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PARP inhibitors in ovarian cancer

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ABSTRACT

Poly-ADP-ribose polymerase inhibitors (PARPis) are the most active and interesting therapies approved for the treatment of epithelial ovarian cancer. They have changed the clinical management of a disease characterized, in almost half of cases, by extreme genetic complexity and alteration of DNA damage repair pathways, particularly homologous recombination (HR) deficiency. In this review, we provide an updated overview of the available results of recent clinical trials on the three Food and Drug Administration and European Medicines Agency approved PARPis in ovarian cancer: olaparib, niraparib, and rucaparib. Furthermore, we anticipate the future perspective of combination regimens with antiangiogenic, immunocheckpoint inhibitors, and other biological agents as strategies to overcome resistance mechanisms, potentiate the therapeutic efficacy, and expand their clinical use in non-HR deficient tumors.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological disease due to its insidious nature and ineffectiveness of screening tests for early detection [1]. Frank symptoms appear once the tumor has spread from ovary into peritoneal cavity, thereby causing 70% of patients to present with advanced disease at diagnosis; moreover, only 20–40% of patients with stage III or IV cancer receiving surgery and chemotherapy are still alive 5 years after diagnosis. In this setting, the best approach is represented by optimal cytoreductive surgery followed by platinum-based chemotherapy, with the addition of bevacizumab in first line treatment of "high risk" patients to improve both progression free survival (PFS) and overall survival (OS) [2]. Platinum-free interval (PFI), commonly defined as the time frame from the last platinum dose of the front-line therapy to the date of relapse, remains an important prognostic and predictive factor for response to subsequent lines of chemotherapy in recurrent ovarian cancer (ROC). However, in the era of precision medicine, an improved understanding of biological features and mechanisms of ovarian cancer (OC) has led to the identification of other factors able to modulate treatment response, thus allowing overcoming the dichotomous outdated classification of patients into platinum-sensitive and platinum-resistant) [3]. In this regard, breast related cancer antigens (BRCA) and homologous recombination deficiency (HRD) status can be considered as novel predictive biomarkers of response to chemotherapy as well as to poly-adenosine diphosphate (ADP) ribose polymerase (PARPs) inhibitors (PARPis) treatment [4].

Mechanism of action of PARPs and PARPs inhibitors

PARPs are a family of 17 nucleoproteins characterized by a common catalytic site that transfers an ADP-ribose group on a specific acceptor protein using NAD^+ as cofactor. Interestingly, most PARP members are able to transfer only a mono-ADP ribose group to their target proteins, whereas PARP1, PARP2, PARP3, PARP5a, PARP5b characteristically add repeated ADP-ribose units, thus generating long poly(ADP-ribose) (PAR) chains [5]. This post-translational protein modification is named PARylation and allows PARPs involvement in different cellular activities. In this regard, PARP1 is the best characterized PARP. PARP1 modulates chromatine structure via PARylation of core histone proteins resulting in chromatine relaxation, thus enabling replication, repair, and transcription processes [6]. As to transcription, PARP1 plays a pivotal role in its regulation by both serving as a transcriptional cofactor and by hindering methylation of specific sequences, like those of housekeeping genes (Fig. 1a/b). To date, activation of PARP-1, dependent on CCCTC binding factor (CTCF), appears to affect DNA

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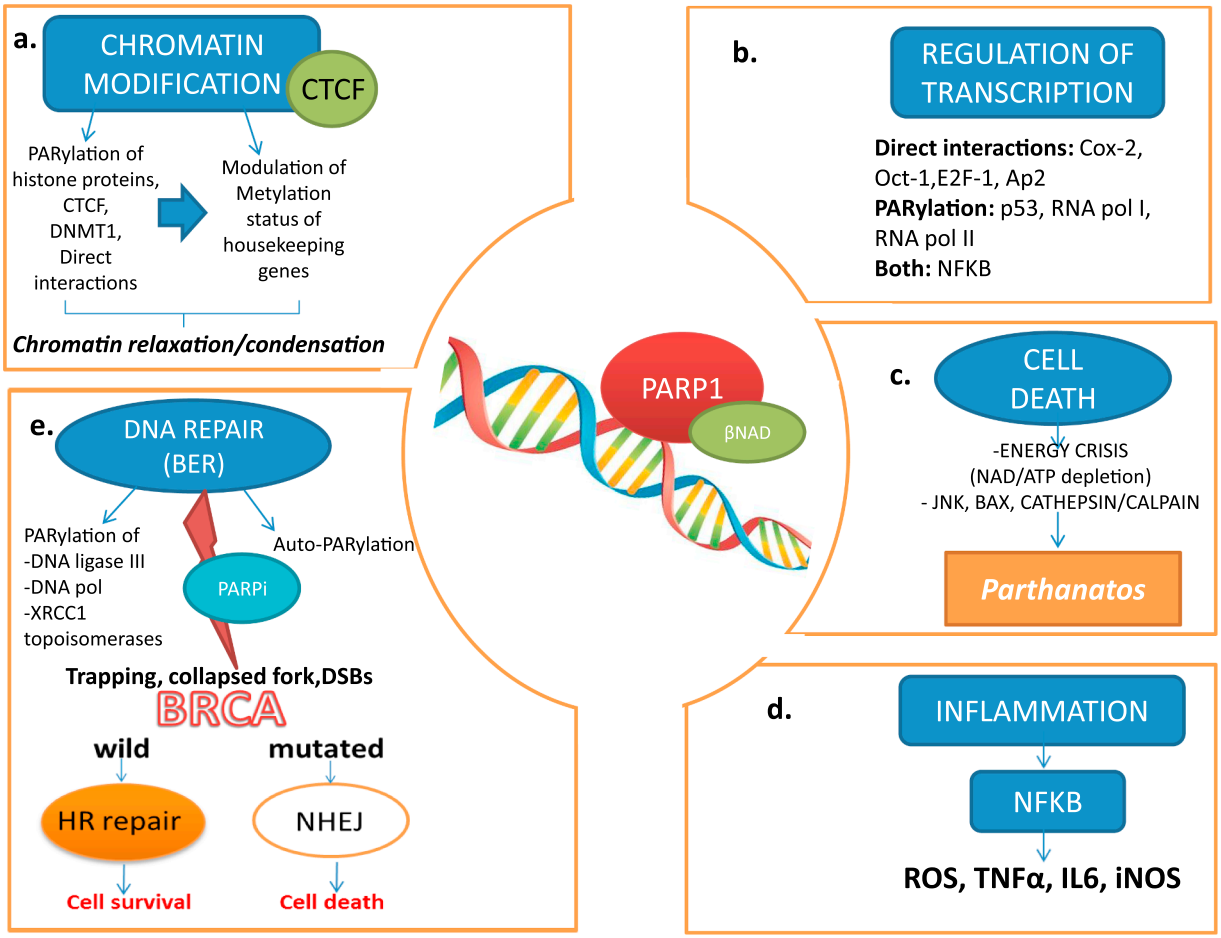

