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Author contributions Study design: HBP, LJP, TJM, AL and AKG; Experimental work: SLH, AG, and RVP; Data collection, interpretation, and analysis: SMT, SLH, MGS, AG, RVP, HBP, LJP, TJM, AL and AKG; article writing: SMT, MGS, and AKG; Correction and final revision: SMT, MGS, HBP, LJP, TJM, and AKG; Approval of the study: All authors.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest LJP and TJM are employees of VITRAC Therapeutics, LLC. AKG reports research funding from Predicine and VITRAC Therapeutics, is a co-founder of Sinochips Diagnostics, and serves as a scientific advisory board member to Biovica, Clara Biotech, and Sinochips Diagnostics. The remaining authors report no conflicts of interest.

Ethical approval All studies were approved by the Institutional Animal Care and Use Committee.

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