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Comment on evolutionary dynamics of cancer multidrug resistance in response to olaparib and photodynamic therapy

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Poly-ADP ribose polymerase (PARP) inhibitors have transformed the treatment landscape of patients with high grade serous and high grade endometrioid ovarian cancer [1]. Landmark phase III randomized trials assessing the role of PARP inhibitors—olaparib, niraparib, rucaparib, veliparib— as an oral maintenance strategy in the front-line and platinum sensitive recurrent setting, have demonstrated benefit in progression free survival without major differences in quality of life when compared to placebo [1]. More recently, long-term follow-up from SOLO-2 study (NCT01874353), demonstrated a benefit in overall survival with maintenance olaparib, compared to placebo, in patients with mutations in *BRCA1/2* and a platinum sensitive relapse [2]. Despite this promising activity, ultimately the majority of patients with recurrent disease will develop resistance to PARP inhibitor therapy. Alterations in *BRCA1/2* and other genes related to homologous recombination repair have emerged as biomarkers of response to PARP inhibition in ovarian cancer [1], but a current challenge includes the lack of accessible biomarkers to detect acquired resistance in individual patients and collectively. There is additionally unmet need for development of new drugs or combination strategies to overcome PARP inhibitor resistance.

Globally, three main mechanisms of PARP inhibitor resistance have been proposed: 1) Drug-target related mechanisms, including upregulations of drug-efflux pumps, 2) Restoration of homologous recombination, such as reversion mutations in *BRCA1/2*, and 3) Loss of DNA end protection and/or restoration of the replication fork (Fig. 1) [3,4]. Among the drug-target related mechanisms, upregulation of the ABCB1 pump, also called P-glycoprotein, reduces cellular drug availability, and is a proposed to be a mechanism of acquired resistance to chemotherapy and PARP inhibition in ovarian cancer (Fig. 1). The frequency of upregulations in *ABCB1* in pre-treated ovarian cancer is not well established and depends on prior therapy exposure, such as taxanes and PARP inhibitors [4]. Patch et al. performed whole genome sequencing in matched ovarian cancer samples (primary and recurrence) showing that 8% of recurrence samples harboured upregulations in *ABCB1* [5]. Similarly, in a post-PARP inhibitor phase II clinical trial assessing the combination of olaparib and cediranib (an oral, small molecule selective vascular endothelial growing factor tyrosine kinase inhibitor) in patients with ovarian cancer previously treated with PARP inhibitors, 15% of the population presented with upregulations in *ABCB1* at baseline [6]. Those with *ABCB1* overexpression had comparatively poorer outcomes. Intriguingly, half of the patients with *ABCB1* upregulation also harboured other resistance mechanisms, suggesting that multiple cellular pathways may contribute to acquired PARP inhibitor resistance [6].

Targeting *ABCB1* in ovarian cancer is an intriguing strategy. In the manuscript accompanying this commentary, Baglo and colleagues propose that the combination of olaparib and photodynamic therapy (PDT) may be synergistic, and thatPDT using a lipidated photosensitizer, which has reduced efflux through the ABCB1 pump, may be able to overcome drug-target related resistance to PARP inhibition in ovarian cancer [7]. PDT is purportedly able to activate photosensitizers within tumours to induce chemical damage and tumor death [8]. Single-agent PDT has a limited role in advanced ovarian cancer. However, combining PDT with current standard of care therapy may prove to be promising in managing multidrug resistance [8].

Baglo and colleagues assessed the combination of olaparib and PDT in ovarian cancer cell lines [7]. Two kinds of photosensitizers were used, the benzoporphyrin derivate (BPD) and its lipidated formulation. While BPD is a substrate of the ABCB1 pump, its lipidated formulation can reduce the BPD efflux and may help abrogate P-glycoprotein resistance [7,9]. In the study, two matched fluorescent high grade serous ovarian cancer cell lines were used to assess cell viability. The sensitive subline

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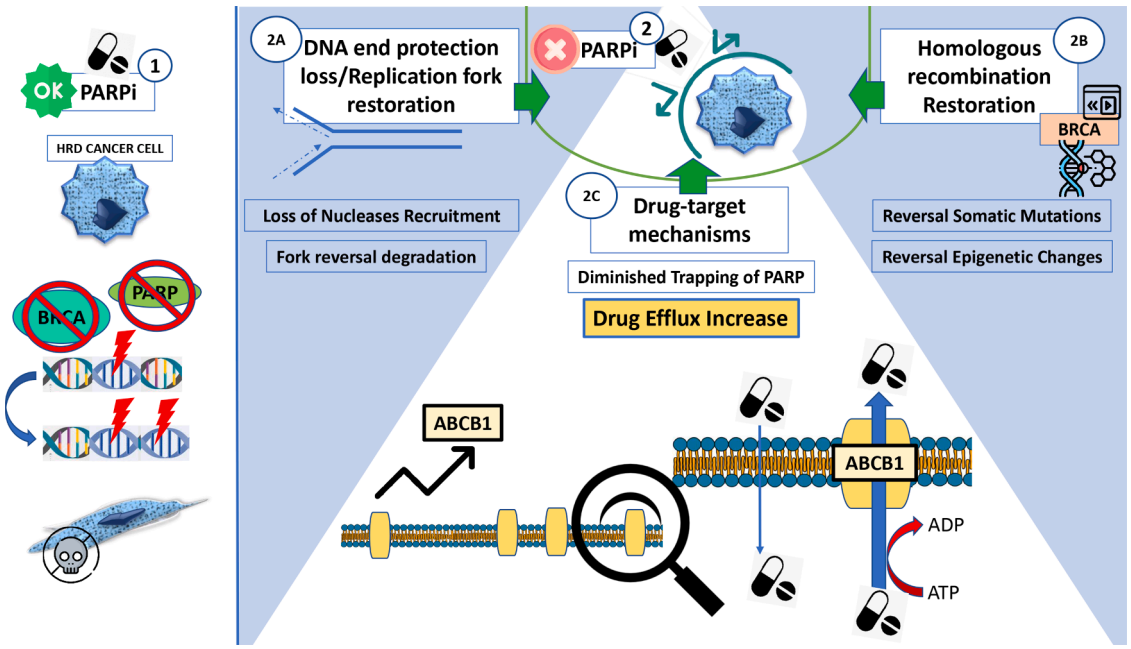