Fig. 1. Mechanism of action of PARPs.

methylation, thus suggesting the existence of a close connection between DNA methylation and PARylation. CTCF is a highly conserved chromatin insulator which binds to specific consensus sequences located on imprinting control regions, there by inhibiting *de novo* methylation. Recent studies have shown that CTCF is able to activate PARP-1 itself, determining ADP-ribosylation of DNA (cytosine-5)-methyltransferase-1 (DNMT1) and inhibition of its activity [7] (Fig. 1a). PARP1 also participates in cell death mechanisms. When high levels of DNA damage are reached (i.e., in aged and stressed cells, and, commonly, in highly proliferative cancer cells), PARP-1 overactivation results in cellular depletion of ATP and NAD. This energy crisis leads to activation of a complex interplay among c-Jun N-terminal kinases (JNK), the mitochondrial protein Bax, and cathepsin/calpain proteases, resulting in cleavage of apoptosis-inducing factor (AIF). Once in the nucleus, AIF forms a DNA-degrading complex with H2AX and cyclophilin A. This form of regulated necrosis is named *Parthanatos* [8] (Fig. 1c). Moreover, PARP1 promotes the expression of such proinflammatory genes as interleukin-6 (IL6) and tumor necrosis factor (TNF), via interaction with nuclear factor kappa-light-chain-enhancer of activated B cell (NFkB) transcriptional factor [9] (Fig. 1d). Noteworthy, PARP1, PARP 2, and PARP 3 catalyze PARylation during DNA damage response. The human genome is constantly subjected to damage under environmental and endogenous stresses, with ensuing DNA lesions like single (SSB) and double strand DNA breaks (DSB). Base excision repair (BER) is the major SSB repair pathway, while homologous recombination (HR) and non-homologous end-joining (NHEJ) act as the main DSB repair machinery in the cells. PARP1 detects and binds to SSB by means of its zinc finger binding domains. This interaction leads to a conformational change, which in turn allosterically activates PARP1. Then, PARylation of such nuclear proteins as topoisomerase, DNA ligase III, DNA polymerase β, and scaffolding proteins (i.e., XRCC1) occurs at sites of DNA breaks. The process of auto-PARylation is responsible for releasing PARP1 from DNA, thereby restoring its catalytically inactive state ("beads on a string" conformation) [10]. In contrast, the involvement of PARP 2 and PARP3 into the DNA damage response is less thoroughly known. Nevertheless, PARP2 is known to be involved in BER/SSB repair pathway, while PARP3 participates in DSB repair through NHEJ [11]. PARP1 also contributes to HR system functioning by recruiting critical DNA repair factors such as NBS1 and MRE11 to sites of DSB and by preventing Ku70/80 proteins from binding to areas of DNA damage. Ku proteins are essential components of the error-prone NHEJ pathway, and PARP-1 exerts an active role in its inhibition [12]. HR predominates instead as a mechanism of repair during mid S and mid G2 phases of cell cycle and requires functional BRCA proteins for repairing DSBs. BRCA1 has an active role in signaling DNA damage and in cell-cycle check-point regulation, whereas BRCA2 has a more direct role in DNA repair by controlling activity and assembly of the essential recombination enzyme RAD51 [13]. Women harboring deleterious BRCA mutations have an average cumulative risk of developing OC by age 70 between 39% and 60%; it is estimated to be 11–30% in case of harmful BRCA1 mutations and BRCA2 deficiency, respectively [14]. In any cell, PARP1 inhibition causes failure of SSB repair but does not affect DSB repair. However, persistent SSBs have been shown to stall and collapse replication fork resulting in DSB. If, in the same cell, BRCA proteins are also deficient, DBSBs are repaired by NHEJ process, thus resulting in chromosomal instability, cell cycle arrest, and apoptosis. This is an explicative example of what the so-called "synthetic lethality" is, i.e., the condition in which a defect in either one

of two genes has little or no effect while their combination (BRCA and PARP genes) results in sickness (synthetic sickness) or even death (synthetic lethality) (Fig. 1e). Two preclinical studies [15,16] published in 2005 demonstrated that BRCA1 and BRCA2-mutant cells and xenografts are highly sensitive to PARP inhibitors (PARPis), therefore providing strong support for their clinical development. PARPis were initially developed to potentiate antitumor activity of ionizing radiations and genotoxic agents (temozolomide and topotecan). Indeed, all PARP is demonstrated *in vitro* and *in vivo* radio or chemo potentiation consistent with their ability of inhibiting DNA damage repair [17]. The mechanism of action of PARPis is not only related to inhibition of PARP catalytic activity, but also to an allosteric conformational change that stabilizes PARP1 and PARP2 association with DNA. This ability of "trapping" PARP-DNA complex explains the different magnitude in cytotoxicity exerted by different PARPis. Of the five PARPis until now tested, olaparib, niraparib, and rucaparib trap PARP ~ 100-fold more efficiently than veliparib, while talazoparib appears to be the most potent PARP trapper studied so far [18]. However, to date, niraparib, olaparib and rucaparib are the only three Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved PARPis approved in the maintenance setting for patients with EOC who achieved a CR or PR following platinum-based chemotherapy. Approximately, 15% of EOC cases harbor germline mutations in BRCA1 or BRCA2 (gBRCA 1/2) when applying as selection criteria age of onset, family history of breast and/or OC, and histological type [19]. However, a considerable part of germline BRCA1/2 mutation carriers is missed since almost half of *BRCA*-positive EOC patients have no significant family history of ovarian or breast cancer. For this reason, germline BRCA1/2 mutation testing is strongly recommended in all EOC patients. Clinical hallmarks of BRCA-mutated OC include platinum chemotherapy-sensitivity, long treatment-free intervals before relapse, sensitivity to PARPis, and improved overall survival. Nevertheless, a subset of "sporadic" (non-hereditary) EOC exhibits comparable clinical profile. Furthermore, alterations in BRCA1 and BRCA2 genes may also occur through somatic mutations or epigenetic silencing; germline or somatic mutations in different HR genes such as ATM, CHEK2, BRIP1, RAD51C, PALB2 are associated with a moderate susceptibility to EOC, thus conferring sensitivity to PARPis [20,21]. Finally, niraparib was shown to significantly benefit patients with no detectable mutations in HR components, suggesting other potential predictive biomarkers and mechanisms contributing to PARPis sensitivity beside HR genes.

Clinical trials of PARPs inhibitors for treatment of ovarian cancer are resumed in Table 1.

Olaparib

Olaparib was the first PARP inhibitor introduced in clinical practice. A phase I trial [22] reported on good safety and tolerability profile of olaparib at a dose of 400 mg bis in die (BID); an objective response rate (ORR) of 46% was registered in heavily pre-treated BRCA1/2-mutated (BRCA 1/2m) cancers. In another phase I trial [23], the antitumor activity of olaparib appeared to be related to platinum sensitivity, because the highest ORR was observed in platinum sensitive BRCA 1/2m patients. Furthermore, in a phase II study [24], olaparib monotherapy demonstrated important antitumor effects in recurrent high grade serous ovarian cancer (HGSOC), regardless of BRCA 1/2 mutation status: ORR was 24% and 41% in patients with no BRCA1/2 mutation and in *BRCA1/2*m patients, respectively. Study 19, an international, randomized, double-blind, placebo-controlled, phase II trial, assigned 265 relapsed HGSOC, fallopian tube, or primary peritoneal cancers, to receive maintenance treatment with olaparib (n = 136) or placebo (n = 129) at a dose of 400 mg BID after a complete (CR) or partial response (PR) to platinum-chemotherapy [25]. The study met its primary endpoint with a net gain of 3.6 months in PFS of patients treated with olaparib compared to those receiving placebo (median PFS 8.4 vs 4.8 months, HR 0.35; $p < 0.001$). In a preplanned subgroup analysis, BRCA 1/2m patients treated with olaparib obtained the greatest clinical benefit with a significant improvement in PFS of 6.9 months (median PFS 11.2 vs 4.3 months; HR 0.18; $p < 0.001$, n = 136). The most commonly reported adverse events (AEs) of any grade were nausea, fatigue, vomiting, and anemia and occurred within the first 4–8 weeks of treatment. Discontinuations due to AEs were infrequent and treatment adherence was 85% and 96% in olaparib and placebo group, respectively. No significant differences were observed between the study groups with regard to symptoms or health-related quality of life. On the basis of these results, in October 2014, EMA approved olaparib as a maintenance treatment in platinum-sensitive, BRCA 1/2m (germline and/or somatic) HGSOC responsive to the last platinum-based chemotherapy after at least 2 prior lines of chemotherapy. On the other hand, an update of 5 years OS data observed in the intention-to-treat population (ITT) (29.8 vs 27.8 months; HR 0.73; $p = 0.025$) and in BRCA 1/2m patients (34.9 vs 30.2 months; HR 0.62; $p = 0.025$) were not statistically significant [26]. Noteworthy, despite the lack of a survival advantage, the significant benefit of maintenance olaparib compared to placebo clearly emerged in explanatory analyses of both median time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST). TFST and TSST were 15.6 (vs 6.2) and 22.0 (vs 15.3) months, and 12.9 (vs 6.9) and 17.0 (vs 14.7) months, in the *BRCA* mutation arm and in the *BRCA* wild-type arm, respectively. However, TFST and TSST are considered intermediate clinical endpoints used to support the PFS results that remains beyond subsequent therapies.

Importantly, after a median follow-up of 5.9 years, 15 patients (11%) were still receiving olaparib and one BRCA 1/2 mut patient in placebo group; moreover, 13% of patients received olaparib for at least 5 years.

A comparative analysis of Study 19 identified and characterized long-term (LT) olaparib responders with respect to short-term (ST) responders in terms of clinical and molecular profiles [27]. LT responders were defined as patients with PFS > 2 years, irrespective of their BRCA1/2 status. On the other hand, ST responders were defined as having a PFS < 3 months, the placebo group PFS being 4.8 months. LT sensitivity to olaparib correlated with chemotherapy CR, while no correlation was found with treatment-free interval following the penultimate platinum-based chemotherapy. Germline and somatic BRCA1/2 mutations were observed to be associated with LT response to olaparib, with prevalence of BRCA2 mutations among LT olaparib responders, as already reported in literature [28]. The most frequent BRCA2 mutations were located in the RAD51-binding domain and in its DNA-binding sites. Altogether, these alterations are expected to interfere with the physiological interactions between BRC domains and RAD51, thus resulting in BRCA2 failure to recruit RAD51 to dsDNA breaks and subsequent hampering of recombination repair. In contrast, BRCA1 silencing through promoter methylation was not associated with response duration. Furthermore, a HRD score (myChoice HRD test, Myriad Genetics [29]) was determined as the sum of three scores calculated for the whole genome: tumor loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transition. A high HRD score was defined as > 42 and was associated with LT response to olaparib. Study 42 was a large single-arm, phase II, study of olaparib (capsules, 400 mg BID) for the treatment of patients with gBRCA1/2m ovarian, breast, prostate, and pancreatic cancers who had received at least 3 prior lines of chemotherapy [30]. The OC cohort included 193 platinum-resistant/refractory patients or platinum-sensitive but ineligible to receive further platinum-based chemotherapy. One hundred forty-seven of these patients were *BRCA* 1/2m. ORR was 34% and the median duration of response was 7.9 months [31]. On the basis of these encouraging data, although derived from a nonrandomized single-arm phase II trial, olaparib was approved by FDA on December 2014 as monotherapy for the treatment of OC in patients with *g*BRCA mutation who had received at least three previous chemotherapy lines. Nonetheless, a randomized phase III trial (*SOLO3)* was started to methodically assess the efficacy and safety of olaparib monotherapy compared

Table 1
Clinical trials results for PARP Inhibitors in ovarian cancer.