Fig. 1. Mechanisms of acquired PARP inhibitor resistance in ovarian cancer. **1.** PARP enzymes are responsible for single strand break repairs in the DNA through base excision repair pathway. DNA double strand break repair is impared in homologous recombination deficient (HRD) cells. The HRD cancer cells are sensitive to PARP inhibition, and vulnerable to death given the synthetic lethality effect of blocking PARP. **2.** Acquired resistance to PARP inhibition is represented by: **2A.** DNA end protection loss and/or replication fork restoration, which may occur due to loss of nucleases recruitment and fork reversal degradation. **2B** Homologous recombination restoration, represented mainly by the acquired somatic mutations or epigenetic changes, restoring the function of homologous recombination proteins. **2C.** Drug-target mechanisms, including diminishment of trapping of PARP and increase of the drug efflux. The former is secondary to the overexpression of the ABCB1 trans-membranal drug efflux pump. The PARP inhibitor is diffused into the cell, without the need of any mediator. The ABCB1 pump is overexpressed in the cell membrane, increasing the efflux of the PARP inhibitor, and reducing the intracellular PARP inhibitor concentration.

harboured an inactivation of *BRCA1* due to methylation (a known biomarker of response to PARP inhibition) [1]. The resistant subline of the co-culture overexpressed P-glycoprotein. Following treatment with single agent olaparib significant decrease in the total cell count was noted [7]. However, the resistant subline was selected. Using a lower dose of olaparib (10 μM), multicycle olaparib and PDT was more effective in reducing the total cell number, compared to single agent therapy. In terms of the subline selection, the olaparib and BPD-based PDT combo was more effective in reducing the sensitive co-culture than the resistant one, showing a dominance of the resistant cells. Interestingly, when olaparib was combined to the lipidated BPD-based PDT, mitigation of resistant cells was more effective. Another important finding from the cell line study from Baglo and colleagues was the demonstration of mechanistic synergy between PDT and olaparib by an enhancement of the DNA damage response (increased p-H_2AX expression), compared to single-agent olaparib or PDT alone.

Acknowledging the limitations of a cell line study, the role of PDT in combination with olaparib is interesting and warrants confirmation in mouse models prior to translating it to clinic. An intriguing analysis would include assessing the role of PDT in combination with other approved PARP inhibitor therapies for ovarian cancer. In fact, both niraparib and veliparib are poor substrates of ABCB1, and may evade this mechanism of resistance more easily [3]. Additional work is needed to optimize the delivery of the photosensitizer and light into the intra-peritoneal cavity. The peritoneal delivery strategies proposed by Baglo and colleagues include intra-operatively and via intra-peritoneal catheter, a strategy which would not currently align with standard timelines for administration of maintenance PARP inhibitors in advanced ovarian cancer [7]. This approach may however be applicable in future in line with work, highlighting those who may benefit from PARP inhibition without the use of chemotherapy (NCT02489006, NCT02855944) [10].

As the indications for PARP inhibitors in ovarian cancer expand rapidly, a focus on drug development in the post-PARP space, particularly in the face of acquired drug resistance, is paramount. A rational re-sensitization approach seeks to exploit synergistic biology, particularly in patients where PARP inhibitors are likely to have ongoing therapeutic effect. Recent examples of such work include: the CAPRI trial (NCT03462342), which examined the combination of olaparib with ceralasertib, an ATR inhibitor, specifically in recurrent, platinum-sensitive homologous recombination-repair deficient ovarian cancer population [11]; and the EFFORT trial (NCT03579316), which was a randomized, non-comparative, two-arm phase II trial of adavosertib, a wee1 inhibitor, with or without olaparib in any recurrent high-grade serous ovarian cancer patients who had previously progressed on PARPi [12]. The robust preclinical work in PDT and ovarian cancer completed by Baglo and colleagues has the potential to translate to successful early-phase clinical trials – another important potential development to add to the armamentarium of therapeutics rationally designed to overcome PARP inhibitor resistance.

CRediT authorship contribution statement

Ainhoa Madariaga: Conceptualization, Writing – original draft, Writing – review & editing. **Lawrence Kasherman:** Writing – review & editing. **Michelle McMullen:** Writing – review & editing. **Luisa Bonilla:** Writing – review & editing.

Declaration of Competing Interest

AM has received honoraria from Astrazeneca. The rest of authors have no conflicts of interest to declare.

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