Study	Treatment arms	PTS	Phase	Setting	Results	P-value
STUDY 19 [25]	Olaparib 400 mg BID Placebo	265	II	Platinum-sensitive recurrent HGSOC, primary peritoneal or fallopian tube	**Median PFS** Overall population: 8.4 vs 4.8 months BRCA mut: 11.2 vs 4.3 months	 $p < 0.0001$ $p < 0.0001$
STUDY 42 [30]	Olaparib 400 mg BID	193	II	Recurrent pre-treated advanced OC, primary peritoneal or fallopian tube cancer BRCAmut (or unsuitable for further platinum therapy)	**ORR**: 34% **MDR**: 7.9 months	
SOLO 2 [32]	Olaparib 300 mg BID Placebo	295	III	Platinum-sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer BRCAmut	**Median PFS** 19.1 vs 5.5 months	 $p < 0.0001$
SOLO 1 [33]	Olaparib 300 mg BID Placebo	451	III	Platinum sensitive after first line platinum based CT, BRCAmut	**Median PFS** NR vs 13.8 months	 $p < 0.001$
NOVA [35]	Niraparib 300 mg Placebo	555	III	Platinum-sensitive recurrent HGSOC; primary peritoneal cancer, or fallopian-tube cancer	**Median PFS** gBRCAmut: 21 vs 5.5 months BRCAwt HRD+: 12.9 vs 3.8 months Overall non-gBRCA: 9.3 vs 3.9 months	 $p < 0.001$ $p < 0.001$ $p < 0.001$
QUADRA [38]	Niraparib 300 mg	45	II	Platinum sensitive HRD positive HGSOC; primary peritoneal cancer, or fallopian-tube cancer	**ORR** 27.5% **DCR** 68.6%	
STUDY 10 [40]	Rucaparib 600 mg BID	42	I/II	Platinum-sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer gBRCAmut (*phase II PART 2A)*	**ORR**: 59.5% **MDR**:7.8 months	
ARIEL 2 PART 1 [41]	Rucaparib 600 MG BID	192	II	Platinum sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer	**Median PFS** BRCAmut: 12.8 months BRCAwt LOH High: 5.7 months BRCAwt LOH low: 5.2 months	 $p < 0.0001$ $p = 0.011$ $p = 0.011$
ARIEL 3 [43]	Rucaparib 600 MG BID Placebo	564	III	Platinum-sensitive recurrent HGSOC or HGEOC, primary peritoneal or fallopian tube cancer	**Median PFS** BRCAmut: 16.6 vs 5.4 months HRD+: 13.6 vs 5.4 months ITTP: 10.8 vs 5.4 months	 $p < 0.0001$ $p < 0.0001$ $p < 0.0001$

PTS: Patients; HGSOC: High Grade Serous Ovarian Cancer; OC: Ovarian Cancer; HGEOC: high-grade endometrioid cancer; BRCA mut: BRCA mutated; CT: Chemotherapy; HRD+: Homologous Recombination Deficiency positive; PFS: Progression Free Survival; ORR: Objective Response Rate; DCR: Disease Control Rate; MDR: Median Duration of Response; gBRCA: germline BRCA mutated; BRCA wt: BRCA wild type; LOH: loss of heterozygosity; ITTP: Intention to treat population; NR: not reached.

with standard chemotherapy in the same population of patients; however, results are still pending. More recently, the international phase III *SOLO2 study* [32] evaluated olaparib as maintenance therapy in platinum-sensitive, relapsed OC patients with a BRCA 1/2 mutation who received at least two lines of previous chemotherapy. Two hundred ninety-five patients were randomized to receive 2:1 olaparib tablets 300 mg orally twice daily or placebo after at least 4 cycles of platinum-based regimens. Maintenance therapy with olaparib significantly improved PFS when compared to placebo (19.1 vs 5.5 months; HR 0.30; $p < 0.0001$). In view of these results, in August 2017, olaparib was FDA-approved for maintenance treatment of adult patients with recurrent EOC, fallopian tube, or primary peritoneal cancer, following a CR or PR to platinum-based chemotherapy, irrespective of BRCA status; a tablet formulation for previous indications was also introduced. Subsequently, in May 2018, EMA expanded olaparib indications. Finally, the role of olaparib as maintenance of platinum-based chemotherapy has been evaluated in the multicenter, randomized, double-blinded phase III *SOLO-1 trial.* The final results were presented recently at the European Society for Medical Oncology (ESMO) 2018 Congress. Three hundred ninety-one BRCA 1–2 m patients were randomized in a 2:1 ratio to first-line maintenance with olaparib 300 mg twice daily or placebo. The median PFS for patients who received placebo was only 13.8 months, while the median PFS for those who received olaparib was not reached but looks to be approximately 3 years longer than the placebo group (HR = 0.30; $p < 0.0001$) [33].

Niraparib

Niraparib is a potent and selective inhibitor of PARP-1 and PARP-2. Its antitumor activity in OC was assessed, for the first time, in a phase I trial including 42 patients with ROC [34]. The maximum tolerated dose was 300 mg once daily (QD); an ORR of 40% in BRCA 1/2m patients, with a median duration of response of 12.9 months, was observed. Of note, an ORR of 67% was achieved in platinum-sensitive disease and BRCA 1/2 wt patients. These results are consistent with the antitumor effect of niraparib observed in a broader OC population in the *ENGOT-OV16/NOVA trial*, a double-blind, randomized *phase III study*, investigating the role of niraparib as maintenance therapy in ROC [35]. Five hundred fifty-three platinum-sensitive relapsed EOC patients were categorized into two cohorts according to the presence or absence of BRCA mutations (203 gBRCA patients and 350 wt BRCA patients). Patients were randomized to receive niraparib at dose of 300 mg QD or placebo until progression or unacceptable toxicity. In the primary efficacy analyses, the BRCAwt cohort was divided into two subgroups according to HRD status. Furthermore, in exploratory analyses, the HRD-positive subgroup was further defined by the presence or lack of a somatic BRCA mutation (sBRCA), respectively (47 patients HRD-positive/sBRCA 1/2m and 115 patients HRD-positive/BRCAwt). PFS was assessed independently in the gBRCA cohort and in the BRCAwt cohort. A hierarchical design was predefined for the BRCAwt cohort in which statistical analysis was first performed in HRD-positive patients, and, in case of significant results, a test of the overall BRCAwt cohort was carried out. PFS was longer among niraparib-treated patients in all groups when compared to placebo. In particular, in the gBRCA group, PFS was 21 vs 5.5 months, respectively (HR 0.27; $p < 0.001$), while in the non-gBRCA cohort PFS was 9.3 vs 3.9 months (HR 0.45; $p < 0.001$), and in the BRCAwt HRD-positive cohort PFS was 12.9 vs 3.8 months (HR 0.38; $p < 0.001$). Interestingly, PFS was higher in the HRD-positive sBRCA 1/2m subgroup, similarly to the gBRCA cohort: 20.9 vs. 11.0 months (HR 0.27; $p = 0.02$.). In the HRD-positive BRCA wt subgroup, PFS was 9.3 and 3.7 months in the niraparib group and in the placebo group (HR 0.38; $p < 0.001$), respectively. Finally, in the

HRD-negative non-gBRCA mutation subgroup, PFS was 6.9 vs. 3.8 months (HR, 0.58; 95% CI, 0.36–0.92; P = 0.02); the most common toxicities of any grade were nausea, thrombocytopenia, fatigue, anemia, constipation, vomiting, and neutropenia, mostly within first 3 cycles. In fact, incidence of grade 3–4 AEs were infrequent beyond the third cycle. However, dose reductions were common among patients receiving a dose < 300 mg. The most frequent treatment emergent event requiring dose reduction was thrombocytopenia. In a retrospective analysis [36] conducted on the ENGOT-OV16/NOVA trial, two risk factors able to predict myelosuppression were identified: body weight < 77 kg and/or basal platelets count < 150,000 μL, suggesting that, when one or both are present, the starting dose of niraparib should be reduced to 200 mg/day. Of note, the PFS assessed in patients who were dose reduced to either 200 or 100 mg was consistent with the PFS observed in patients who were treated with the 300 mg starting dose [37]. In March 2017, FDA approved niraparib at a dose of 300 mg daily as maintenance treatment of recurrent EOC, fallopian tube or primary peritoneal cancer, in patients obtaining CR or PR to platinum-based chemotherapy; in November 2017, EMA approved niraparib for the same indication. In June 2018, at the ASCO Annual Meeting, the results of the Quadra Trial were presented [38]. This was a single-arm phase II study exploring the role of niraparib as monotherapy in the treatment of platinum sensitive, HRD-positive ROC patients. Forty-five HRD-positive, platinum-sensitive patients who had received three or more previous regimens without prior PARPi administration, achieved an ORR of 27.5% with a disease control rate of 68.6% and a duration of response of 9.2 months. Finally, *PRIMA* is an ongoing, double-blind, randomized, phase III placebo-controlled trial that will evaluate the role of niraparib in the maintenance setting of OC following front-line platinum-based chemotherapy. The recruitment process has been already completed but results are still pending. During ESMO 2018, PRIMA results of this Adverse Reactions (**RADAR**) analysis were presented [39]. In particular, 480 patients were treated with a fixed 300 mg starting dose of niraparib or placebo and 247 patients were treated with an individualized dose of niraparib or placebo based on weight and platelet count (200 mg for body weight < 77 kg and platelet count < 150,000 μL and 300 mg in all other patients). AEs grade ≥3 were lower (36%) in the individualized dosing group (pooled niraparib and placebo) as compared with the group that received a fixed starting dose of 300 mg of niraparib or placebo (52.7%).

Rucaparib

Rucaparib is a potent PARP inhibitor, approved by FDA in December 2016 and by EMA in May 2018 for the treatment, as single agent, of HGSOC patients with *gBRCAm* or *sBRCA*m, relapsed after at least two chemotherapy lines, The efficacy was demonstrated by a pooled analysis of two multicenter single-arm clinical trials: *Study 10* and *ARIEL 2* Study [40–42] In particular, Study 10 was a three-part phase I/II study testing oral rucaparib: the phase I (part 1) was designed to define the recommended phase II dose (RP2D) of rucaparib and to explore its preliminary efficacy [40]. In phase I, the RP2D was established at 600 mg BID and in phase II, part 2A, rucaparib treatment showed an ORR of 59.5%, with a median duration of response of 7.8 months in 42 pre-treated platinum-sensitive HGSOC patients carrying a *gBRCA* mutation. In Part 2B, rucaparib was tested in HGSOC patients with gBRCA or sBRCA mutations who had received two to four previous lines of chemotherapy. Finally, part 3 was designed to investigate pharmacokinetics and safety of a higher oral dose of rucaparib in patients with any relapsed solid tumor associated with g/sBRCA mutations. The recruitment of *Study 10* part 2B and 3 has been completed but results are still pending. The *Ariel 2* study was a multicenter, two-part, phase II open label trial investigating the role of rucaparib in relapsed HGSOC or endometrioid ovarian carcinoma after one or more chemotherapy regimens (part 1) and three or four prior chemotherapy regimens (part 2), including patients with either platinum-sensitive, platinum-resistant, and platinum-refractory disease. ARIEL 2 Part 1 [41] enrolled one-hundred and ninety-two platinum-sensitive OC patients and stratified patients into three HRD subgroups: BRCA1/2-m (n = 40), BRCA wt with LOH high (n = 82), and BRCA wt with LOH low (n = 70). The median PFS was significantly longer in the *BRCA* mutated subgroup (12.8 months; HR 0.27, p < 0.0001) and in the *BRCA*wt/LOH high (5.7 months; HR 0.62, $p = 0.011$) compared to *BRCA*wt/LOH low subgroup (5.2 months). Similarly, the ORR was higher in the *BRCA*1/2-m (80%) and in the *BRCA*wt/LOH high (29%) than the *BRCA*wt/LOH low subgroup (10%). This study identified in LOH a predictive molecular biomarker for measuring HRD. Currently, part 2 is still ongoing. These encouraging results were confirmed by the pooled analysis of the two trials [42] that included 106 patients with HGSOC and a deleterious g/sBRCA1/2 mutations: 42 patients were from Study 10 (Part 2A) and 64 from ARIEL 2 (Parts 1 and 2). All patients received at least two prior chemotherapies: 74.5% exhibited sensitivity to their last platinum-based therapy, 18.8% were platinum-resistant, and 8.4% were platinum refractory. Deleterious *BRCA1/2* mutations were present in all patients: 83% of them had germline mutations, while 17% carried somatic alterations; among them, 63.2% were identified in *BRCA1* gene and 36.8% in BRCA2 gene. The ORR were 53.5% CR, 45.3% PR, 34% SD and 8.5% PD. The median duration of response was 9.2 months. The ORR was quite similar in all the BRCA 1/2m subgroups. It was higher in patients who had received two prior lines of chemotherapy (inclusive of platinum-based chemotherapy). Moreover, patients with a PFI > 12 months had a higher ORR than those with a PFI of 6–12 months or ≤6 months. The integrated safety analysis confirmed the manageable toxicity profile of rucaparib. The phase III ARIEL3 study [43] evaluated the efficacy of rucaparib as maintenance treatment following platinum-based therapy in women with platinum-sensitive, relapsed HGSOC, endometrioid ovarian, fallopian tube, and primary peritoneal cancers. Five hundred sixty-four patients were enrolled and randomized to receive rucaparib at a dose of 600 mg twice daily (n = 375) or placebo (n = 189) in a 28-day cycle. The primary endpoint, PFS, was tested using an ordered step-down multiple comparisons procedure for three nested cohorts: (1) g/s*BRCA* 1/2m patients; (2) HRD (*BRCA* 1/2m or *BRCA*wt and high LOH); (3) ITT population. Rucaparib significantly improved the median PFS in all groups as follows: (1) in the deleterious BRCA mutation subgroup, PFS was 16.6 months in the rucaparib group (n = 130) versus 5.4 months in the placebo group (n = 66) (HR 0.23; p = 0.0001); (2) in the HRD subgroup, it was 13.6 months in the rucaparib group (n = 236) vs 5.4 months in the placebo arm (n = 118) (HR 0.32; p = 0.0001); (3) in the ITT population, PFS was 10.8 months in the rucaparib group and 5.4 months in the placebo group (HR 0.36; p = 0.0001). Gastrointestinal toxicity, fatigue and myelosuppression were the most common treatment-emergent adverse events in the rucaparib group but were generally manageable with dose reduction. Based on these data, on 6 April 2018, FDA expanded rucaparib indications to the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers achieving a CR or PR to platinum-based chemotherapy. Finally, ARIEL 4 is an ongoing phase III study, designed to compare the efficacy and the safety of rucaparib versus standard chemotherapy in *BRCA* 1/2m OC patients who had received at least two previous lines of chemotherapy. Patients will be randomized 2:1 to receive rucaparib 600 mg BID or weekly paclitaxel, if their PFI is 1–12 months, or platinum-based chemotherapy, if their PFI is > 12 months.

In summary, olaparib demonstrated high efficacy as maintenance treatment in first (SOLO1) and in subsequent lines of therapies (SOLO2) for platinum sensitive BRCA1/2 mut OC patients. Niraparib (ENGOT-OV16/NOVA) and rucaparib (ARIEL 3) resulted effective in maintenance setting for platinum sensitive ROC regardless BRCA status [32,33,35,43].

PARPis and antiangiogenic agents

Overexpression of PARP1 has been shown to exert a clear pro-angiogenic effect in EOC by upregulation of VEGFA [44]. Antiangiogenic therapies are known to induce a hypoxic cellular state leading to downregulation of HR repair genes (*BRCA1, BRCA2* and *RAD51)*, with consequent enhancement of PARPis sensitivity [45]. However, hypoxia is also related to Hypoxia Inducible Factor 1 alpha (HIF1α) up-regulation, which is considered one of most common mechanisms of resistance to angiogenesis inhibitors. Interestingly, PARP1 may play a pivotal role in HIF-1α stabilization [46]. As a consequence, the use of PARPis may prevent its accumulation and signaling, thus overcoming this resistance mechanism resulting in death of the targeted hypoxic cell. This is a clear example of 'contextual synthetic lethality' due to tumor microenvironment, in which hypoxia-induced repair-deficient tumor cells can be targeted by disrupting backup pathways. The combination of cediranib, an oral tyrosine kinase inhibitor of VEGF receptor (VEGFR) and olaparib vs olaparib alone was tested in a phase II *study* in platinum-sensitive ROC [47]. Median PFS was significantly longer for cediranib/olaparib treated patients than for patients on olaparib alone (17.7 vs 9 months, HR 0.42; $p = 0.005$). A post-hoc exploratory analysis revealed an increased activity of cediranib plus olaparib vs olaparib alone in the subgroup of patients with wild type or unknown BRCA status, with an improvement in the median PFS from 5.7 to 16.5 months (HR = 0.32; p = 0.008) and in the ORR from 32% to 76% (p = 0.006). Among gBRCAm patients, there was a lesser trend towards increased activity for the combination arm, with a slighter gain of PFS (from 16.5 to 19.4 months) and ORR (benefit from 63% to 84%). Notably, side-effects (fatigue, diarrhea, and hypertension) of any grade occurred in the combination arm, resulting in dose reductions in more than 75% of patients. Three phase III trials are currently ongoing to validate this combination in different settings. The aim of *GY004* trial was to compare olaparib monotherapy vs olaparib and cediranib combination vs standard platinum-based chemotherapy in patients with platinum-sensitive recurrent ovarian/fallopian tube cancers. *GY005* trials evaluating the same therapeutic options in recurrent platinum-resistant or refractory OC. Finally, *ICON 9* trial is examining maintenance therapy with cediranib and olaparib or maintenance olaparib alone after platinum-based chemotherapy in patients with recurrent platinum-sensitive high-grade OC. The combination of olaparib 400 mg BID with bevacizumab 10 mg/kg q2w was investigated in a phase I study in patients with advanced solid tumors; a good tolerability without serious AEs or dose-limiting toxicities were recorded [48]. On the basis of these results, a phase III trial, *PAOLA1*, was planned to determine the efficacy of olaparib or placebo combined with bevacizumab as maintenance treatment in patients with OC treated with standard first-line platinum-based chemotherapy plus bevacizumab. Finally, the results of a phase I trial of bevacizumab (15 mg/kg q21 days) plus niraparib (300 mg oral QD) demonstrated an ORR of 45% in 12 patients and DCR of 91% in the combination treatment arm [49]. Class toxicities (hypertension, anemia, thrombocytopenia, fatigue, constipation, nausea) were manageable and only one dose-limiting toxicity was reported: grade 3 thrombocytopenia that persisted for ≥5 days. Results from *AVANOVA*, a phase II ongoing trial, comparing single-agent niraparib with niraparib plus bevacizumab in 94 women with platinum-sensitive OC, are still pending.

PARPis and immune checkpoint inhibitors

Enhancement of tumor antigenicity sensitizes cancers to checkpoint blockade therapy. Several studies have shown that BRCA1/2*m* and wt-BRCA1-2 HRD ovarian tumors display a higher neo-antigen load than HR-proficient cancers [50]. PARPis have been postulated to enhance the response to immunotherapy in HRD OC by yielding a greater mutational burden, thereby expanding neoantigen expression. In fact, the presence of danger signals, following DNA damage, activates the stimulator of interferon genes (STING) pathway which plays a pivotal role in the innate immunity by inducing type I interferon and pro-inflammatory cytokine production [51]. Moreover, PARPis administration upregulates PD-L1 expression on tumor cells, which in turn attenuates PARPis efficacy via cancer-associated immunosuppression. As a consequence, the targeted blockade of PD-L1 pathway can restore antitumor immunity and potentiate the antitumor activity of PARPis [52]. Altogether, these observations provide a scientific rationale for evaluating the combination of immune checkpoint blockade with PARPis in OC clinical trials. The phase I/II TOPACIO trial [53] demonstrated niraparib in combination with pembrolizumab, an anti-PD-1 antibody, to be a promising option for the treatment of platinum-resistant OC. Following dose finding in phase I, the RP2D of niraparib and pembrolizumab was assessed at 200 mg orally QD and 200 mg IV every 21 days, respectively. During phase II, among 60 out of 62 enrolled patients who were considered evaluable for initial response assessment, 64% of them were platinum-resistant, 19% had platinum-refractory disease, and 17% had platinum-sensitive OC ineligible for further platinum. In the whole population, ORR and DCR were 25% and 68% respectively, while in the BRCA1/2m cohort (11 patients), ORR and DCR were 45% and 73% respectively. With regard to olaparib, the phase I/II basket MEDIOLA trial evaluated the combination with durvalumab, an anti-PDL1 antibody, for the treatment of gBRCA 1/2*m* platinum-sensitive relapsed OC [54]. Thirty-two patients received olaparib 300 mg (tablets) BID for 4-weeks, followed by a combination of olaparib 300 mg BID and durvalumab 1.5 g intravenous (IV) every 4 weeks, until disease progression. DCR at 12 weeks was 81% while ORR was 63%. This combination was well tolerated, with a low incidence of grade 3 toxicities and all-grade immune-related AEs. The results of TOPACIO trial and MEDIOLA study were presented at European Society of Gynaecological Oncology (ESGO) congress 2018. In another phase II study the combination of durvalumab and olaparib was tested in 34 ROC patients (6 gBRCAm and 28 BRCAwt) with platinum sensitive or resistant disease. The preliminary efficacy results, presented during the ESMO congress 2018, showed a response rate and DCR of 15% and 53%, respectively [55]. The combination of olaparib at a dose of 300 mg BID with tremelimumab, a CTLA-4 antibody, at a dose of 10 mg/kg monthly, was tested in another phase I trial [55] for the treatment of BRCA 1/2m ROC and demonstrated good safety. Several studies assessing the efficacy of PARPis in combination with immunotherapy are ongoing. A phase I/II trial is evaluating side effects and optimal dose of olaparib in combination with durvalumab and tremelimumab for the treatment of ROC. The phase III FIRST trial was designed to evaluate platinum and TSR-042 (PD-L1 inhibitor) followed by Niraparib and TSR-042 maintenance therapy versus adaptive standard platinum-based treatment for newly diagnosed advanced OC patients. In addition, ENGOT-ov46/AGO/DUO-O is a phase III study whose aim is to assess the efficacy and safety of standard of care platinum-based chemotherapy and bevacizumab followed by maintenance bevacizumab either as monotherapy, or in combination with durvalumab, or in combination with durvalumab and olaparib for newly diagnosed advanced OC patients. Regarding rucaparib, the phase III ATHENA study, is investigating the association with nivolumab as maintenance treatment in OC patients, after response to frontline platinum-based chemotherapy.

PARPis and other agents

As PARPis emerged as an effective therapeutic strategy in HR-deficient tumors, the real challenge is to establish whether PARPis can also be effective in HR-proficient carcinomas. The condition of HR proficiency, which plays a major role in PARPis resistance, can occur *de novo* or be acquired. In the latter case, genetic or epigenetic events occurring under selective pressure due to PARPis exposure are responsible for reversing the original HR alterations, thus leading to HR restoration. The most common acquired mechanism of resistance to PARPis is a

Table 2
FDA- EMA approved indications for PARP inhibitors in ovarian cancer.

	Olaparib	Niraparib	Rucaparib
Dosing	Capsules: 400 Mg BID Tablets: 300 Mg BID	Capsules: 300 Mg	Tablet: 600 Mg BID
Pivotal Trial	STUDY19 [25] STUDY 42 [24] SOLO 2 [32]	NOVA TRIAL [35]	STUDY 10 [40] ARIEL 2 [41] ARIEL 3 [43]
FDA Approved Indications	2014: Recurrent gBRCA-OC with > 3 previous lines of chemotherapy (Capsules formulations) 2017: Maintenance therapy of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a CR or PR to platinum-based chemotherapy. (Tablets formulations)	2017: Maintenance therapy of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR platinum-based chemotherapy.	2016: Monotherapy treatment for patients with platinum sensitive, relapsed or progressive, g/sBRCA mutated, epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum based chemotherapy 2018: Maintenance therapy of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.
EMA Approved Indications	2014: Maintenance therapy for patients BRCA mutated with platinum-sensitive relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based 2018: Maintenance therapy for patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy regardless of *BRCA* status. (Tablets formulations)	2017: Maintenance therapy for patients with platinum-sensitive relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer who are CR or PR to platinum-based chemotherapy	2018: Monotherapy treatment for patients with platinum sensitive, relapsed or progressive, g/sBRCA mutated, epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum based chemotherapy

gBRCA: germline mutation; sBRCA: somatic mutation; g/sBRCA: germline/somatic BRCA mutation; OC: ovarian cancer; CR: complete response; PR: partial response.

somatic genetic reversion of the original truncating BRCA mutation that restores functional protein expression [56]. Alternatively, an acquired epigenetic reversion of BRCA1, such as promoter hypermethylation, has been shown to restore normal BRCA1 protein expression levels [57]. Of note, tumors carrying a specific BRCA1 mutation, which disrupts the N-terminal RING domain, respond poorly to platinum drugs and PARPis and rapidly develop resistance [58]. Another possible mechanism of PARPis resistance may be the decreased expression of PARP enzymes due to epigenetic silencing or accelerated/high protein turnover[59]. Furthermore, intracellular concentrations of PARPis could be reduced by increased P-glycoprotein–mediated efflux, thus resulting in decreased antitumor effect [60]. The loss of 53BP1 in BRCA1m tumors, partially restoring the error-free repair mechanism mediated by HR, enhances DNA-damage tolerance and induces PARPis resistance [61]. Finally, HR proficient OC with concurrent amplification of cyclin-E genes has been demonstrated to be resistant to PARPis [62]. As a consequence, the rationale to combine PARPis with molecularly targeted agents capable of inhibiting HRR may represent a promising effective strategy to expand their use in HR-proficient OC [63]. Among all the combinations that are currently under assessment, the association with PI3K inhibitors appears the most reasonable approach, as its phase I evaluation in ovarian and triple-negative breast cancers has just been completed [64]. The rationale for this trial was based on two preclinical studies published in 2012 [65,66], which showed that PI3K inhibition significantly decreased BRCA1/2 expression, thus resulting in acquired HRD underlying the antitumor effects of PARPis. In the phase I study, combined exposure to olaparib and BMK120 showed an ORR of 29% in 46 advanced OC patients, irrespective of platinum-sensitivity status [67]. The maximum tolerated dose was 50 mg QD of BKM120 and 300 mg BID of olaparib. Randomized phase II studies are warranted to further define the efficacy of PI3K/PARP-inhibitor combinations compared with PARPis alone in different settings of ROC. Finally, the use of PARPis after PARPis represents an interesting field of investigation. In this direction, the OReO/ENGOTOv-38 is ongoing trial that will evaluate efficacy and safety of maintenance re-treatment with olaparib in patients that retain platinum sensitivity despite progression on olaparib maintenance therapy.

Conclusions

The lack of a therapeutic strategy tailored to special biomarkers has always been a crucial obstacle in the systemic treatment of advanced-stage OC. The development of PARPis offers a therapeutic strategy for patients with OC. All the EMA- FDA-approved PARPis, olaparib, rucaparib and niraparib, are characterized by a similar efficacy in the maintenance setting for patients with platinum-sensitive OC. To date, the overlapping indications of regulatory Agencies (Table 2) do not support the medical oncologists in choosing which is the best PARP inhibitor to administer. Some different considerations may help to personalize the treatment on the basis of the clinical and molecular features of the patient. First of all, one obvious issue requiring examination is the specific toxicity profile showed by each agent: olaparib is widely known to increase serum levels of creatinine in about 44% of patients; rucaparib has been related to elevated AST and ALT levels in about 75% of patients while approximately 30% of patients receiving niraparib experienced grade 3 thrombocytopenia. Regarding efficacy data, the lack of phase III data for olaparib, compared to rucaparib and niraparib, does not support its use in a non-mutated BRCA population. However, the HRD positive population treated with niraparib is different from ROC patients treated with rucaparib because in the ARIEL3 HRD positive cohort included also gBRCA 1/2m patients. Moreover, different tests were used to define the HRD positive status: in the *ENGOT-OV16/NOVA trial* was used myChoice® HRD test by Myriad that quantitates genomic instability of the tumor on the sum of these 3 measurements (LOH, telomeric allelic imbalance, and large-scale transitions), conversely in the ARIEL3 trial was used the Foundation Medicine T5 next-generation sequencing assay (Foundation Medicine, Cambridge, MA, USA) to calculate the percentage of genomic LOH in tumor biopsy. In light of the benefit showed by niraparib in the BRCAwt HRD-positive population, it is becoming increasingly important, in clinical practice, to identify these patients through a validated test. In this regard, myChoice® HRD test failed as a negative predictive marker of response, since even HRD negative patients, achieved a modest benefit to niraparib therapy. On the other hand, the current challenge is to confer HR deficiency in HR- proficient tumors thus sensitizing them

to PARPis. This is the rationale behind a growing number of clinical trials exploring combination strategies designed to selectively disrupt HR in cancer cells. Further studies are required in order to better define potential predictors of response beyond BRCA mutations and HRD status, thus resulting in a broader target population of OC patients. Finally, looking at exciting results of olaparib in maintenance setting after platinum-based first line chemotherapy for BRCA 1/2m patients, the future matter will be whether to anticipate the maintenance with olaparib in first-line and eventually repurpose it to the sensitive platinum recurrence.

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Conflict of interest statement

There are no conflicts of interest associated with this publication.

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